Highly bioavailable curcumin derivative ameliorates Crohn’s disease symptoms: A randomized, double-blind, multicenter study

Highly bioavailable curcumin derivative ameliorates Crohn's disease symptoms: A randomized, double-blind, multicenter study

Short title: A new curcumin derivative for Crohn's disease

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Abbreviations: AE, adverse event; CD, Crohn's disease; CDAI, Crohn's disease activity index; IBD, inflammatory bowel disease; IL, interleukin; NF-κB, nuclear factor-κB; SESCD, Simple Endoscopic Score for Crohn's Disease; TNF, tumor necrosis factor; UC, ulcerative colitis; 5-ASA, 5-aminosalicylic acid.

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Abstract

Background & Aims: The new curcumin derivative Theracurmin® has a 27-fold higher absorption rate than natural curcumin powder. Theracurmin® is an inhibitor of nuclear factor-κB, which mediates the expression of inflammatory cytokines. The effect of Theracurmin® on inflammatory bowel disease in humans has not been explored; therefore, we investigated the efficacy and safety of Theracurmin® in patients with Crohn's disease.

Methods: In this randomized, double-blinded study performed at 5 independent medical centers in Japan, Theracurmin® (360 mg/day, n=20) or placebo (n=10) was administered to patients with active mild-to-moderate Crohn's disease for 12 weeks. The agent's efficacy was assessed by evaluating clinical and endoscopic remission, healing of anal lesions, and blood levels of inflammatory markers.

Results: In the Theracurmin® group, a significant reduction in clinical disease activity was observed in week 12 relative to that in week 0 (P=0.005). On intention-to-treat analysis, clinical remission rates were 35%, 40%, and 40% at weeks 4, 8, and 12, respectively, which were significantly higher than those in the placebo group (all 0%; P=0.033, P=0.020, and P=0.020, respectively). Furthermore, reduction in endoscopic Crohn's disease severity (P=0.032) was observed at week 12 in the Theracurmin® group. The endoscopic remission rates were 15% and 0% in the Theracurmin® and placebo groups, respectively. Significant healing of anal lesions (P=0.017) was observed at week 8 in the Theracurmin® group. No serious adverse events were observed in either group throughout the study.

Conclusions: Theracurmin® shows significant clinical and endoscopic efficacy together with a favorable safety profile in patients with active mild-to-moderate Crohn's disease.

Clinical trial UMIN registration ID: UMIN000015770.

Keywords: bioavailability; cytokine inhibition; inflammatory bowel disease

Introduction

Crohn's disease (CD) and ulcerative colitis (UC) are the two major manifestations of chronic inflammatory bowel disease (IBD). Histologically, CD is characterized by discontinuous but full-thickness inflammatory granulomas and fistulae that may develop anywhere along the digestive tract.[1] The etiology of CD is not fully understood, and no cure exists to date. Therefore, the aim of current drug therapies is to control inflammation or prevent its exacerbation. As CD symptoms are promoted by cytokines including tumor necrosis factor (TNF)-α, interleukin (IL)-23, and IL-17,[1] the development of anti-TNF-α[2,3] and anti-IL-12/23 antibodies[4] has improved the natural courses of CD in recent years. However, these so-called biologics present multiple challenges, including the presence of primary and secondary non-responders. In fact, many patients require surgical intervention after failing to achieve remission with biologic therapy; therefore, current biologics are associated with multiple clinical drawbacks, including serious adverse effects, that cause additional morbidities.

Curcumin is a natural substance that has been used for centuries as a food additive in the form of yellow turmeric powder extracted from the *Curcuma longa* Linn plant.[5] It strongly inhibits the expression of nuclear factor-κB (NF-κB) and downstream inflammatory cytokines such as TNF-α.[6,7] We previously reported that curcumin reverses experimentally induced colitis in mice[8]; these findings were also confirmed in a follow-up study.[9] Additionally, a clinical trial of patients with UC revealed that curcumin effectively induced and maintained remission while exhibiting no safety concerns.[10] Furthermore, curcumin enemas alone[11] and oral administration of curcumin capsules in combination with 5-aminosalicylic acid (5-ASA)[12] were reported to reduce endoscopic severity in patients with UC. Nonetheless, data on the therapeutic effect of curcumin on CD are only limited thus far.

Curcumin's high safety profile may be due to the fact that it is a natural substance; however, its absorption in the gut is very slow. Meanwhile, the newly synthesized curcumin derivative Theracurmin® has a 27-fold higher absorption rate than conventional curcumin powder.[13] Theracurmin® is a highly absorptive form of curcumin produced via microparticle and surface-controlled colloidal dispersion instead of the method by which natural curcumin is chemically altered

to improve resorption.[13,14] Curcumin bulk powder particles measure 22.75 μm in size and are barely absorbed from the digestive tract, whereas Theracurmin® has an average particle size of 0.19 μm and is easily absorbed from the digestive tract (probably the small intestine) and transported into the blood.[13] Hence, Theracurmin® is effective not only at the local site in the digestive tract but also in the blood where immunocompetent cells are contained. Although a previous study investigated the efficacy of Theracurmin® in a mouse model of experimentally induced enteritis,[15] its effect on IBD in humans has not been explored. Therefore, in this study, we aimed to assess the efficacy and safety of Theracurmin® in patients with active mild-to-moderate CD.

Materials and Methods

Patients

Between April 2015 and December 2017, 5 independent medical centers in Japan (Hamamatsu University School of Medicine, Hamamatsu South Hospital, Shiga University of Medical Science, Kurume University School of Medicine, and Sapporo Kosei General Hospital) enrolled a total of 30 patients (UMIN ID: UMIN000015770). The inclusion criteria were 1) a definitive diagnosis of CD based on radiologic, endoscopic, and histologic criteria set by the Research Committee of Inflammatory Bowel Disease that is affiliated with the Japan Ministry of Health; 2) age 20–60 years; 3) CD of the small intestine, large intestine, or both; 4) a CD activity index (CDAI) score ≥180 but <450; and 5) use of ≤10 mg/day prednisolone. CD duration and clinical course were not considered among the inclusion criteria. The exclusion criteria were 1) use of >3 g of a mesalamine preparation daily or having received topical mesalamine (enema/suppository) treatment within 42 weeks before enrollment in this study (these treatments are not allowed under the Japanese medical insurance system), 2) use of >10 mg/day prednisolone or topical steroid preparation within 4 weeks prior to enrollment, 3) use of medications not covered by insurance at the start of clinical trials in Japan (e.g., ustekinumab, vedolizumab), 4) being pregnant or nursing, 5) serious renal or hepatic disease, 6) >50% stenosis of the normal lumen observed on small bowel imaging, 7) any malignancy, and 8) short bowel

syndrome caused by enterectomy. The following patients were withdrawn from the study: 1) those showing serious complications; 2) those who opted to withdraw owing to personal reasons; and 3) those who required additional drug therapy (thus violating the inclusion criteria). All adverse events (AEs) were recorded in a diary maintained by each patient. Laboratory tests including complete blood counts and blood biochemistry analyses were performed at baseline, week 4, week 8, and at the end of the treatment period (week 12). All authors had access to the study data and reviewed and approved the final manuscript.

Treatment design and randomization

We performed a randomized, multicenter, double-blind, placebo-controlled clinical trial. Patients were assigned to the Theracurmin® or placebo group by a clinical pharmacist using a computer-generated randomization scheme, usually with 2:1 probability. The clinical pharmacist was employed by the Department of Medical Management and Informatics, Hokkaido Information University, and was therefore not involved in administering the drug to the patients. Patients meeting the selection criteria were administered Theracurmin® 360 mg/day (180 mg in the morning and evening) or placebo for 12 weeks, as outlined in Figure 1.

Patients receiving mesalamine, immunomodulators, biologics, or enteral nutrition were eligible for inclusion, but the doses of any concomitant medications could not be changed during the study. However, a reduction in the dose of concomitant corticosteroids was allowed if any corticosteroid-related AEs occurred. Only the study statisticians and members of the data-monitoring committee had access to the unblinded data, but no individual had contact with the study subjects. Theracurmin® and placebo were identical in appearance (white capsule), and both were purchased from Theravalues Co., Ltd. (Tokyo, Japan).

Clinical assessment and trial endpoints

The primary endpoint was the difference in CDAI improvement between the Theracurmin® and

placebo groups when comparing week 12 to week 0. Secondary endpoints included the percentage of patients in clinical remission (defined as CDAI <150) at weeks 4, 8, and 12; the rate at which the CDAI score was reduced by 70 or more points (CR-70); the Simple Endoscopic Score for Crohn's Disease (SESCD) difference between the Theracurmin® and placebo groups at week 12; the endoscopic remission rate (SESCD ≤4) at week 12; percentage of patients with clinical improvement of anal lesions with Theracurmin® at weeks 4, 8, and 12; clinical laboratory values at week 12 in the Theracurmin® and placebo groups; and changes in clinical laboratory values between week 0 and week 12 in Theracurmin®-administered patients. With respect to clinical laboratory values, we mainly focused on C-reactive protein, hemoglobin, and albumin. Physicians examined the patient's anus at week 0 for anal lesions; the presence of fistula and anal fissure was confirmed by visual inspection, whereas the presence of perianal abscess was confirmed by both visual inspection and digital examination. These anal lesions were evaluated as either improved or not improved based on the physicians' judgment.

Ethical considerations

The study protocol was reviewed and approved by the Committee on the Ethics of Clinical Trials Involving Human Subjects at each institution. Furthermore, the trial adhered to the principles of Good Clinical Practice and the ethical standards laid down in the 1964 Helsinki Declaration and its subsequent amendments. Informed consent was obtained from all patients after the purpose of the study and nature of the procedures were explained to them.

Statistical analysis

Owing to the lack of previous data on the expected effect of Theracurmin® on CD, a formal power analysis calculation of sample size was not performed in this pilot trial. Therefore, 30 patients were enrolled in this exploratory trial. Statistical analysis was performed using the SPSS statistical software (SPSS for Windows, Version 16.0, Ekuseru-Toukei 2010; Social Survey Research Information Co.,

Ltd., Tokyo, Japan). Continuous variables are presented as mean ± standard deviation or mean ± standard error of the mean. Subgroups were compared by applying Student's t-test or the Mann-Whitney U-test, unless stated otherwise. Categorical variables are presented as percentages and were analyzed using Fisher's exact test. The *P* values were two-sided, and *P* values of <0.05 were considered statistically significant.

Results

Patients' baseline demographic variables

The patients' mean age was 35.1 years (range 21–65 years); the average age at diagnosis of CD was 27.1 years (range 13–41 years). The patients' mean height and weight were 167.6 cm and 56.6 kg, respectively. The numbers of current smokers, ex-smokers, and never smokers were 7, 3, and 20, respectively; the overwhelming majority had never smoked. Similarly, the proportions of patients who had received 5-ASA, immunomodulators, steroids, and anti-TNF-α were 90%, 33.3%, 3.3%, and 6.7%, respectively. According to the Montreal classification, the numbers of patients with L1, L2, and L3 lesions were 2, 5, and 23, respectively. The mean CDAI score before Theracurmin® administration was 211.0, while the mean SESCD was 13.2. Patients were randomized to receive 360 mg/day Theracurmin® (n=20) or placebo (n=10). A total of 10 patients had a history of intestinal resection; of these patients, 6 (1, ileocecal resection; 5, partial ileum resection) were allocated to the Theracurmin® group and 4 who all underwent partial ileum resection were assigned to the placebo group. Seventeen patients in the Theracurmin® group and 9 in the placebo group ultimately completed the study, whereas 3 patients in the Theracurmin® group and 1 in the placebo group dropped out at their own volition (Figure 1).

Effects of Theracurmin® on the CDAI score

The CDAI score in the Theracurmin® group was significantly decreased at week 12 relative to that at week 0 (*P*=0.005) (Figure 2A). Subsequently, we examined whether there was a significant difference

in CDAI score at all time points between the placebo and Theracurmin® groups. No difference in CDAI score was observed between the placebo and Theracurmin® groups at weeks 4 and 8; however, the Theracurmin® group had significantly lower CDAI score at week 12 (P=0.035). Moreover, we further evaluated the stool frequency and abdominal pain parameters separately in relation to the CDAI score before and after Theracurmin® administration. The stool frequency parameter showed a significant reduction, from 92.7 ± 18.1 before Theracurmin® administration to 70.8 ± 30.9 at week 12 (P=0.02, data not shown). The abdominal pain parameter also decreased from 40.0 ± 20.2 before Theracurmin® administration to 25.8 ± 21.9 at week 12, albeit with no significant difference (P=0.08, data not shown). Therefore, both the stool frequency and abdominal pain parameters seemed to be involved in the CDAI score reduction caused by Theracurmin®; nevertheless, it was suggested that stool frequency might be more involved. Likewise, clinical remission rates (CDAI score <150) in the Theracurmin® group were 35% at week 4 and 40% at weeks 8 and 12; these were significantly higher than the rates in the placebo group, which were all 0% (P=0.033, P=0.020, and P=0.020, respectively) (Figure 2B). Furthermore, the rate at which the CDAI score achieved a reduction of 70 points or more (CR-70) was 10% in the placebo group and 40% in the Theracurmin® group (Figure 2B).

Changes in the endoscopic index

As shown in Figure 3A, the SESCD significantly decreased at week 12 relative to week 0 in the Theracurmin® group (P=0.032), but not in the placebo group (P=0.220). At week 12, although there was no significant difference between the two groups, the SESCD tended to be lower in the Theracurmin® group than in the placebo group. To investigate the effect of Theracurmin® on endoscopic improvement limited to small intestinal lesions only, the SESCD was examined in 16 patients with small intestinal lesions in the Theracurmin® group; of these 16 patients, 10 were able to follow the course of endoscopy. The SESCD limited to the small intestine of these patients was 6.1 ± 3.0 before Theracurmin® administration and 3.9 ± 2.1 after 12 weeks of administration; while there was no statistically significant difference (P=0.073, data not shown), a trend for improvement was

observed. The endoscopic remission rate (SESCD ≤4) was 15% in the Theracurmin® group and 0% in the placebo group (Figure 3B). As examples, an open, active longitudinal ulcer observed at week 0 in a Theracurmin® group patient healed and scarred at week 12; mucosal healing was also observed in another patient (Figure 4).

Efficacy of Theracurmin® on anal lesions

At baseline, 18 of the 30 patients presented with typical CD anal lesions (13 in the Theracurmin® group and 5 in the placebo group). By week 8 after the initiation of treatment, significant differences were found between the 2 groups, with anal lesion improvement rates of 0% and 63.3%, respectively (P=0.017) (Figure 5). Patients in the Theracurmin® group experienced better anal lesion healing than those in the placebo group at weeks 4 and 12; however, the difference was not significant. No serious AEs were observed in either group throughout the observation period.

Changes in blood test results after Theracurmin® administration

At week 0, the blood urea nitrogen level was significantly higher in the placebo group (13.1 vs. 9.6 mg/dL, P=0.007); however, other measured items showed no significant difference (Supplemental Table 1). At the end of Theracurmin® or placebo administration (week 12), no differences in blood parameters were observed between the 2 groups (Supplemental Table 2). The serum sodium level in the Theracurmin® group was significantly lower at week 12 than at week 0 (139.7 vs. 140.8 mEq/L, P=0.041); however, no significant differences were observed with respect to the other components, including C-reactive protein and hemoglobin levels (Supplemental Table 3).

Adverse events

No serious adverse events were identified in this study. Only one patient exhibited appetite loss as a very minor event, which did not interfere with the completion of the clinical trial.

Discussion

Ours was the first study to evaluate the efficacy and safety of Theracurmin® in patients with active CD. Overall, Theracurmin® was effective in patients with active mild-to-moderate CD as it significantly improved both clinical and endoscopic measures of this disease. Furthermore, mucosal healing was achieved in some patients, and significant improvements in anal lesions were observed by week 8 of Theracurmin® administration. Additionally, Theracurmin® appeared to have a favorable safety profile, as no agent-related serious AEs were observed throughout the study.

Our study demonstrated the clinical and endoscopic effects of Theracurmin® but did not show a significant improvement in systemic biomarkers. In actual clinical practice, there exist numerous cases in which clinical and endoscopic symptoms are highly active in patients with IBD despite normal biomarkers. In the present study, clinically "moderately ill" patients were targeted; nevertheless, it was considered that inflammatory biomarkers were low at the start of the study owing to the inclusion of several patients with relatively mild disease. Therefore, it seems that the endoscopic and clinical scores were significantly improved but the biomarkers were not.

In this study, the rate of steroid use appears to be low among patients at the start of the study (Table 1). The reasons for this are as follows: First, this study targeted patients with relatively mild to moderate disease severity. Second, because patients treated with budesonide were excluded from this study, it is considered that the rate of steroid use consequently decreased, as described above.

Curcumin and 5-ASA share some pharmacological properties, even though curcumin (and Theracurmin®) has better safety profiles; 5ASA can suppress arachidonic acid metabolism via the cyclooxygenase enzyme, inhibit NF-κB activity, block phospholipase D breakdown, and inhibit the pro-inflammatory cytokine IL-1β.[16] Similarly, curcumin blocks the activation of NF-κB and inhibits the release of cyclooxygenase-2 and TNF-α[6,7]; the latter is the most widely recognized inflammatory cytokine in the context of IBD. Notably, curcumin inhibits the JAK/STAT pathway (which induces the expression of several cytokines[17]) and upregulates IL-22,[18,19] which promotes healing of ulcers. As curcumin may induce mucosal regeneration in patients with CD through such mechanisms,[20]

Theracurmin® ought to be an effective intervention as well. Because we did not collect mucosal biopsy specimens at the lesion site in all cases before and after this study, we did not examine whether Theracurmin® suppressed NF-κB in the inflammatory mucosa. Nonetheless, we would like to conduct more research on this subject. Additionally, although fecal calprotectin can be measured to assess inflammatory reaction in the intestinal mucosa,[21] we did not evaluate it in this pilot study. However, it seems important to evaluate this point; hence, we would definitely include it among the evaluation items in future additional studies.

As described above, curcumin elicits several anti-inflammatory effects. However, unmodified natural curcumin exhibits very low bioavailability owing to its poor absorption when administered orally, which impedes its use in the clinical setting.[22] Therefore, new drug delivery systems, adjuvants, or curcumin analogues that improve the bioavailability of curcumin have been developed.[23] Theracurmin® is a nanoparticle-based drug delivery system with a high absorption rate, as has been demonstrated in preliminary studies involving healthy volunteers and individuals with cancer.[23-25] With respect to Theracurmin® dosage in previous clinical trials,[23-26] patients with knee osteoarthritis were administered 2,100 mg/day for 4 weeks,[24] whereas patients with pancreatic cancer who were refractory to conventional treatment were administered 400 mg/day for at least 9 months; no AEs were reported in these studies.[23-26] Considering the dose ranges used in preliminary studies, we selected a Theracurmin® dose of 360 mg/day for patients with mild-to-moderate CD; no Theracurmin®-related AEs were observed during the 3 months of administration, indicating the agent's safety at this dose. Nevertheless, further studies are warranted to confirm its long-term profile.

In this study, the clinical and endoscopic efficacy of Theracurmin® in patients with mild-to-moderate CD, albeit modest, was very encouraging, particularly owing to this compound's favorable safety profile. However, its efficacy as a monotherapeutic remission induction agent may be limited in patients with severe CD. In a study involving patients with UC, unmodified curcumin in combination with 5-ASA had significantly better clinical and endoscopic efficacy than curcumin alone.[12] Furthermore, an increase in IL-1 expression played a role in the loss of response to anti-TNF

biologics[27]; since curcumin inhibits IL-1 generation,[28] it may help reverse the loss of response to infliximab.[29]

Theracurmin® treatment lasted 3 months in our study, which might be too short for assessing its long-term efficacy and safety. Its modest efficacy as a remission induction therapy may indicate that Theracurmin® would be a better maintenance therapy than induction therapy in patients with IBD, particularly given its safety profile. Conventionally, 5-ASA preparations or immunomodulators are often used as maintenance therapies for patients with IBD; however, these medications are associated with serious AEs. In contrast, Theracurmin® as maintenance therapy ought to be superior because of its lack of AEs. These notions need to be validated in future studies of Theracurmin® as remission maintenance therapy.

There were some limitations in this study. First, this pilot exploratory trial consisted of a relatively modest sample size. Our results showed a remarkable advantage of Theracurmin® over placebo, but no formal power calculations were performed owing to the lack of data prior to testing the efficacy of Theracurmin® in this particular setting. Therefore, larger trials are needed to support our findings before Theracurmin® can be widely introduced into routine clinical practice for treating CD. Second, Theracurmin® was administered only at a dose of 180 mg twice daily (i.e., 360 mg/day), and we did not perform a dose-response study. Although we found that 360 mg/day was effective, it remains unknown if Theracurmin® is similarly effective at lower doses. Third, the study period of 3 months was relatively short, and the potential longer-term efficacy of Theracurmin® was not adequately evaluated. Fourth, only 21 of the 30 patients included in the study (70%) had access to endoscopic evaluation at week 12 (15 in the Theracurmin® group and 6 in the placebo group).

In conclusion, this first-of-its-kind study in patients with active mild-to-moderate CD showed that Theracurmin® exhibits definitive but modest clinical efficacy as well as ulcer-healing properties. Given that Theracurmin® has a favorable safety profile, the outcomes of this study should promote further clinical investigations of Theracurmin® in patients with more severe CD as well as in those with UC, the other major IBD manifestation. The overall therapeutic efficacy of Theracurmin® as maintenance

therapy in the IBD setting also warrants additional exploration.

Specific author contributions:

1. Study concept and design (KS, HH, JN)

2. Acquisition of data (KS, KI, SB, AA, HY, KM, MN, HT, AM, MK, NI, ST1, RT, ST2, SO, HH)

3. Statistical analysis (KS, HH, JN)

4. Drafting of manuscript (KS, HH)

5. Critical revision of the manuscript for important intellectual content and final approval (all authors)

6. Study supervision (KS, HH)

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References

1. Baumgart D C, Sandborn W J. Crohn's disease. Lancet 2012; 380: 1590-1605.
2. Hanauer S B, Feagan B G, Lichtenstein G R, Mayer L F, Schreiber S, Colombel J F, Rachmilewitz D, Wolf D C, Olson A, Bao W, Rutgeerts P; ACCENT I Study Group. Maintenance infliximab for Crohn's disease: the ACCENT I randomised trial. Lancet 2002; 359: 1541-1549.
3. Colombel J F, Sandborn W J, Rutgeerts P, Enns R, Hanauer S B, Panaccione R, Schreiber S, Byczkowski D, Li J, Kent J D, Pollack P F. Adalimumab for maintenance of clinical response and remission in patients with Crohn's disease: the CHARM trial. Gastroenterology 2007; 132: 52-65.
4. Sandborn W J, Gasink C, Gao L L, Blank M A, Johanns J, Guzzo C, Sands B E, Hanauer S B, Targan S, Rutgeerts P, Ghosh S, de Villiers W J, Panaccione R, Greenberg G, Schreiber S, Lichtiger S, Feagan B G; CERTIFI Study Group. Ustekinumab induction and maintenance therapy in refractory Crohn’s disease. N Engl J Med 2012; 367: 1519-1528.
5. Govindarajan V S. Turmeric-chemistry, technology, and quality. Crit Rev Food Sci Nutr 1980; 12: 199-301.
6. Jobin C, Bradham C A, Russo M P, Juma B, Narula A S, Brenner D A, Sartor R B. Curcumin blocks cytokine-mediated NF-kappa B activation and proinflammatory gene expression by inhibiting inhibitory factor I-kappa B kinase activity. J Immunol 1999; 163: 3474-3483.
7. Hanai H, Sugimoto K. Curcumin has bright prospects for the treatment of inflammatory bowel disease. Curr Pharm Des 2009; 15: 2087-2094.
8. Sugimoto K, Hanai H, Tozawa K, Aoshi T, Uchijima M, Nagata T, Koide Y. Curcumin prevents and ameliorates trinitrobenzene sulfonic acid-induced colitis in mice. Gastroenterology 2002; 123: 1912-1922.
9. Ali T, Shakir F, Morton J. Curcumin and inflammatory bowel disease: biological mechanisms and clinical implication. Digestion 2012; 85: 249-255.
10. Hanai H, Iida T, Takeuchi K, Watanabe F, Maruyama Y, Andoh A, Tsujikawa T, Fujiyama Y, Mitsuyama K, Sata M, Yamada M, Iwaoka Y, Kanke K, Hiraishi H, Hirayama K, Arai H, Yoshii

S, Uchijima M, Nagata T, Koide Y. Curcumin maintenance therapy for ulcerative colitis: randomized, multicenter, double-blind, placebo-controlled trial. Clin Gastroenterol Hepatol 2006; 4: 1502-1506.

11. Singla V, Pratap Mouli V, Garg S K, Rai T, Choudhury B N, Verma P, Deb R, Tiwari V, Rohatgi S, Dhingra R, Kedia S, Sharma P K, Makharia G, Ahuja V. Induction with NCB-02 (curcumin) enema for mild-to-moderate distal ulcerative colitis - a randomized, placebo-controlled, pilot study. J Crohns Colitis 2014; 8: 208-214.
12. Lang A, Salomon N, Wu J C, Kopylov U, Lahat A, Har-Noy O, Ching J Y, Cheong P K, Avidan B, Gamus D, Kaimakliotis I, Eliakim R, Ng S C, Ben-Horin S. Curcumin in combination with mesalamine induces remission in patients with mild-to-moderate ulcerative colitis in a randomized controlled trial. Clin Gastroenterol Hepatol 2015; 13: 1444-1449.
13. Sasaki H, Sunagawa Y, Takahashi K, Imaizumi A, Fukuda H, Hashimoto T, Wada H, Katanasaka Y, Kakeya H, Fujita M, Hasegawa K, Morimoto T. Innovative preparation of curcumin for improved oral bioavailability. Biol Pharm Bull 2011; 34: 660-665.
14. Dei Cas M, Ghidoni R. Dietary Curcumin: Correlation between Bioavailability and Health Potential. Nutrients 2019; 11: E2147.
15. Ohno M, Nishida A, Sugitani Y, Nishino K, Inatomi O, Sugimoto M, Kawahara M, Andoh A. Nanoparticle curcumin ameliorates experimental colitis via modulation of gut microbiota and induction of regulatory T cells. PLoS One 2017; 12: e0185999.
16. Lyakhovich A, Gasche C. Systematic review: molecular chemoprevention of colorectal malignancy by mesalazine. Aliment Pharmacol Ther 2010; 31: 202-209.
17. Zhang X, Wu J, Ye B, Wang Q, Xie X, Shen H. Protective effect of curcumin on TNBS-induced intestinal inflammation is mediated through the JAK/STAT pathway. BMC Complement Altern Med 2016; 16: 299.
18. van Ede K, Li A, Antunes-Fernandes E, Mulder P, Peijnenburg A, Hoogenboom R. Bioassay directed identification of natural aryl hydrocarbon-receptor agonists in marmalade. Anal Chim

Acta 2008; 617: 238-245.

19. Veldhoen M, Hirota K, Westendorf A M, Buer J, Dumoutier L, Renauld J C, Stockinger B. The aryl hydrocarbon receptor links TH17-cell-mediated autoimmunity to environmental toxins. Nature 2008; 453: 106-109.
20. Sugimoto K, Ogawa A, Mizoguchi E, Shimomura Y, Andoh A, Bhan A K, Blumberg R S, Xavier R J, Mizoguchi A. IL-22 ameliorates intestinal inflammation in a mouse model of ulcerative colitis. J Clin Invest 2008; 118: 534-544.
21. Lehmann FS, Burri E, Beglinger C. The role and utility of faecal markers in inflammatory bowel disease. Therap Adv Gastroenterol 2015; 8: 23-36.
22. Yang K Y, Lin L C, Tseng T Y, Wang S C, Tsai T H. Oral bioavailability of curcumin in rat and the herbal analysis from Curcuma longa by LC-MS/MS. J Chromatogr B Analyt Technol Biomed Life Sci 2007; 853: 183-189.
23. Kanai M, Imaizumi A, Otsuka Y, Sasaki H, Hashiguchi M, Tsujiko K, Matsumoto S, Ishiguro H, Chiba T. Dose-escalation and pharmacokinetic study of nanoparticle curcumin, a potential anticancer agent with improved bioavailability, in healthy human volunteers. Cancer Chemother Pharmacol 2012; 69: 65-70.
24. Kanai M, Otsuka Y, Otsuka K, Sato M, Nishimura T, Mori Y, Kawaguchi M, Hatano E, Kodama Y, Matsumoto S, Murakami Y, Imaizumi A, Chiba T, Nishihira J, Shibata H. A phase I study investigating the safety and pharmacokinetics of highly bioavailable curcumin (Theracurmin) in cancer patients. Cancer Chemother Pharmacol 2013; 71: 1521-1530.
25. Sunagawa Y, Hirano S, Katanasaka Y, Miyazaki Y, Funamoto M, Okamura N, Hojo Y, Suzuki H, Doi O, Yokoji T, Morimoto E, Takashi T, Ozawa H, Imaizumi A, Ueno M, Kakeya H, Shimatsu A, Wada H, Hasegawa K, Morimoto T. Colloidal submicron-particle curcumin exhibits high absorption efficiency-a double-blind, 3-way crossover study. J Nutr Sci Vitaminol 2015; 6: 37-44.
26. Shin Y A, Suk M H, Jang H S, Choi H J. Short-term effects of Theracurmin dose and exercise

type on pain, walking ability, and muscle function in patients with knee osteoarthritis. J Exerc Rehabil 2017; 13: 684-692.

27. Lacruz-Guzmán D, Torres-Moreno D, Pedrero F, Romero-Cara P, García-Tercero I, Trujillo-Santos J, Conesa-Zamora P. Influence of polymorphisms and TNF and IL1β serum concentration on the infliximab response in Crohn's disease and ulcerative colitis. Eur J Clin Pharmacol 2013; 69: 431-438.
28. Gupta S C, Patchva S, Aggarwal B. Therapeutic roles of curcumin: lessons learned from clinical trials. AAPS J 2013; 15: 195-218.
29. Schneider A, Hossain I, VanderMolen J, Nicol K. Comparison of remicade to curcumin for the treatment of Crohn's disease: A systematic review. Complement Ther Med 2017; 33: 32-38.

Figure legends

Figure 1. Summary of the study design and treatment outcomes.

Figure 2. Clinical improvement (A) and remission (B) with Theracurmin®. Clinical remission, CDAI score <150. CR-70 represents the rate at which the CDAI score decreased by 70 points or more. CDAI, Crohn's disease activity index.

Figure 3. Theracurmin®-induced efficacy as verified clinically and endoscopically. SESCD, Simple Endoscopic Score for Crohn's Disease.

Figure 4. Endoscopic efficacy of Theracurmin®. SESCD, Simple Endoscopic Score for Crohn's Disease.

Figure 5. Efficacy of Theracurmin® for treating anal lesions.

Table 1. Clinical features of Theracurmin®- and placebo-administered patients with Crohn's disease

Variable	Theracurmin® (n=20)	Placebo (n=10)	*P* value
Sex (male/female)	13/7	8/2	0.398
Age (years)	36.3 ± 8.9 (21–60)	32.9 ± 13.4 (21–65)	0.418
Age at diagnosis (years)	27.9 ± 7.8 (14–41)	25.5 ± 7.3 (13–38)	0.462
Duration of disease (years)	9.1 ± 8.1 (0–27)	8.0 ± 12.2 (0–38)	0.787
Height (cm)	167.9 ± 10.8	167.0 ± 3.4	0.809
Weight (kg)	56.5 ± 10.4	57.0 ± 8.9	0.909
Smoking, n (%)			
Current/ex-/never smoker	5 (25.0)/2 (10.0)/13 (65.0)	2 (20.0)/1 (10.0)/7 (70.0)	0.953
Perianal disease, n (%)	13 (65.0)	5 (50.0)	0.429
History of surgery, n (%)	6 (30.0)	4 (40.0)	0.584
Concomitant use, n (%)			
5-Aminosalicylates	18 (90.0)	9 (90.0)	1.000
Immunomodulators	6 (30.0)	4 (40.0)	0.584
Elemental diet	10 (50.0)	4 (40.0)	0.605
Corticosteroid	1 (5.0)	0 (0)	0.472
Biologics	1 (5.0)	1 (10.0)	0.605
Montreal classification, n (%)			
A1/A2/A3	1 (5.0)/17 (85.0)/2 (10.0)	1 (10.0)/9 (90.0)/0 (9.5)	0.530
L1/L2/L3	1 (5.0)/4 (20.0)/15 (75.0)	2 (20.0)/1 (10.0)/7 (70.0)	0.382
B1/B2/B3	13 (66.7)/4 (19.0)/3 (14.3)	5 (50.0)/4 (40.0)/1 (10.0)	0.503
CDAI (points)	210.9 ± 38.7	211.2 ± 32.1	0.981
SESCD (points)	12.4 ± 5.8	15.0 ± 5.8	0.268

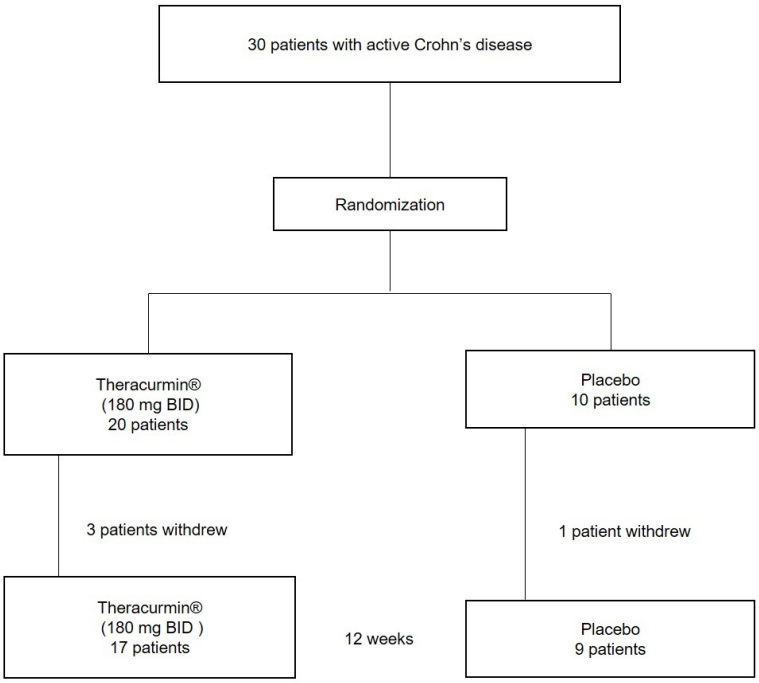
A1: 16 years and under, A2: between 17 and 40 years, A3: over 40 years

L1: ileal, L2: colonic, L3: ileocolonic, L4: isolated upper disease

B1: non-stricturing, non-penetrating, B2: stricturing, B3: penetrating

CDAI, Crohn's disease activity index; SESCD Simple Endoscopic Score for Crohn's disease

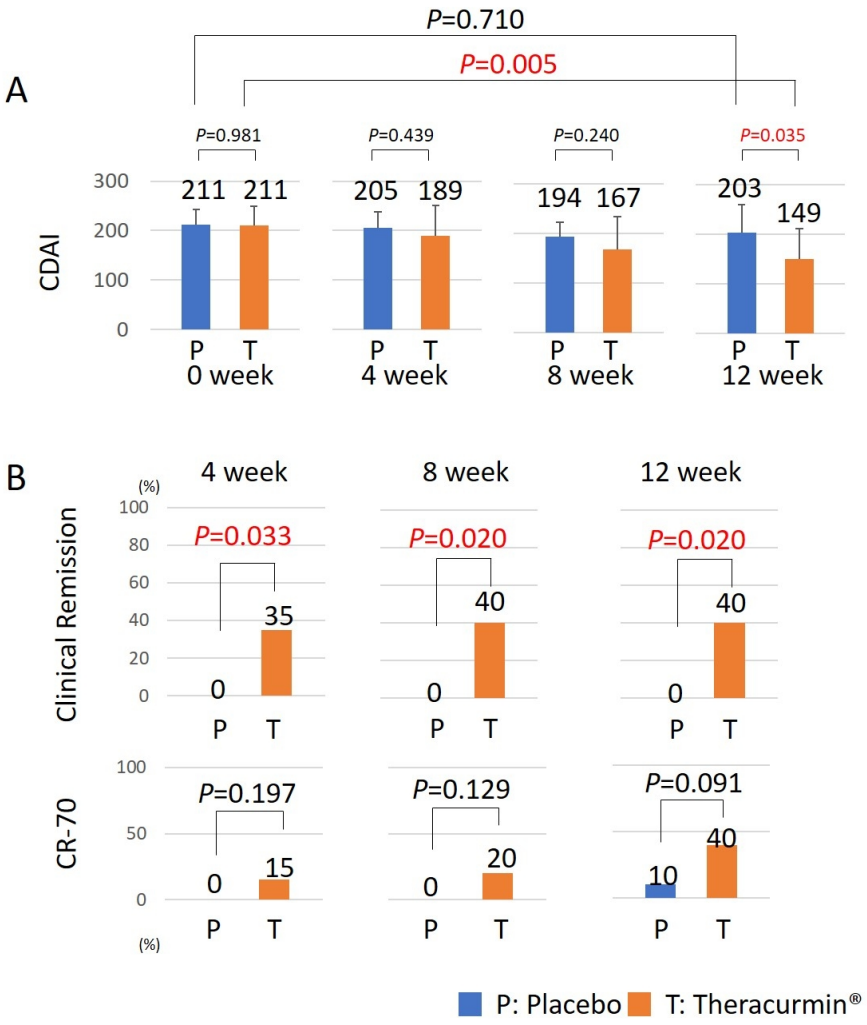
Figure 1



Summary of the study design and treatment outcomes.

193x255mm (150 x 150 DPI)

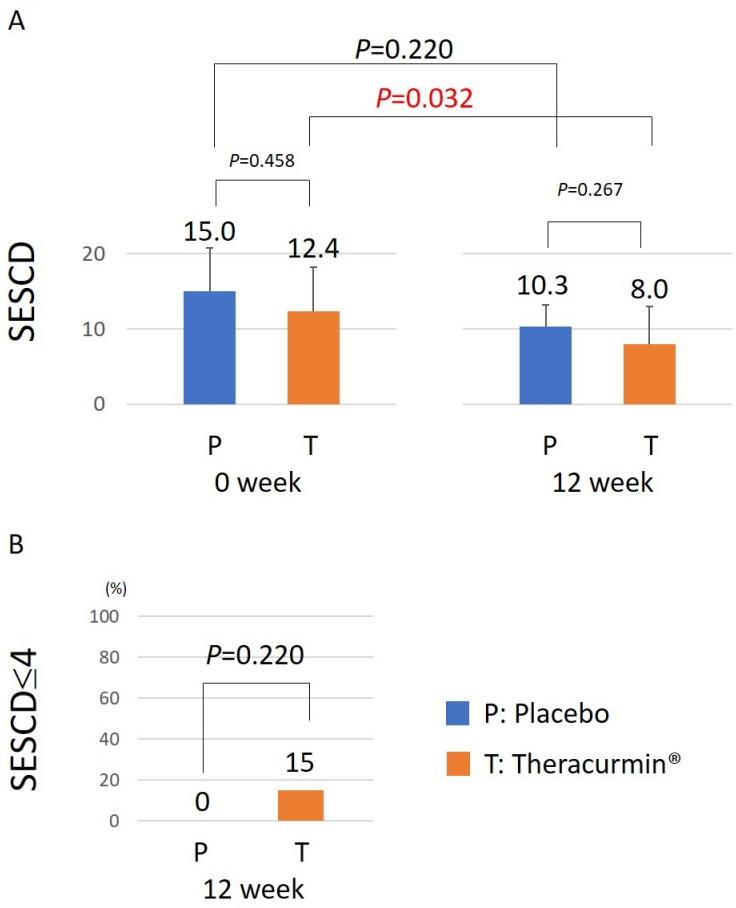
Figure 2



Clinical improvement (A) and remission (B) with Theracurmin®. Clinical remission, CDAI score <150. CR-70 represents the rate at which the CDAI score decreased by 70 points or more. CDAI, Crohn's disease activity index.

192x254mm (150 x 150 DPI)

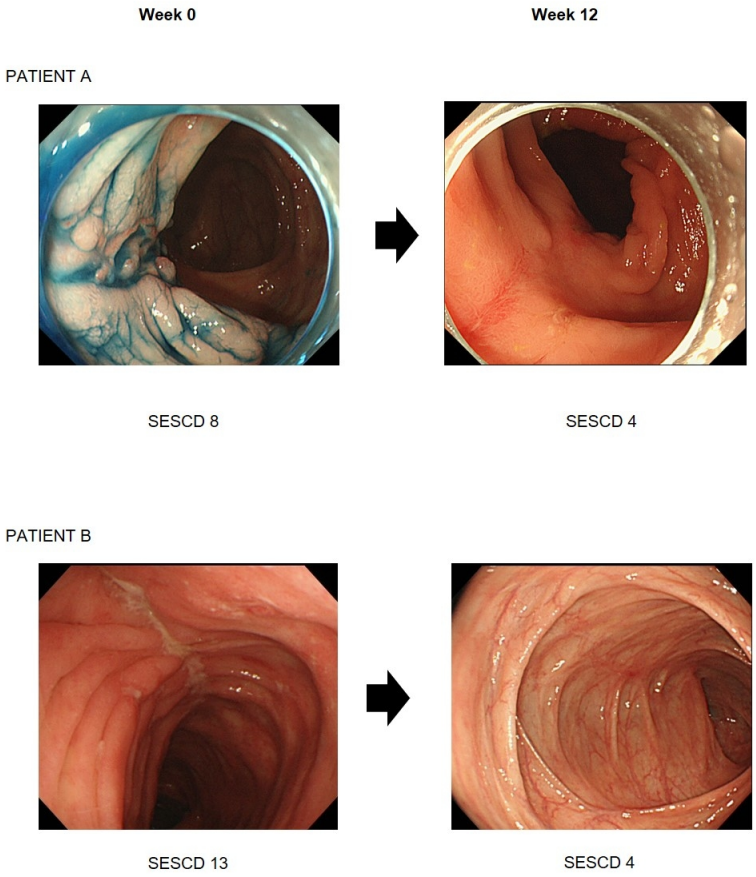
Figure 3



Theracurmin®-induced efficacy as verified clinically and endoscopically. SESCD, Simple Endoscopic Score for Crohn's Disease.

190x253mm (150 x 150 DPI)

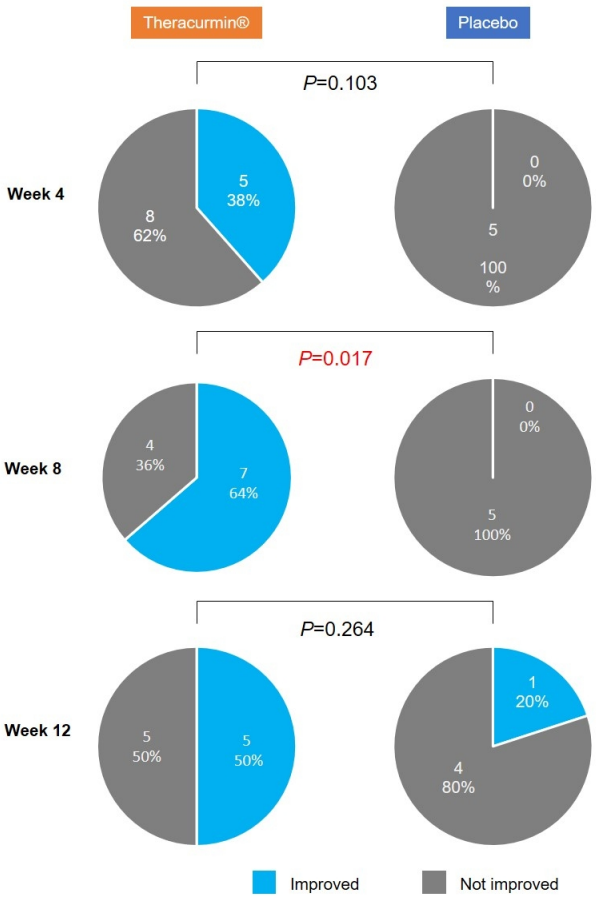
Figure 4



Endoscopic efficacy of Theracurmin®. SESCD, Simple Endoscopic Score for Crohn's Disease.

190x254mm (150 x 150 DPI)

Figure 5



Efficacy of Theracurmin® for treating anal lesions.

190x254mm (150 x 150 DPI)

Supplemental Table 1. Clinical laboratory values at week 0 in the Theracurmin® and placebo groups

	Theracurmin® (n=20)	Placebo (n=10)	*P*-value
Total protein (g/dL)	7.3 ± 0.7	7.6 ± 0.8	0.418
Albumin (g/dL)	3.9 ± 0.7	3.7 ± 0.6	0.439
BUN (mg/dL)	9.6 ± 2.2	13.1 ± 4.0	0.007
Creatinine (mg/dL)	0.7 ± 0.2	0.8 ± 0.2	0.403
Total cholesterol (mg/dL)	162.2 ± 30.6	144.1 ± 23.4	0.153
LDH (IU/L)	141.8 ± 29.0	127.9 ± 40.9	0.329
HDL cholesterol (mg/dL)	48.7 ± 12.2	51.0 ± 8.0	0.634
Triglyceride (mg/dL)	128.1 ± 113.9	90.3 ± 42.4	0.375
Total bilirubin (mg/dL)	0.6 ± 0.3	0.5 ± 0.2	0.465
Blood sugar (mg/dL)	94.5 ± 14.9	105.0 ± 41.5	0.354
AST (IU/L)	21.1 ± 10.6	20.9 ± 8.6	0.958
ALT (IU/L)	19.5 ± 11.3	17.8 ± 8.1	0.683
γGT (IU/L)	39.3 ± 43.8	25.0 ± 8.1	0.319
CRP (mg/dL)	1.04 ± 1.49	1.49 ± 1.34	0.425
Sodium (Eq/L)	140.8 ± 1.4	140.4 ± 1.6	0.557
Potassium (mEq/L)	3.9 ± 0.4	4.1 ± 0.4	0.192
Chloride (mEq/L)	103.7 ± 2.7	103.3 ± 2.8	0.722
White blood cells (/μL)	6085.2 ± 2697.4	5812.5 ± 2315.3	0.788
Platelet (/μL)	30.4 ± 10.3	67.5 ± 104.8	0.132
ESR (mm/hour)	28.8 ± 23.5	42.6 ± 29.9	0.197
Hemoglobin (g/dL)	12.7 ± 1.7	12.5 ± 1.6	0.709
Hematocrit (%)	38.1 ± 4.6	38.4 ± 4.3	0.871
MCV (fL)	86.5 ± 5.4	84.9 ± 8.1	0.523
Serum iron (μg/dL)	72.2 ± 54.1	45.1 ± 28.3	0.154
Ferritin (ng/dL)	48.1 ± 36.2	47.9 ± 40.7	0.991
UIBC (μg/dl)	248.6 ± 81.0	271.1 ± 78.7	0.543

BUN, blood urea nitrogen; LDH, lactate dehydrogenase; HDL, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; γGT, γ-glutamyltransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; UIBC, unsaturated iron-binding capacity.

Supplemental Table 2. Clinical laboratory values at week 12 in the Theracurmin® and placebo groups

	Theracurmin® (n=20)	Placebo (n=10)	*P*-value
Total protein (g/dL)	7.4 ± 0.5	7.4 ± 1.0	0.969
Albumin (g/dL)	3.9 ± 0.6	3.6 ± 0.7	0.265
BUN (mg/dL)	9.6 ± 4.2	13.0 ± 5.4	0.095
Creatinine (mg/dL)	0.7 ± 0.2	0.8 ± 0.2	0.146
Total cholesterol (mg/dL)	162.8 ± 29.3	139.1 ± 31.0	0.065
LDH (IU/L)	144.3 ± 29.2	135.6 ± 23.1	0.436
HDL cholesterol (mg/dL)	46.8 ± 12.4	47.8 ± 8.3	0.832
Triglyceride (mg/dL)	108.5 ± 54.5	97.1 ± 55.4	0.617
Total bilirubin (mg/dL)	0.6 ± 0.3	0.5 ± 0.3	0.323
Blood sugar (mg/dL)	99.1 ± 18.5	102.5 ± 30.5	0.735
AST (IU/L)	23.2 ± 11.7	21.1 ± 5.7	0.603
ALT (IU/L)	20.6 ± 15.3	19.3 ± 10.0	0.815
γGT (IU/L)	51.1 ± 80.9	23.5 ± 9.1	0.297
CRP (mg/dL)	1.29 ± 2.22	1.63 ± 1.48	0.672
Sodium (Eq/L)	139.7 ± 1.5	140.3 ± 1.8	0.403
Potassium (mEq/L)	4.0 ± 0.4	4.2 ± 0.2	0.192
Chloride (mEq/L)	103.2 ± 2.5	103.7 ± 2.4	0.617
White blood cells (/μL)	6141.3 ± 2473.5	6532.7 ± 3698.4	0.753
Platelet (/μL)	29.7 ± 11.3	71.5 ± 115.5	0.173
ESR (mm/hour)	23.4 ± 25.8	37.8 ± 31.0	0.275
Hemoglobin (g/dL)	13.0 ± 1.7	12.7 ± 1.7	0.586
Hematocrit (%)	38.5 ± 3.9	38.6 ± 4.7	0.965
MCV (fL)	86.3 ± 5.0	84.4 ± 6.7	0.43
Serum iron (μg/dL)	81.2 ± 45.9	47.4 ± 34.3	0.073
Ferritin (ng/dL)	53.4 ± 54.3	50.2 ± 41.9	0.879
UIBC (μg/dl)	231.4 ± 41.2	268.6 ± 52.1	0.09

BUN, blood urea nitrogen; LDH, lactate dehydrogenase; HDL, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; γGT, γ-glutamyltransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; UIBC, unsaturated iron-binding capacity.

Supplemental Table 3. Changes in clinical laboratory values between weeks 0 and 12 in Theracurmin®-administered patients

	Week 0	Week 12	*P*-value
Total protein (g/dL)	7.3 ± 0.7	7.4 ± 0.5	0.765
Albumin (g/dL)	3.9 ± 0.7	3.9 ± 0.6	0.967
BUN (mg/dL)	9.6 ± 2.2	9.6 ± 4.2	0.986
Creatinine (mg/dL)	0.7 ± 0.2	0.7 ± 0.2	0.9
Total cholesterol (mg/dL)	162.2 ± 30.6	162.8 ± 29.3	0.958
LDH (IU/L)	141.8 ± 29.0	144.3 ± 29.2	0.806
HDL cholesterol (mg/dL)	48.7 ± 12.2	46.8 ± 12.4	0.67
Triglyceride (mg/dL)	128.1 ± 113.9	108.5 ± 54.5	0.545
Total bilirubin (mg/dL)	0.6 ± 0.3	0.6 ± 0.3	0.562
Blood sugar (mg/dL)	94.5 ± 14.9	99.1 ± 18.5	0.455
AST (IU/L)	21.1 ± 10.6	23.2 ± 11.7	0.588
ALT (IU/L)	19.5 ± 11.3	20.6 ± 15.3	0.807
γGT (IU/L)	39.3 ± 43.8	51.1 ± 80.9	0.59
CRP (mg/dL)	1.04 ± 1.49	1.29 ± 2.22	0.698
Sodium (Eq/L)	140.8 ± 1.4	139.7 ± 1.5	0.041
Potassium (mEq/L)	3.9 ± 0.4	4.0 ± 0.4	0.421
Chloride (mEq/L)	103.7 ± 2.7	103.2 ± 2.5	0.558
White blood cells (/μL)	6085.2 ± 2697.4	6141.3 ± 2473.5	0.951
Platelet (/μL)	30.4 ± 10.3	29.7 ± 11.3	0.849
ESR (mm/hour)	28.8 ± 23.5	23.4 ± 25.8	0.564
Hemoglobin (g/dL)	12.7 ± 1.7	13.0 ± 1.7	0.6
Hematocrit (%)	38.1 ± 4.6	38.5 ± 3.9	0.779
MCV (fL)	86.5 ± 5.4	86.3 ± 5.0	0.907
Serum iron (μg/dL)	72.2 ± 54.1	81.2 ± 45.9	0.622
Ferritin (ng/dL)	48.1 ± 36.2	53.4 ± 54.3	0.744
UIBC (μg/dl)	248.6 ± 81.0	231.4 ± 41.2	0.48

BUN, blood urea nitrogen; LDH, lactate dehydrogenase; HDL, high-density lipoprotein cholesterol; AST, aspartate transaminase; ALT, alanine transaminase; γGT, γ-glutamyltransferase; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; MCV, mean corpuscular volume; UIBC, unsaturated iron-binding capacity.