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INFLAMMATORY BOWEL DISEASE

Curcumin-QingDai Combination for Patients With Active Ulcerative Colitis: A Randomized, Double-Blinded, Placebo-Controlled Trial

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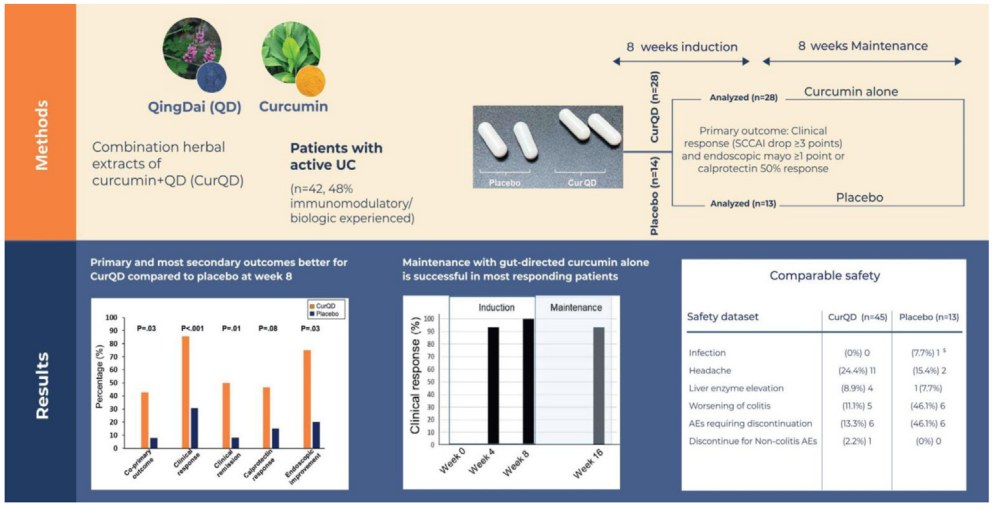

BACKGROUND & AIMS: **We evaluated the efficacy of herbal combination of curcumin-QingDai (CurQD) in active ulcerative colitis (UC).**

METHODS: **Part I was an open-label trial of CurQD in patients with active UC, defined by a Simple Clinical Colitis Activity Index score of 5 or higher and a Mayo endoscopic subscore of 2 or higher. Part II was a placebo-controlled trial conducted in Israel and Greece, randomizing active UC patients at a 2:1 ratio to enteric-coated CurQD 3 g/d or placebo for 8 weeks. The co-primary outcome was clinical response (reduction in the Simple Clinical Colitis Activity Index of ≥3 points) and an objective response (Mayo endoscopic subscore improvement of ≥1 or a 50% fecal calprotectin reduction). Responding patients continued either maintenance curcumin or placebo alone for**

Abbreviations used in this paper: AhR, aryl-hydrocarbon receptor; CurQD, curcumin-QingDai; CYP1A1, cytochrome P450 1A1; IQR, interquartile range; PAH, pulmonary arterial hypertension; QD, QingDai; SCCAI, Simple Clinical Colitis Activity Index; UC, ulcerative colitis.

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an additional 8 weeks. Aryl-hydrocarbon receptor activation was assessed by cytochrome P450 1A1 (CYP1A1) mucosal expression.

RESULTS: **In part I, 7 of 10 patients responded and 3 of 10 achieved clinical remission. Of 42 patients in part II, the week 8 co-primary outcome was achieved in 43% and 8% of CurQD and placebo patients, respectively ($P = .033$). Clinical response was observed in 85.7% vs 30.7% ($P < .001$), clinical remission in 14 of 28 (50%) vs 1 of 13 (8%; $P = .01$), a 50% calprotectin reduction in 46.4% vs 15.4% ($P = .08$), and endoscopic improvement in 75% vs 20% ($P = .036$) in the CurQD and placebo groups, respectively. Adverse events were comparable between groups. By week 16, curcumin-maintained clinical response, clinical remission, and clinical biomarker response rates were 93%, 80%, and 40%, respectively. CurQD uniquely up-regulated mucosal CYP1A1 expression, which was not observed among patients receiving placebo, mesalamine, or biologics.**

CONCLUSIONS: **In this placebo-controlled trial, CurQD was effective for inducing response and remission in active UC patients. The aryl-hydrocarbon receptor pathway may merit further study as a potential UC treatment target. ClinicalTrials.gov ID: NCT03720002.**

Keywords: Inflammatory Bowel Disease; Ulcerative Colitis; Treatment; Complementary Medicine.

See editorial on page 235.

Patients with mild–moderate active ulcerative colitis (UC) who have not responded to mesalamine, as well as patients with moderate–severe UC, are treated by a host of immune-suppressive and biologic therapies.[1] However, because of considerations of limited efficacy, safety concerns, and costs, there is still an unmet need to explore novel and affordable agents for active UC. In previous placebo-controlled trials, we and others have shown the efficacy and safety of curcumin, a herbal traditional medicine compound, as an add-on therapy to mesalamine in mild–moderately active UC.[2–4] QingDai (QD, indigo) is another herbal compound used to treat psoriasis and hematologic disorders.[5] In experimental murine models, QD ameliorated colitis via activation of the aryl-hydrocarbon receptor (AhR).[6,7] The clinical efficacy of QD to induce remission in patients with active UC was shown in 2 placebo-controlled trials from Japan and a small open-label study from the United States.[8–10] Over the past 6 years we have used these 2 food supplements in a combination of curcumin with QD (CurQD) in active UC patients and have observed considerable clinical and endoscopic responses with an acceptable safety profile.[11] Therefore, we embarked on the present placebo-controlled trial, which aimed to explore the efficacy and safety of CurQD in patients with active UC.

Methods

Design and Patients

This was a prospective multicenter trial conducted at 2 centers (Sheba Medical Center, Tel-Aviv University, Israel, and Evangelismos-Polykliniki' General Hospital of Athens, Athens, Greece). The study comprised 2 parts. In part I, a prospective open-label phase 1b study of 10 patients receiving CurQD for 4 weeks was conducted. Part II was a double-blind, randomized, placebo-controlled, induction trial of CurQD for 8 weeks, with roll over to an additional 8 weeks of maintenance treatment for responders (see later).

Eligible patients for both parts were older than age 18 years and had UC diagnosed by established clinical–endoscopic and histologic criteria. To be eligible, patients had to have active UC defined by a Simple Clinical Colitis Activity Index (SCCAI) score of 5 or higher,[12–14] and active colonic inflammation defined by a score of 2 or higher in the modified Mayo endoscopic subscore, which extended proximally to the rectum (>15 cm) at the screening lower endoscopy. Patients' concomitant medications, including biologics if received, had to be maintained at a stable dose for 4 to 12 weeks before inclusion according to predetermined criteria (Supplementary Methods) and were maintained at this dose throughout the trial duration. Concomitant corticosteroids were allowed at a dose of 20 mg/d or less of prednisone or equivalent, provided the dose was stable for at least 2 weeks before study inclusion. If enrolled on corticosteroids, the dose had to be unchanged until the outcome assessment at week 8. No forced tapering was applied for patients who continued in the subsequent maintenance phase (weeks 8–16).

Exclusion criteria were pregnancy; allergy to curcumin or QD; active infection, either enteric or elsewhere; patients with uncontrolled renal, liver, lung, or cardiovascular disease; uncontrolled hypertension, diabetes, migraines, or neurologic disease; chronic pancreatitis; or gallstone disease. Patients with significant laboratory abnormalities also were excluded. Patients never before treated for UC also were excluded, as were patients receiving tofacitinib. The study was approved by the institutional review boards at both centers and all patients signed an informed consent. The trial was registered in Clinicaltrials.gov: NCT03720002.

Study Drugs, Randomization, and Procedures

CurQD was administered as 3 capsules of 500 mg herbal extract dry powder QD (a total of 1.5 g) and 3 capsules of 500 mg dry powder curcumin (a total of 1.5 g). These doses were chosen based on our previous trial with this curcumin compound,[3] with some dose reduction to reduce the total pill burden. The QD dose was based pragmatically on our clinical practice using this supplement since 2016,[11] because the Naganuma et al[8] study was not yet published at the time of protocol finalization, but the 1.5-g dose chosen was comparable with a middle dose between the 1-g and 2-g arms of the trial. EUDRAGUARD biotic polymer pH-dependent coated hydroxypropyl methylcellulose CurQD capsules and identical opaque-coated placebo capsules (Supplementary Figure 1) were supplied by EviNature (Binyamina, Israel; manufactured at a Good Manfucturing Practice facility: Bara Herbs, Yokenaam, Israel), and were opaque-coated to maintain visual blinding. CurQD passed regulatory-required testing for heavy metals, pesticides, and microbial contaminants, as well as determination of indigo and indirubin content by liquid chromtography-mass spectrometry analysis (Supplementary Methods and Supplementary Figure 2).

Screening of patients comprised a physical examination, blood tests, stool tests for enteric infections, liver ultrasonography, and a cardiac transthoracic echocardiogram. Fecal calprotectin was measured by an enzyme-linked immunosorbent assay (Bühlmann, Schönenbuch, Switzerland) in which levels greater than 50 μg/g were considered abnormal. A sigmoidoscopy also was performed with the Mayo subscore determined by 2 blinded endoscopists.

In part I, patients received open-label CurQD treatment for 4 weeks. A day 3 telephone visit was performed to inquire about headache and adjust the dose if necessary (Supplementary Methods). All aforementioned procedures were repeated and clinical outcomes for part I were determined at week 4. As predetermined with the institutional review board, achieving the primary outcome in 30% or more of patients without severe adverse events was required to launch part II of the trial.

In the double-blind, placebo-controlled, part II trial, patients underwent similar screening and randomly were assigned at a 2:1 ratio to receive 8 weeks of either 3 g/d CurQD or identical placebo (Figure 1 and Supplementary Figure 1). Randomization was centrally performed by blocks of 6, which were computer-generated in sequences at Sheba Clinical Trials Unit, and were known to only 2 unblinded study coordinators. Randomization blocks were sent to the respective designated study coordinator in each center along with

What You Need to Know

Background

Curcumin and QingDai (QD, Indigo) are herbal compounds previously found to be effective in mild–moderate and moderate–severe ulcerative colitis (UC), respectively, but data on their use still are limited.

Findings

In a randomized placebo-controlled trial we found the combination of curcumin with QD (CurQD) to be efficacious in inducing response in patients with active UC, of whom half were immunomodulator or biologic-experienced. CurQD induced the activation of the mucosal aryl-hydrocarbon receptor.

Implications for patient care

CurQD offers an herbal-based nutraceutical treatment option for active UC and may point to the aryl-hydrocarbon–receptor pathway as a potential target for drug development for inflammatory bowel disease.

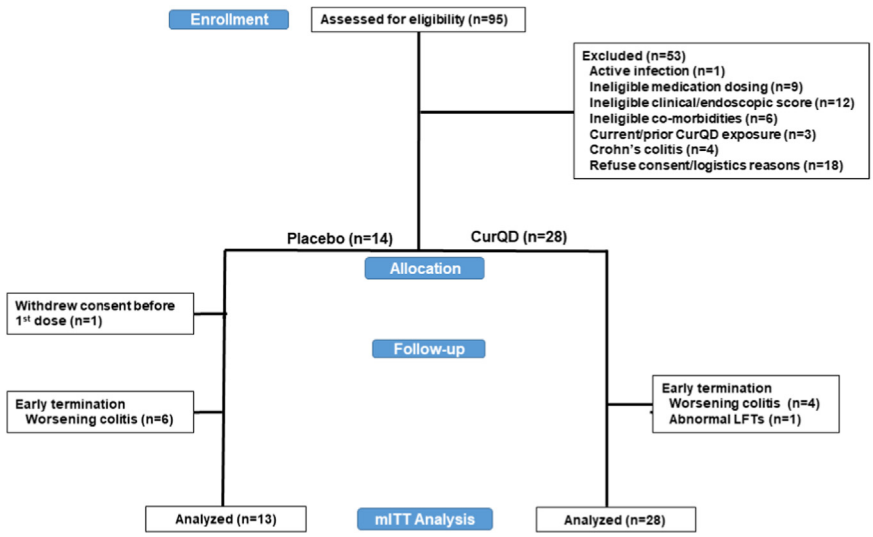

Figure 1. CONSORT flow chart of study patients. CurQD, curcumin-QingDai; LFT, liver funtion tests; mITT, modified intention-to-treat.

number-coded identical capsule boxes. Study investigators, study site personnel, and patients were masked to treatment allocation and study drugs throughout the study. Study visits in part II took place in week 4 and at the primary outcome time point at week 8 or earlier in the case of early termination. Clinical, calprotectin, and lower endoscopy assessments were performed along with repeat liver ultrasonography and cardiac echocardiogram. All patients filled out an electronic SCCAI every other day to assess time to onset of effect. Patients responding to therapy at the end of induction (week 8) were eligible to continue blinded 1.5 g curcumin alone (without QD), or corresponding placebo, as per their original treatment allocation, for an additional 8 weeks.

Trial End Points and Assessment

The primary outcome of part I of the trial was the percentage of patients in clinical remission at week 4. Clinical remission was defined as a SCCAI score of 2 or less.[3,12–14] The co-primary outcome of part II was the proportion of patients with clinical response (reduction in SCCAI of $\geq$3 points from baseline) and objective evidence of reduced inflammatory activity (Mayo score improvement of $\geq$1 or 50% calprotectin reduction) at week 8. Secondary outcomes at week 8 were the percentage of patients in clinical remission (SCCAI, $\leq$2), the percentage with clinical response, rates of biomarker ($\geq$50% decrease in calprotectin) and endoscopic improvement (decrease $\geq$1 point of the endoscopic Mayo subscore), the rate of achievement of mucosal healing (Mayo subscore, $\leq$1), and the time-to-response defined as the number of days to achieve a decrease of 3 or more points of the SCCAI score and time to achieve cessation of rectal bleeding. For the extension study, the power to detect a difference was presumed to be limited. Thus, only exploratory analyses were performed to assess the percentage of patients in clinical remission (SCCAI, $\leq$2) and the percentage of patients who maintained clinical response at week 16.

Assessment of Cytochrome P450 1A1 Expression in Colonic Tissue

See the Supplementary methods for details.

Statistical Analysis

Outcomes were assessed by a modified intention-to-treat (mITT) analysis, including all patients who ingested at least 1 dose of study drug. Continuous variables were checked for normality by the Shapiro–Wilk test and compared by the Student t test or the Mann–Whitney test, as appropriate. Categoric parameters were compared by the Fisher exact test. Nonresponder imputation was applied for patients dropping off before week 8. At the time the study was planned, no data were available on effect size of QD treatment in active UC, and no formal sample size calculation could be performed. Therefore, it was decided pragmatically to include 42 patients (14 placebo, 28 active drug) in the part II pilot randomized trial. Upon later publication of the Naganuma et al[8] trial, which found a 14% response in the placebo arm and a 75% response in the active QD arm, a postprotocol sample size calculation using this reported effect size indicated that our pragmatically chosen sample size was adequate to detect this difference with a power of 80% and an α error of 5%. All statistics were performed using MedCalc statistical software (Marieke, Denmark). A P value less than .05 was considered significant.

Results

Part I

Part I enrolled 17 patients in an open-label study. Seven of these patients erroneously took a double dose of QD (ie, 3 g/d instead of 1.5 g/d), and were excluded from the efficacy analysis and included only in the safety data set (Supplementary Table 1 and Supplementary Figure 3). Clinical remission (SCCAI, $\leq$2) was achieved by 3 of 10 patients, clinical response (reduction in SCCAI, $\geq$3) by 7 of 10 patients, and a biomarker response (calprotectin decrease, $>$50%) in 4 of 10 patients (Supplementary Figure 4).

Part II

Patients. A total of 95 patients (not included in part I) were screened in the 2 study centers in Israel and Greece. Of these, 53 patients were ineligible and were excluded owing to mild endoscopic activity and other reasons (Figure 1). Of 42 patients randomized to the 2 study arms, one patient withdrew consent after randomization before ingesting any study medication and therefore was excluded from the preplanned mITT analysis. Patients' clinical-demographic disposition was overall comparable between the 2 arms (Table 1). All patients had failed or were intolerant to at least 1 line of UC treatment: 97.5% of patients to mesalamine and 48.8% to biologic and/or immunomodulators (29.3% previously received immunomodulators, 36.6% were biologic-experienced, and 17.1% previously received a combination of both).

Primary and secondary outcomes. In the predefined mITT analysis, 12 of 28 (43%) patients met the week 8 co-primary outcome in the CurQD arm vs 1 of 13 (8%) in the placebo arm ($P = .033$; RR, 1.62; 95% CI, 1.13–2.31) (Figure 2). For secondary outcomes, clinical remission was achieved by 14 of 28 (50%) vs 1 of 13 (8%; $P = .01$), and clinical response was achieved in 24 of 28 (85.7%) vs 4 of 13 (30.7%; $P < .001$), in the CurQD and placebo

Table 1. Patients' Background Disposition

	CurQD (n = 28)	Placebo (n = 13)	*P* value
Median age, *y* (25–75 IQR)	35 (23–48)	25 (23–30)	.17
Women	13 (46.4%)	8 (61.5%)	.51
Median BMI	22.8 (19.1–26.7)	24.2 (18.9–28)	.26
Median disease duration, *y*	3 (1.7–8)	4 (1–8)	.57
Extraintestinal manifestations	6 (23.1%)	7 (53.8%)	.08
Disease extent			
Left sided (E2)	20 (71.4%)	7 (53.8%)	.31
Extensive colitis (E3)	8 (28.6%)	6 (46.1%)	.31
Previous medications			
Corticosteroids	11 (39.3%)	7 (53.8%)	.51
Aza/6MP	5 (17.9%)	3 (23.1%)	.69
Biologics	7 (25%)	5 (38.5%)	.49
SCCAI at baseline	8 (7–11)	9 (6.7–11)	.72
Mean baseline fecal calprotectin level	948 (±365)	972 (±487)	.84
Endoscopic score at baseline			
Mayo 2	16 (57.1%)	9 (69.2%)	.51
Mayo 3	12 (42.9%)	4 (30.8%)	.51
Concomitant medications			
Oral mesalamine	20 (71.4%)	9 (69.2%)	1.0
Aza/6MP	3 (10.7%)	1 (7.7%)	1.0
Corticosteroids	2 (7.1%)	1 (7.7%)	1.0
Biologics	5 (17.9%)	2 (15.4%)	1.0

NOTE. Concomitant biologics in the CurQD group were vedolizumab (n = 4) and infliximab (n = 1), and in the placebo group were vedolizumab (n = 1) and infliximab (n = 1).
Aza, azathioprine; BMI, body mass index; CurQD, curcumin-QingDai; IQR, interquartile range; SCCAI, Simple Clinical Colitis Activity Index; 6MP, 6-mercaptopurine.

groups, respectively (Figure 2). By week 8, endoscopic Mayo subscore response of a reduction of 1 point or more was achieved in 75% vs 20% of patients (P = .036), and a reduction of calprotectin by more than 50% from baseline was recorded in 13 of 28 (46.4%) vs 2 of 13 (15.4%; P = .08), in the CurQD and placebo groups,

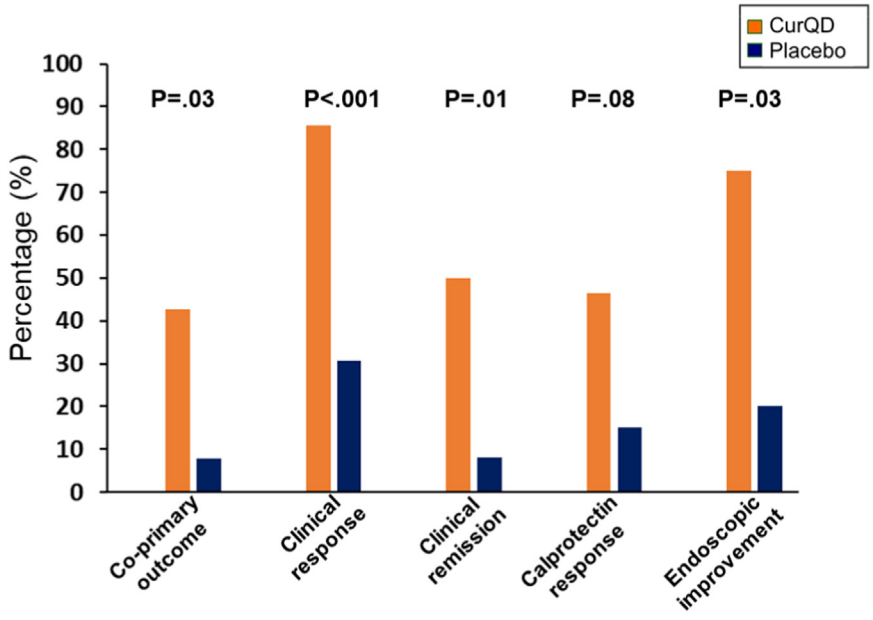

Figure 2. Primary and secondary outcomes of the part II randomized placebo-controlled study. CurQD, curcumin-QingDai.

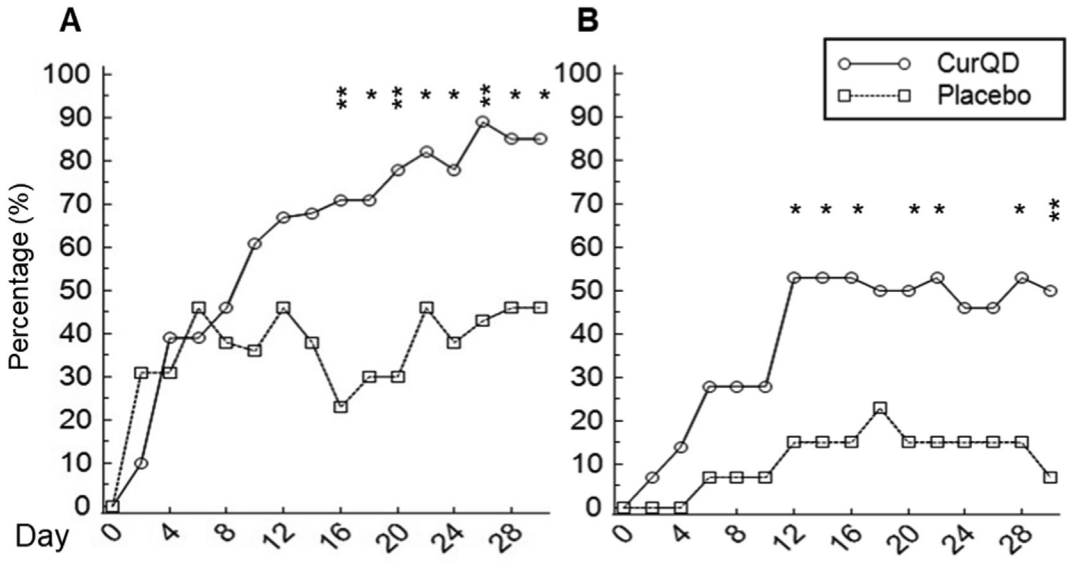

Figure 3. (*A*) Proportion of patients with clinical response (reduction of Simple Clinical Colitis Activity Index by ≥3 points from baseline) over time, as recorded by patients' electronic diaries every other day. (*B*) Proportion of patients with no rectal bleeding (rectal bleeding score, 0) in patients with a bleeding score of 1 or higher at baseline. *$P < .05$, **$P < .01$. CurQD, curcumin-QingDai.

respectively. The median calprotectin levels were reduced significantly from baseline by week 8 in patients receiving CurQD ($P < .001$), but not in patients receiving placebo ($P = .8$) (Supplementary Figure 5). The onset of the CurQD effect was relatively rapid: statistically significant differences between CurQD and placebo for the proportion of patients with a clinical response (reduction in SCCAI of ≥3 points) and with no rectal bleeding (rectal bleeding subscore, 0) were apparent by days 16 and 12, respectively (Figure 3). As per protocol, 3 of 41 patients enrolled on a stable prednisone dose (<20 mg/d) all continued at the same dose until week 8.

Maintenance in responding patients. Eleven of 15 patients who responded to CurQD and rolled over to continue curcumin alone from week 8 to week 16 were in clinical remission at week 16 (SCCAI, ≤2), and 14 of 15 maintained clinical response (Figure 4). Other exploratory outcomes, including median SCCAI score at week 16, the rate of clinical-biomarker response (reduction in SCCAI of ≥3 points and >50% reduction of calprotectin from baseline), and median calprotectin level by week 16 of maintenance with curcumin alone are shown in Supplementary Figures 6 to 8. Only 2 patients from the placebo group continued maintenance placebo treatment, thereby precluding meaningful analysis. By week 16, of the 3 patients enrolled on a stable corticosteroid dose less than 20 mg/d, 2 of the 3 patients (1 CurQD, 1 placebo) were weaned and were off corticosteroids and 1 patient (CurQD) was not.

Cytochrome P450 1A1 mucosal expression. Previous studies have suggested indigo and indirubin (constituents of QD) (Supplementary Figure 2) exert an agnostic effect on the AhR and implicated this pathway in an anticolitis effect in mouse models.[6,7,15] Therefore, in a

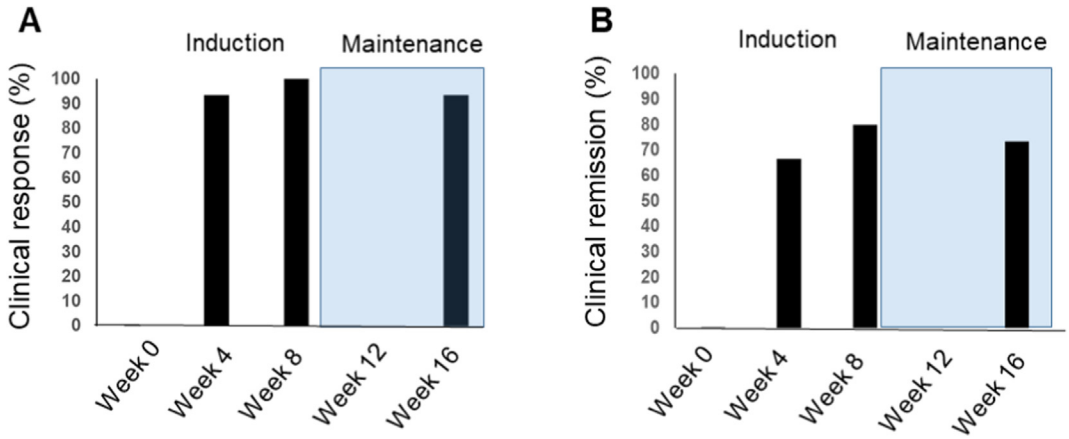

Figure 4. (*A*) Maintenance of response by curcumin alone at week 16 among patients with clinical response to 8 weeks of curcumin-QingDai (CurQD) induction. (*B*) Maintenance of remission by curcumin alone at week 16.

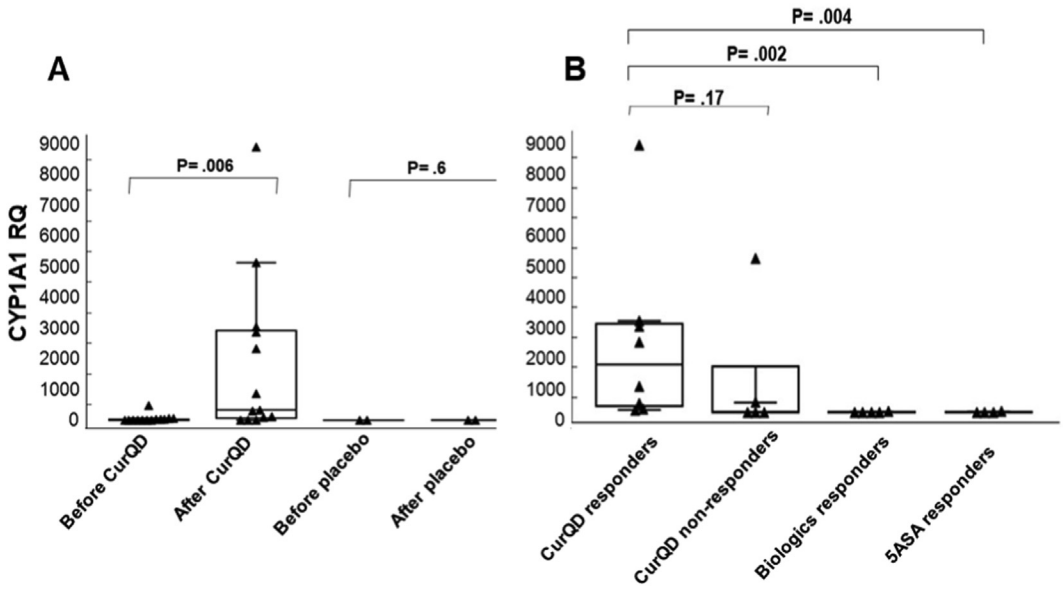

Figure 5. Results of reverse-transcription polymerase chain reaction messenger RNA expression levels of cytochrome (CY) P1A1 in rectal mucosa. (*A*) Before and after treatment in patients receiving QD (n = 13) vs placebo (n = 2). (*B*) In patients responding to QD (Mayo subscore of 0 or 1; n = 8), nonresponders (n = 5), patients with mucosal healing after biologics (n = 5) or after mesalamine (n = 4). CurQD, curcumin-QingDai; RQ, relativequantification; 5ASA, mesalamine.

subset of patients, we performed reverse-transcription polymerase chain reaction of bulk rectal mucosa to assess baseline and post-treatment expression levels of cytochrome P450 1A1 (CYP1A1), a downstream gene that is up-regulated as a result of AhR activation.[16] The expression of CYP1A1 in rectal mucosa increased significantly from a median of 13.9 (15%–75%; interquartile range [IQR], 2.8–29.6) at baseline to 334 (IQR, 67.2–2922; n = 11; $P = .006$) at week 8 after treatment with CurQD, but did not change with placebo (1.55; 0.73–2.4 vs 2.2, 0.9–3.5, before and after placebo, respectively; n = 2; $P = .7$) (Figure 5*A*). The up-regulation of CYP1A1 expression was more pronounced in patients responding to CurQD with mucosal healing (subscore, 0/1) than in nonresponders, although this difference did not reach statistical significance (1600; IQR, 213–2967; n = 8 vs 14; IQR, 1.9–1513; n = 5; $P = .17$) (Figure 5*B*). To better elucidate if CYP1A1 up-regulation was unique to CurQD or merely an epiphenomenon of mucosal healing, we also explored its expression in consenting UC patients not enrolled in the trial, who achieved mucosal healing while treated by other medications and who had a lower endoscopy as part of their clinical care. This additional comparison showed that the tissue expression of CYP1A1 in patients who achieved mucosal healing after CurQD treatment was significantly higher than in UC patients who achieved mucosal healing after treatment with biologics (anti–tumor necrosis factor and vedolizumab) or with mesalamine (1600; IQR, 213–2967; n = 8 vs 2.1; IQR, 0.3–15; n = 5; $P = .002$, and vs 4.6; IQR, 1.6–16.4; n = 4; $P = .004$, respectively) (Figure 5*B*).

Safety. Analysis of adverse events was performed on the entire safety data set, comprising both part I and II of the study, including the 7 patients with erroneous double-dose (3 g/d) ingestion of QD. Overall, there were no new safety signals (Supplementary Table 2). In part II, early termination owing to worsening colitis occurred in 6 of 13 (46.2%) in the placebo group compared with 4 of 28 (14.3%) in the CurQD group ($P = .048$) (Figure 1). One 19-year-old man randomized to CurQD experienced an asymptomatic increase of liver aminotransferase values over 10 times the upper normal limit by week 4, requiring treatment cessation. Liver enzyme levels reverted to normal over the next 8 weeks, at which time point the patient flared again and required an initiation of biologic therapy. Interestingly, the patient previously had a similar self-limited hepatotoxic response to a mesalamine compound (Asacol, Tillotts Pharma AG, Switzerland), which contains a similar methacrylic pH-dependent copolymer coating as the coating applied for the herbal compounds in our trial. Liver ultrasonography and cardiac echocardiograph with assessment of pulmonary arterial hypertension were unchanged in all patients between baseline and end of treatment.

Discussion

Despite the advent of biologics and small-molecule drugs for UC, a considerable proportion of patients do not respond to these novel agents, experience adverse events, or have limited drug access because of cost and reimbursement issues. These considerations, coupled with the lure of natural medicine, cause many inflammatory bowel disease patients to seek integrative medicine remedies, which are also among the topics most sought on social media.[17,18] This underscores the need

for more research to provide an evidence basis to corroborate or refute the purported efficacy of integrative compounds. In this randomized placebo-controlled trial, we showed that combination CurQD was superior to placebo for induction of response and remission in active UC patients, including in patients with moderate–severely active UC, of whom half were biologic- or immunomodulator-experienced.

Curcumin is the active ingredient of the herb Rhizoma Curcuma Longa and has been shown to ameliorate colitis in murine models through pleiotropic mechanisms including inhibition of Toll-like receptor 4/nuclear factor-κB/activator protein-1 signal transductions.[19–21] Two meta-analyses of placebo-controlled trials concluded curcumin was superior to placebo in inducing remission in active UC,[22,23] and a recent European Crohn and Colitis Organization practice position stated that curcumin may be effective in inducing remission in mild-to-moderately active UC as add-on therapy to mesalamine.[24] Similarly, QD previously was found efficacious for inducing remission in 2 placebo-controlled trials from Japan,[8,9] including in patients who were resistant to biologic therapy.[25] Using a combination of these 2 herbal compounds, the primary outcome and most secondary outcomes in our trial were met, reaffirming the superiority of CurQD over placebo to treat active UC. Moreover, echoing our clinical experience,[11] CurQD exerted its effect relatively rapidly within 2 weeks (Figure 3), showing a net-benefit over placebo to achieve a rectal bleeding score of 0, which was at least comparable with that observed in the post hoc analyses of the vedolizumab and tofacitinib trials.[26,27]

In contrast with the well-established pleiotropic immune effects exerted by curcumin,[19–21] QD, via its indigo and indirubin moieties, was suggested to induce cytoplasmic-to-nucleus translocation of the transcription factor AhR, which induces the gene expression of CYP1A1 and CYP1A2.[6,7,16] AhR is activated by multiple ligands, including microbiota-derived tryptophan metabolites, which are governed by host CARD9 gene, resulting in expansion of interleukin 22 regulatory cell subsets, enhanced barrier integrity, and recovery from colitis in murine models.[28] A previous study showed up-regulation of CYP1A1 in patients receiving QD, but the small study size and the open-label design limited interpretation of the results.[10] We extended these observations to show that up-regulation of the AhR pathway is unique to QD treatment and not merely an epiphenomenon of resolved mucosal inflammation because it was not seen in UC patients responding to biologics or to mesalamine. Collectively, these results may indicate the AhR pathway as a novel treatment target for drug development in inflammatory bowel disease.

When used in high doses for prolonged periods, QD was associated uncommonly with reversible pulmonary arterial hypertension (PAH).[29] Over the past years, treating several hundreds of patients, we have used CurQD for 6 to 12 weeks to induce remission followed by curcumin maintenance, and have not witnessed a single PAH case.[30] A similar protocol was used herein, whereby CurQD was administered for a limited duration of 8 weeks followed by maintenance of remission using curcumin alone. Using a stringent protocol of cardiac echocardiogram before and after treatment, no PAH cases were detected, although the number of treated patients was limited. However, the present results provide additional reassuring support that a routine echocardiogram is probably not necessary for patients taking this combination compound for induction and later are tapered to curcumin alone for the maintenance phase. Mild to moderate headaches within the first few days of therapy were more common numerically among our CurQD vs our placebo patients (Supplementary Table 2). These were reported previously,[8,29] and resolved in most patients without any change of therapy and did not require treatment discontinuation. A single case of asymptomatic liver enzyme level increase (10× the upper normal limit) mandated per-protocol treatment cessation. Interestingly, this patient had a similar marked liver enzyme level increase when previously receiving a mesalamine formulation (Asacol) with a pH-dependent coating comprising methacrylate/methacrylic copolymer,[31] similar to the EUDRAGUARD pH-dependent coating applied in the CurQD used in this trial. Given this unique repetitive reaction, it is possible that the liver abnormality in this particular patient was caused by hypersensitivity to the pH-dependent coating rather than the curcumin or QD compounds themselves. Regardless, liver enzyme levels reverted to normal within several weeks of stopping the study medication.

A notable point, and possible limitation, is that we tested the CurQD combination vs placebo, without an active comparator. Previous curcumin trials by us and others showed a net benefit over placebo of roughly 39% to 52% induction of response,[3,4] and QD trials in Japan showed a 56% to 68% net response induction.[8] However, comparing the present results with previous ones is arguable given the different disease severity (mild–moderate in curcumin trials) and the noncongruent outcomes measures and compounds used (for QD).

Our study had a modest cohort size. Notwithstanding, it did achieve its primary outcome with sufficient power, and most secondary outcomes, attesting in part to a non-negligible effect size. Another limitation was the absence of histologic outcomes that were not part of the protocol owing to limited funding resources. Nonetheless, the observed superiority of CurQD over placebo objectively was supported by both endoscopic and biomarker end points. Finally, although CurQD and placebo were supplied in opaque capsule form (Supplementary Figure 1) to maintain visual, smell, and taste blinding, we could not definitively exclude that patients may have deliberately opened the capsule to investigate their content.

In conclusion, this multicenter trial showed that combination CurQD is superior to placebo for inducing response and remission in patients with active UC, including biologic-experienced moderate–severe patients. The proposed limited-period CurQD induction followed by curcumin maintenance may allow for maximizing the efficacy and safety of this herbal supplement combination therapy. More studies are warranted to investigate this nutraceutical treatment strategy in UC and to investigate the AhR pathway as a possible novel therapeutic target in inflammatory bowel disease.

The patients and the public were not involved in the design, or conduct, or reporting of our research because this was not customary at the time of study conception, but patient societies will be contacted to disseminate the results

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at http://doi.org/10.1016/j.cgh.2023.05.023.

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Uri Kopylov (Conceptualization: Equal; Data curation: Equal; Formal analysis: Supporting; Investigation: Lead; Methodology: Equal; Project administration: Equal; Writing – original draft: Equal)

Conflicts of interest
These authors disclose the following: Shomron Ben-Horin has received advisory board and/or consulting fees from AbbVie, Takeda, Janssen, Celltrion, Pfizer, GSK, Ferring, Novartis, Roche, Gilead, NeoPharm, Predicta Med, Galmed, Medial Earlysign, and Eli Lilly, research support from AbbVie, Takeda, Janssen, Celltrion, Pfizer, and Galmed, and receives consulting fees and holds equity in EviNature (spin-off company of Sheba Center, which has filed for intellectual property rights on the combination of curcumin and QD); Nir Salomon has received speaking fees from Takeda, Bara Herbs, and ITS Medical, and receives consulting fees and holds equity in EviNature (spin-off company of Sheba Center, which has filed for intellectual property rights on the combination of curcumin and QD); Uri Kopylov has received speaker fees from AbbVie, Janssen, BMS, Rafa, Novartis, Pfizer, and Takeda, research support from Takeda and Janssen, and consulting fees from Takeda and CTS; Rami Eliakim has received consultant and speaker fees from Janssen, AbbVie, Takeda, and Medtronic; Bella Ungar has received consultation fees from Neopharm, Takeda, Janssen, and AbbVie; Gerassimos Mantzaris has received consultant and/or speaker fees from AbbVie, Angelini, Genesis, MSD, Celgene, Celtrion, Ferring, Aenorasis, Hospira, Janssen, Pfizer, Takeda, Angelini, Falk Pharma, Mylan, and Vianex, and research support from AbbVie, Ferring, Genesis, MSD, Galenica, Mylan, and Vianex; Nikos Viazis has participated in advisory boards and/or has received grants from AbbVie, MSD, Janssen, Takeda, Pfizer, Amgen, Vianex, Galenica, and Ferring; Eran Zittan has received research support and consulting fees from Janssen, AbbVie, Takeda, Neopharm, Celgene, and Pfizer; Rami Eliakim has received consultant and speaker fees from Janssen, AbbVie, Takeda, and Medtronic; Henit Yanai has received research grants from Pfizer, consulting fees from AbbVie, Janssen, Pfizer, and Takeda, speaker fees from AbbVie, Janssen, Pfizer, and Takeda, and data safety monitoring board or advisory board fees from AbbVie, Pfizer, and Takeda; Iris Dotan has received grants from Abbott, AbbVie, Athos, Arena, Altman Research, Cambridge Healthcare, Celltrion, Celgene/BMS, Ferring, Falk Pharma, Food Industries Organization, Gilead, Galapagos, Iterative Scopes, Integra Holdings, Janssen, Neopharm, Nestle, Pfizer, Rafa Laboratories, Roche/Genentech, Sangamo, Sublimity, Sandoz, Takeda, and Wildbio; Adi Lahat has received advisory boards and/or consulting fees from AbbVie, BMS, Janssen, Takeda, Pfizer, Celltrion, and BMS; Nitsan Maharshak has received advisory board, speaking, and/or consulting fees from Pfizer, Takeda, Janssen, Ferring, BiomX, BMS, and Nestle, and grant support from Takeda, Janssen, Abbott, AbbVie, Pfizer, Corundum Innovation, Ltd, Nestle, and Trobix; and Ayal Hirsch has received consulting fees from Neopharm, Takeda, Janssen, and AbbVie. The remaining authors disclose no conflicts.

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Data Availability
All data generated or analyzed during this study are included in this article. Further requests can be directed to the corresponding authors.

Supplementary Methods

Background Concomitant and Prior Medications Management Protocol

1.2.1 If a patient is receiving oral mesalamine, the dose must be stable for at least 4 weeks before inclusion.

1.2.2 If a patient is receiving immune-modulator medication (azathioprine, 6-mercaptopurine, methotrexate), the dose must be stable for at least 12 weeks before inclusion.

1.2.3 If a patient is on topical mesalamine (suppositories or enema), the dose must be stable for at least 2 weeks before inclusion and will not be altered throughout the 1-month study period.

1.2.4 If a patient is receiving biologics, the dose must be stable as follows: stable infliximab dose for the 2 months before inclusion, stable adalimumab dose for 1 month before inclusion, and stable vedolizumab dose for 2 months before inclusion; stable golimumab dose for 1 month.

1.2.5 If a patient was treated with biologics or immunomodulators (azathioprine, 6-mercaptopurine, methotrexate) or corticosteroids or mesalamine and the treatment was stopped before entering the study, the screening visit will be performed after the following waiting periods: infliximab or vedolizumab: at least 1 month after the patient received the last dose; and adalimumab, golimumab, immunomodulator, corticosteroids, or mesalamine: at least 2 weeks after the patient received the last dose.

1.2.6 A maximal dose of corticosteroids that will be allowed is prednisone 20 mg/d (stable for at least 2 weeks before inclusion).

1.2.7 Concomitant tofacitinib is not allowed; at least a 2-week interval is needed after stopping tofacitinib and study enrollment.

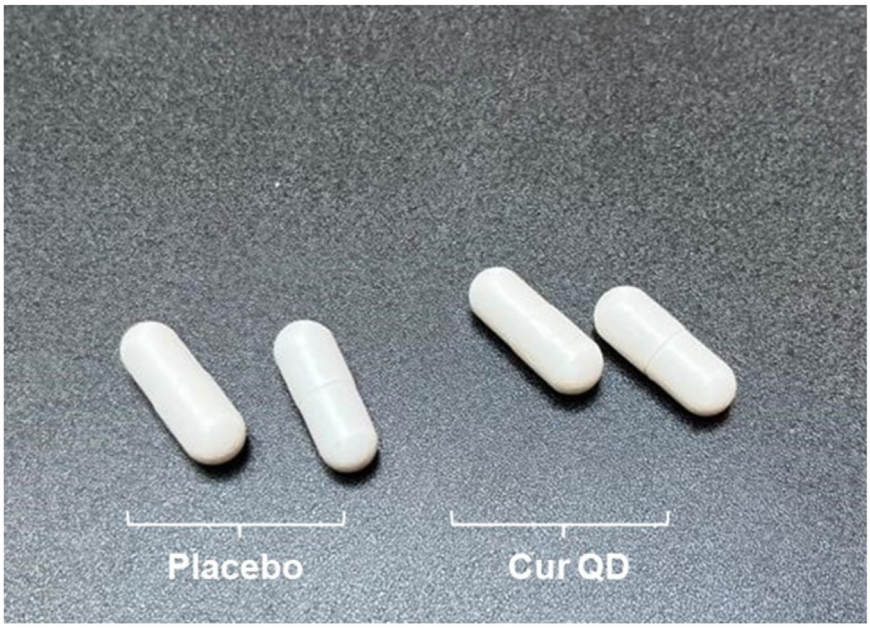
QingDai Adverse-Events Dose Adjustment Protocol

Headache is a common side effect among patients taking QD, occurring in approximately 5% of patients. From our experience, a QD dose adjustment can ameliorate this phenomenon. Thus, in concurrence with our clinical experience, the following strategy in case of reported headache was applied.

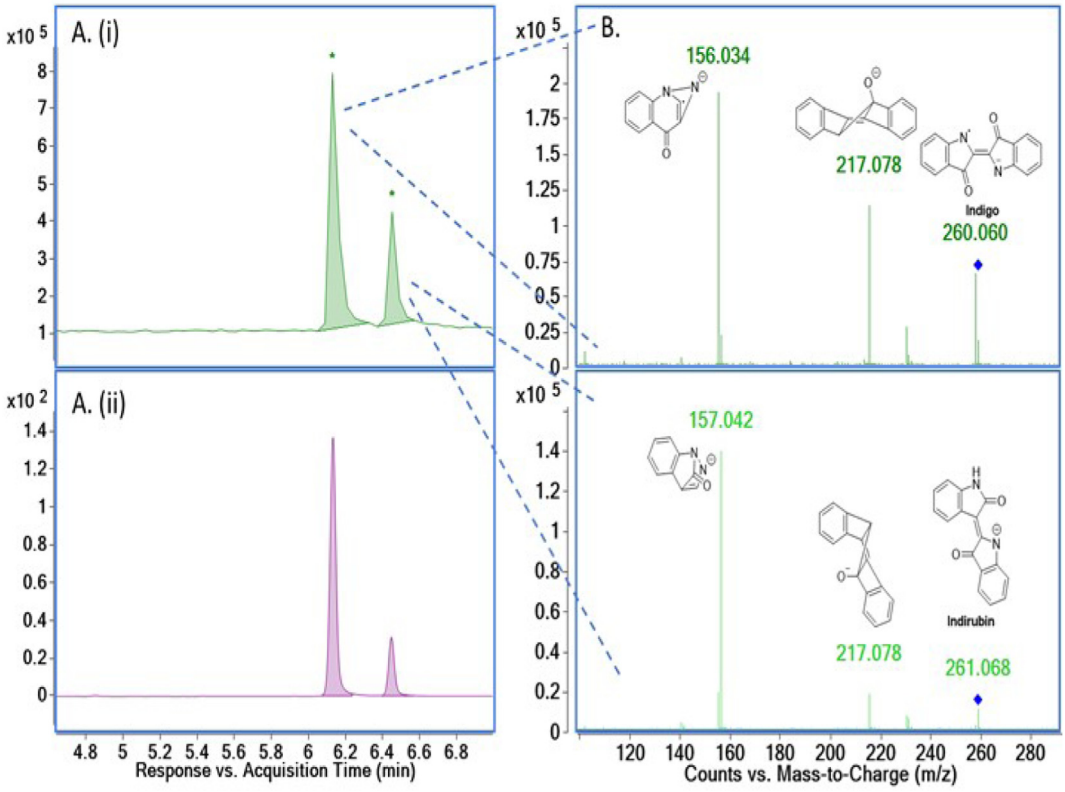
All patients started ona 1.5-g dose of QD (divided into three 0.5-mg capsules) and 1.5 g curcumin. In case of a reported headache within 48 to 72 hours from initiation of the study drug, patients are instructed to reduce their QD dose to 0.5 g (1 capsule) per day for 5 days. Pending resolution of the headache, patients then increase their dose to 1 g (2 capsules) per day for 5 days, and then increase to the full 1.5-g dose. In case a patient reports a recurrence of the headache upon dose escalation, the dose is de-escalated back to the lower dose and maintained until trial conclusion. If a headache does not resolve within 48 hours of the dose adjustment or if it is severe, the patient is instructed to stop the drug and be terminated from the study.

Assessment of Cytochrome P1A1 Expression in Colonic Tissue

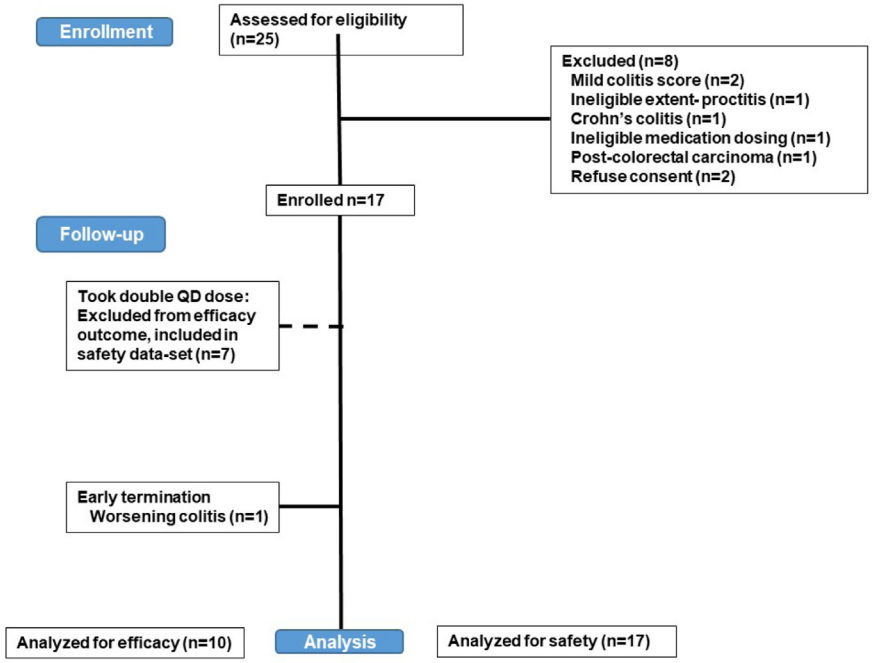
Rectal biopsy specimens were obtained in a subset of trial patients and in UC patients treated by other medications outside this trial who were included in this analysis as additional controls. Snap-frozen mucosal samples were thawed, lysed, and homogenized in TRI-Reagent and extracted according to the manufacturer's instructions (Life Technologies). Reverse-transcription was performed on 1 μg total RNA using the High-Capacity RNA to Complementary DNA kit (Applied Biosystems). ΔΔ Reverse-transcription polymerase chain reaction was performed on an ABI Step ONE Plus system (Applied Biosystems). Gene symbol accession number: CYP1A1 Hs01054796_g1; *GAPDH* (housekeeping gene) Hs99999905_m1.



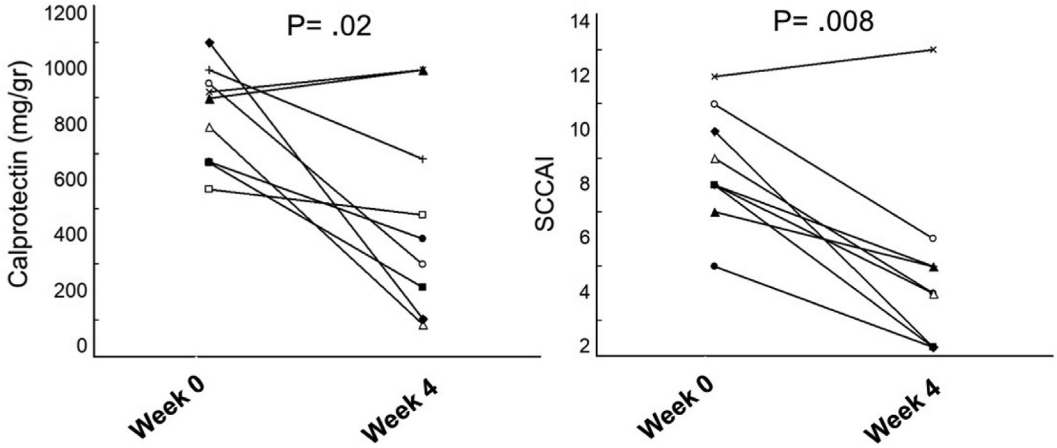
Supplementary Figure 1. Drug masking using opaque capsules for study compounds. CurQD, curcumin-QingDai.



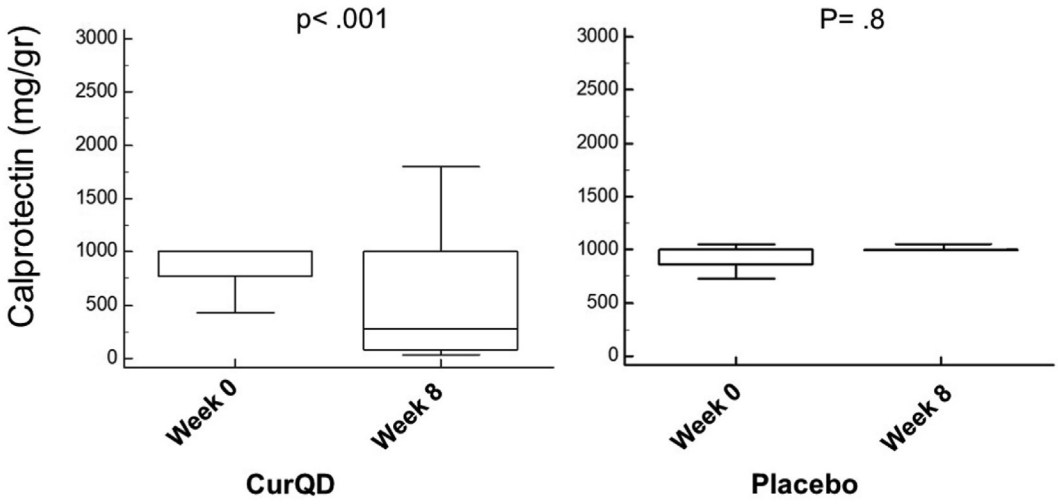
Supplementary Figure 2. Liquid chromatography-mass spectormetry analysis. (*A*, i) Extracted ion chromatogram of the deprotonated precursor ions indigo (260.060 m/z, [M-H]-) and radical anion indirubin (261.068 m/z, [M]-). The x-axis represents retention time, and the y-axis represents signal intensity. (*A*, ii) UV chromatogram (detection wavelength, 611 nm) of indigo and indirubin. (*B*) Fragmentation mass spectra by collision-induced dissociation of indigo and indirubin. ◇Precursor ions. The x-axis represents mass to charge, and the y-axis represents signal intensity. Putative assignments of characteristic fragment ions are shown.



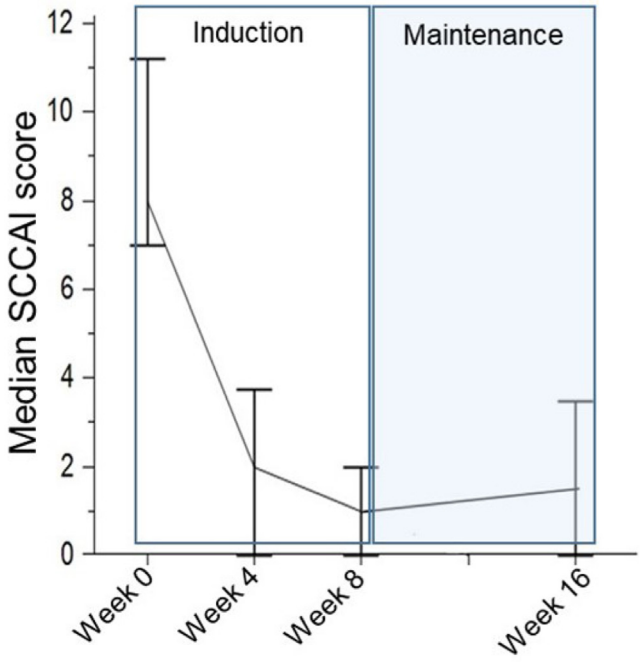
Supplementary Figure 3. Flow chart of the part 1 study. QD, QingDai.



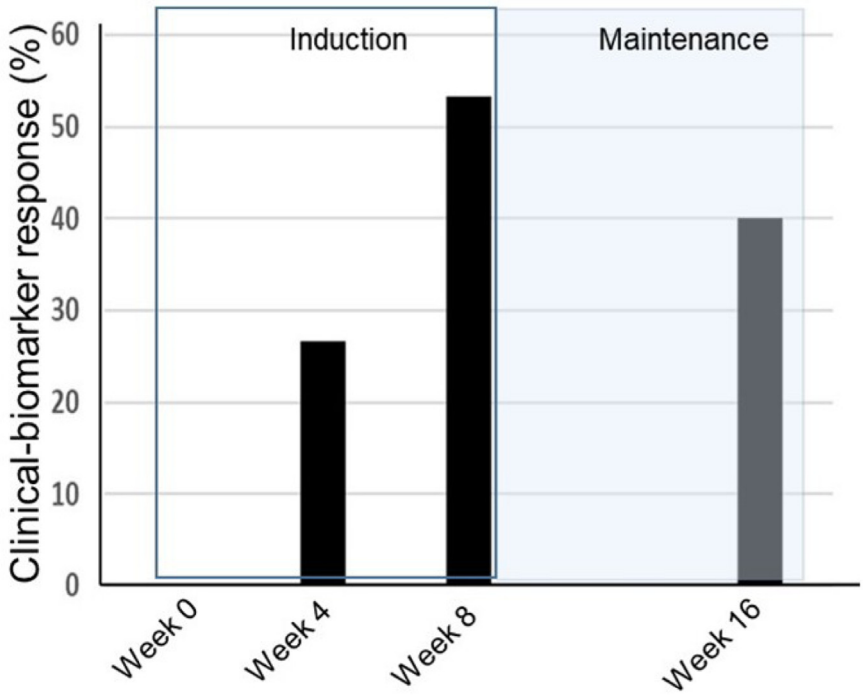
Supplementary Figure 4. Calprotectin and Simple Clinical Colitis Activity Index (SCCAI) scores for individual patients in the part 1 study. The median calprotectin level was reduced from 900 (25%–75% interquartile range [IQR], 665–962) to 391 (25%–75% IQR, 187–758; $P = .02$). The median SCCAI decreased from 8 (25%–75% IQR, 7.75–10.25) to 4 (25%–75% IQR, 2–5.25; $P = .008$).



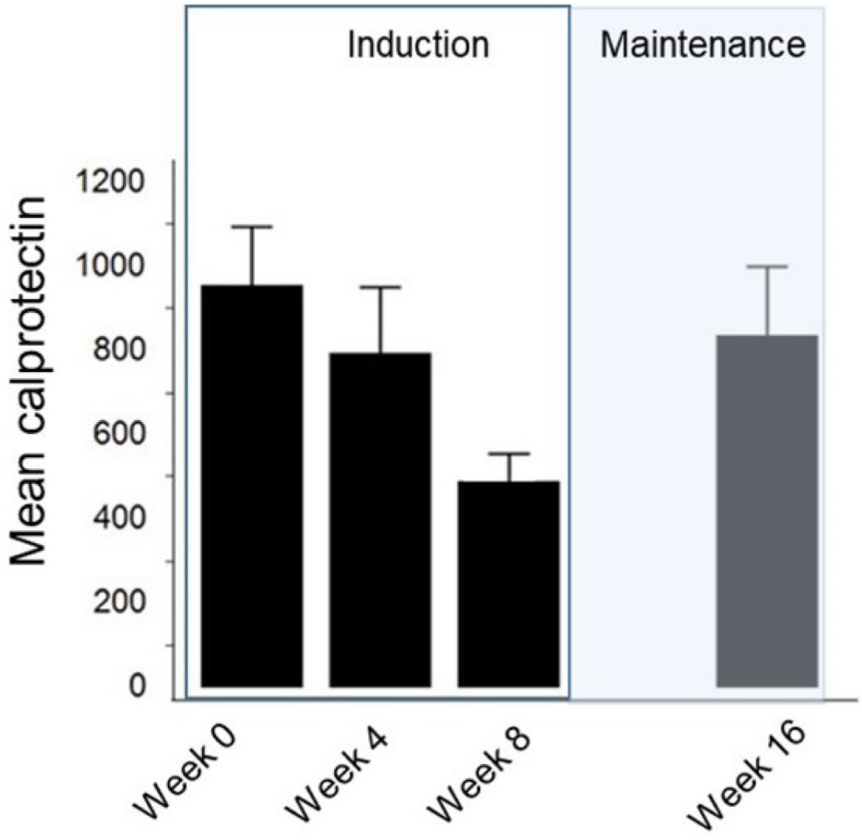
Supplementary Figure 5. The median calprotectin levels in the respective intervention groups in the part 2 placebo-controlled trial. CurQD, curcumin-QingDai.



Supplementary Figure 6. The median Simple Clinical Colitis Activity Index (SCCAI) up to week 8 with CurQD induction and at week 16 after 8 additional weeks of maintenance with curcumin alone.



Supplementary Figure 7. Clinical-biomarker response (reduction in Simple Clinical Colitis Activity Index of $\geq$3 points from baseline and $\geq$50% calprotectin reduction) among clinical responders at week 8 and up to week 16 after additional 8 weeks of maintenance with curcumin alone.



Supplementary Figure 8. The mean calprotectin values among clinical responders at week 8 and up to week 16 after an additional 8 weeks of maintenance treatment with curcumin alone.

Supplementary Table 1. Part 1 Open-Label Study Patients' Disposition

	Number
Median age, *y* (IQR)	39 (23–45)
Women	4 (40%)
Disease extent	
Left sided (E2)	5 (50%)
Extensive colitis (E3)	5 (50%)
Previous medications	
Corticosteroids	6 (60%)
Aza/6MP	2 (20%)
Biologics	5 (50%)
SCCAI at baseline (IQR)	8 (8–10)
Median baseline calprotectin level (IQR)	971 (669–1000)
Endoscopic score at baseline	
Mayo 2	4 (40%)
Mayo 3	6 (60%)

Aza, azathioprine; IQR, 25%–75% interquartile range; SCCAI, Simple Clinical Colitis Activity Index; 6MP, 6-mercaptopurine.

Supplementary Table 2. Overview of Treatment-Emergent Adverse Events (Safety Analysis Set, Including Parts 1 and 2)

	CurQD (n = 45)	Placebo (n = 13)
Infection	0 (0%)	1 (7.7%)[a]
Nausea	2 (4.4%)	0 (0%)
Fatigue	2 (4.4%)	1 (7.7%)
Headache	11 (24.4%)	2 (15.4%)
Fever	2 (4.4%)	0 (0%)
Myalgia	1 (2.2%)	0 (0%)
Liver enzyme level increase	4 (8.9%)	1 (7.7%)
Worsening of colitis	5 (11.1%)	6 (46.1%)
AEs requiring discontinuation	6 (13.3%)	6 (46.1%)
Discontinue for noncolitis AEs	1 (2.2%)	0 (0%)

AE, adverse event.
[a]Infection was otitis externa.