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Symptomatic uncomplicated diverticular disease management: an innovative food-grade formulation of *Curcuma longa* and *Boswellia serrata* extracts

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Abstract

Background: The treatment of symptomatic uncomplicated colonic diverticular disease (SUDD) is still under debate, and new data show a pathogenic role of dysbiosis and low-grade inflammation in intestinal mucosa. Recent research has highlighted the anti-inflammatory effects of botanical extracts such as *Curcuma longa* L. and *Boswellia serrata* Roxb. ex Colebr. The aim of this work is to investigate the potential role of a new delivery formulation of the association of curcumin and boswellia phytosome extracts (CBP) in SUDD.

Methods: In a 30-day one-group longitudinal explanatory study, patients (men and women) were treated with an innovative association of CBP standardized extracts, 500 mg bid.

Results: Treatment of SUDD with the association of CBP was followed by a significant decrease in abdominal pain ($p<0.0001$). The study group showed that CBP supplementation was efficacious within 10 days and that efficacy was maintained almost constant until the 30th day of intervention.

Conclusion: A phytosome of curcumin and boswellia extracts may be useful for the relief of SUDD pain. However, controlled studies should be performed for final conclusions to be drawn.

Keywords: Boswellia, curcumin, dietary supplement, food grade, phytosome, SUDD.

Citation

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Introduction

The clinical pattern of diverticulosis is broad – while 80–85% of patients with diverticulosis will never develop symptoms, about 10–15% will experience symptoms (diverticular disease) and acute diverticulitis will occur in only 5% of cases.[1,2] Symptomatic uncomplicated diverticular disease (SUDD) is a clinical condition mostly characterized by intermittent or persistent episodes of abdominal pain. In most cases, left lower abdominal pain lasting at least 24 hours is observed in association with the presence of colonic diverticula and in the absence of acute inflammatory conditions related to complications such as abscesses, perforation, fistula, obstruction, or peritonitis[3,4]. Additional symptoms of SUDD may be bloating and irregular bowel function, that is, constipation or diarrhea. From the symptomatic point of view, SUDD may overlap with irritable bowel syndrome (IBS): in both cases there is no evidence of severe and acute inflammation. Indeed, fever and increased white blood cell count or increased inflammatory markers, such as C-reactive protein, are neither observed in SUDD nor in IBS, while all of the above signs are present in acute diverticulitis.[5] What differentiates SUDD from IBS is the duration and site of abdominal pain, which is mainly located in the lower left abdomen and lasts for more than 24 hours in SUDD. In 2010, Tursi confirmed that a combination of clinical and laboratory data may differentiate SUDD from IBS.[6] The pathogenesis of SUDD is still a matter of discussion, although dysbiosis and microscopic inflammatory damage seem to be involved.[7] As a consequence, to date, a standard treatment for

SUDD is not available and non-absorbable antibiotics, anti-inflammatory drugs, and probiotics are mostly used.[8,9]

Recent research shows the presence of low-grade inflammation of colonic mucosa in SUDD with increased inflammatory infiltrates in colonic mucosa as well as increased expression of tumor necrosis factor-α (TNFα).[10] Therefore, instead of broad-spectrum antibiotics, a new therapeutic strategy based on the use of anti-inflammatory drugs has been developed for the treatment of patients with SUDD. Various studies show the efficacy of mesalazine, also known as mesalamine or 5-aminosalicylic acid, in the treatment of SUDD.[11] Interesting experimental data are now available on the anti-inflammatory effect of various natural compounds that could be used to treat the inflammatory processes observed in SUDD. In particular, the extracts of turmeric plant (*C. longa* L.) and *Boswellia serrata* could be useful candidates.

C. longa L. is a perennial herb plant widespread in South East Asia and extensively cultivated in China, India, Indonesia, and Thailand. The active components of the roots are three curcuminoids: curcumin, demethoxycurcumin, and bisdemethoxycurcumin. These curcuminoids are linked to the important physiological and biological effects of curcumin, acting as effective anti-inflammatory agents with multiple activities, including antioxidant and metabolic modulation. Curcumin's effects have been well demonstrated in several clinical studies showing effectiveness in inflammatory bowel disease (IBD), arthritis, prediabetes, and in the early stages of some cancers.[12] A recent meta-analysis on 15 randomized clinical trials shows that curcumin downregulates inflammation and oxidation products by decreasing the levels of IL-6, high-sensitivity C-reactive protein, and malondialdehyde.[13] Experimental studies in animal models of IBD demonstrated that treatment with curcumin may decrease TNFα, an inflammatory cytokine associated with IBD as well as with diverticular disease and acute diverticulitis.[14,15] It is well known that curcumin has a low human bioavailability and, to exploit its clinical potential effects and overcome this issue, several formulations have been developed, including the application of food-grade phytosome technology. Comparison studies have shown that a curcumin phytosome significantly ameliorates the bioavailability of curcuminoids in plasma and in the intestinal mucosa.[16,17] In addition, curcumin phytosome administration also shows a protective effect toward gastrointestinal barrier damage.[18]

Oleo gum resins from *B. serrata* Roxb. ex Colebr have been used in traditional medicine in India and Africa as a remedy to cure various inflammatory diseases.[19] Preclinical and clinical studies showed interesting data on the effects of *B. serrata* extracts and its active components, boswellic acids.[20–22] However, pharmacokinetics studies revealed low and erratic systemic absorption of boswellic acids in animals and humans. In order to improve the bioavailability of boswellia, a lecithin-based (phytosome) delivery form of standardized *B. serrata* extracts has been developed showing the optimization of boswellic acid delivery in healthy volunteers.[23] Boswellia phytosome was shown to be effective and safe in the management of gut discomforts such as IBS and in attenuating symptoms associated with mild ulcerative colitis in remission, thereby reducing the need for drugs and medical consultations.[24–26] In combination with curcumin, boswellia was shown to inhibit the production of inflammatory cytokines Il-6, IL-8, TNFα, and reactive oxygen species *in vitro*[27] and in a clinical study for joint health.[28]

Based on these data, an intervention study was performed in order to evaluate, for the first time, the efficacy of a new food-grade delivery system of curcumin and boswellia phytosome (CBP) for the relief of symptoms associated with SUDD.

Materials and methods

Study design

This is a one-group longitudinal explanatory study performed at the Department of Public Health of the University of Pavia, Italy. The objective of the study was to evaluate the efficacy and safety of CBP (Indena SpA) in patients with lower left abdominal pain as a major symptom of SUDD. The study was conducted in accordance with the Declaration of Helsinki and the ICH Guidelines for Good Clinical Practice, following approval from the Local Independent Ethics Committee (Ethic code number: 0612/22052019). Written informed consent was obtained from each participant. The study was conducted from February 1, 2019, to January 15, 2020.

Population

Male and female patients with a diagnosis of SUDD were potential candidates for the study. The inclusion criteria were as follows: age 40–80 years; a diagnosis of SUDD (lower left abdominal pain lasting more than 24 hours in the absence of serious complications such as abscess, fistula, peritonitis, rectal bleeding not due to hemorrhoids, ileus, stenosis); abdominal pain occurrence on at least 4 of the previous 7 days before study inclusion; at least four diverticula observed on flexible colonoscopy or virtual colonoscopy at baseline (within 100 days prior to the inclusion in the study); and at least four of eight specified symptoms present for at least 2 days prior to inclusion and still present at study inclusion (i.e. abdominal pain localized mainly in the lower left abdomen, abdominal pain enhanced after meals, abdominal pain decreased after defecation or wind, bloating, constipation (defined as ≤2 defecations/week), diarrhea (defined as ≥3 loose stools per day), a sensation of incomplete evacuation after defecation, and painful lower left abdomen at palpation). Exclusion criteria were chronic IBD (Crohn's disease or ulcerative colitis), fever (>38.0°C by axillary measurement) or other signs of serious complications, a medical history of severe renal disease (defined as serum creatinine >1.5 mg/dL), or liver disease (defined as altered values of liver function tests).

Treatment and concomitant medications

Patients included in the study received CBP 500 mg bid for 30 days. The choice of dose was based on previous clinical experiences with CBP.[24,29] The possibility of combining

curcumin and boswellia extracts in one single food-grade delivery system allows a treatment approach more suitable in terms of the number of tablets consumed.

Treatment compliance was calculated as the ratio between the administered medication (as determined by returned medication) and the expected intake during the actual treatment period for each patient. All patients were instructed to follow nutritional recommendations, including the consumption of meals rich or poor in fibers (according to their bowel habits) and adequate intake of liquids (at least 1.5 L/day). The concomitant administration of any other drugs for the treatment of gastrointestinal tract disorders that could affect the results or interfere with the study medication was not permitted, with the exception of short-acting spasmolytics (e.g. butylscopolaminium bromide) and short-acting analgesics (e.g. paracetamol) (the consumption of these drugs was monitored). Opioids were prohibited.

Clinical evaluation

Study visits were scheduled at baseline (day 1) and at days 15 and 30. Patients filled a daily diary from day 1 onward, which was evaluated at all visits. The diary contained the score of the most severe lower abdominal pain intensity experienced every day. The score was defined by the patient at the end of each day using a validated visual analog scale score for pain (0: 'no pain', 10: 'most severe pain').[30,31] Moreover, the number of daily stools and the main stool consistency were reported every day. At the end of the study, according to Kruis et al., a global assessment of efficacy (GAE) using a 4-point scale was defined by each patient (1: 'ineffective', 2: 'moderately effective slight improvement of complaints', 3: 'effective marked improvement in symptoms', 4: 'very effective – as good as no symptoms').[14,32] At each visit, vital signs were evaluated and urine and serum samples were collected. Laboratory assessments were performed and analyzed with reference to the normal ranges. Compliance with study medication was evaluated by pill counting and the concomitant use of spasmolytics and analgesics was recorded. Adverse events were checked at all study visits.

Supplement description

For the clinical study, the sunflower lecithin-based formulation of *C. longa* L. and *B. serrata* standardized extracts (500 mg) was prepared by Indena S.p.A., as oblong-shaped, film-coated tablets, corresponding to a content of 17.0–23.0% w/w of curcumin and 7.0–11.0% w/w of boswellia extracts, respectively by high performance liquid chromatography (HPLC) assay. The active ingredient is a solid dispersion containing the standardized association of curcumin extract (≥90% as total curcuminoids assessed by HPLC assay) and boswellia extract (≥65.0% of total triterpenic acids assessed by HPLC assay). The remaining food-grade components of the phytosome tablets are calcium carbonate E170 (95DC M; Dr Paul Lohman®), polyvinylpolypyrrolidone E1202 (Polyplasdone™ XL; Ashland), sodium croscarmellose E468 (Solutab® A-IP; Blanver Farmoquimica LTDA), silicon dioxide E551 (Syloid® 244FP; Grace), talc E553b (Mondo Minerals B.V.), magnesium stearate E470b (Ligafood®; Peter Greven Nederland C.V.), and hydroxypropyl methylcellulose E463-based film-coating (Opadry® Clear; Colorcon). Before releasing, the film-coated tablets containing the food-grade lecithin formulation were tested for appearance, average mass, uniformity of mass, HPLC-content of curcumin and boswellia extracts, disintegration time, and microbiological quality.

Study endpoints

The primary endpoint was the change in intensity of abdominal pain during the 30 days of treatment. Secondary endpoints included (1) the number of patients with complete pain relief, (2) the median time to complete pain relief based on patient diary entries, (3) the number of patients requiring spasmolytics and analgesics, (4) the GAE as assessed by the patient, and (5) the correlation with the baseline defecation habit. Safety endpoints included adverse events, laboratory results, and vital signs.

Statistical analysis

This is a one-group longitudinal explanatory study in which all the participants received the supplement and were observed over time (i.e. 30 days); there is no control group and, as a consequence, the study is not randomized.

Given this is a pilot study and no prior evidence exists of an association of curcumin and boswellia in patients with SUDD, the sample size was determined by the feasibility of recruitment. For the recruited sample size, power analysis was determined post-hoc based on 100 simulations with simr package and was equal to 0.87 with an alpha equal to 0.05.[33,34]

To evaluate the treatment effect over time on lower abdominal pain intensity, as measured by a numerical rating scale from 0 to 10, we used a Cumulative Link Mixed Model (CLMM), implemented in the ordinal R package.[35,36] All models were adjusted for sex, age, and use of additional drugs (yes/no). We first conducted a global analysis fitting a CLMM with time as fixed effects. A random intercept and slope in the form of time/patient was added in the model in order to account for intrapatient correlation produced by the repeated measurements across time. We then fitted a model with time, defecation group, and their interaction (time*group) as fixed effects and we compared the goodness-of-fit of the two models (i.e. with interaction *versus* no interaction) via a likelihood ratio test (LRT). Given the small sample size and the low power, a $p<0.10$ for the LRT can be considered as statistically significant and the effect of time separately in each group was tested. Pain intensity differences were calculated by subtracting the pain intensity at each time point from the pain intensity at baseline and then summed up over the relevant time span obtaining the sum of pain intensity difference (SPID).

In this way, we summarized the treatment response over three clinically relevant periods: SPID from day 1 to day 10 ($SPID_{1–10}$), SPID from day 11 to day 20 ($SPID_{11–20}$), and SPID from day 21 to day 30 ($SPID_{21–30}$). Statistical differences were first evaluated using non-parametric Wilcoxon signed rank test, with the option that allows consideration of the correlation between SPID across the periods we analyzed. A decreasing trend of SPID was tested using both a linear growth model and a spline model with a transition point at $SPD_{11–20}$ to accommodate for possible non-linear trends. The first model, i.e. the linear growth model, assumes constant change over time, while the second model, i.e. the spline model, divides the data into two segments of time and allows fitting of a linear mixed model considering a piecewise-linear trend, having different slopes. The first spline represents the linear change from $SPD_{1–10}$ to the transition point $SPD_{11–20}$ and the second spline represents the linear change from the transition point $SPD_{11–20}$ to $SPD_{20–30}$.

An independent sample Kruskal–Wallis test was used to investigate statistically significant differences between defecation group and GAE. The Spearman rank-order correlation coefficient was calculated to investigate the correlation between GAE and pain score at day 1. All the analyses were performed using R 3.5.1 statistical software.[37] Descriptive statistics are reported as mean ± standard deviation (SD) and frequency distribution.

Table 1. Baseline descriptive characteristics of patients.

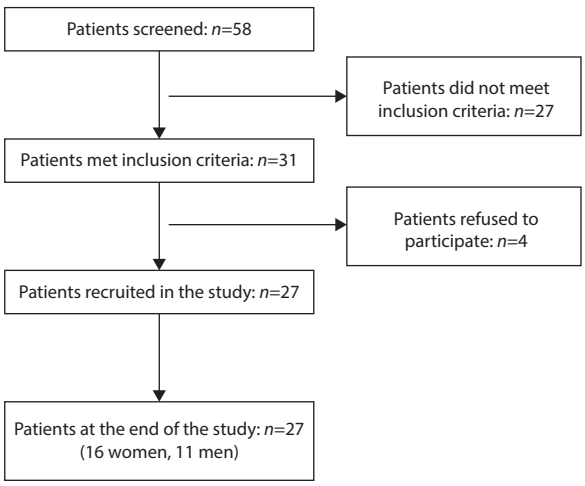
Variables	Intervention (mean values ± SD)
General characteristics	
Studied patients	27
Sex (women/men)	16/11
Age, years	65.22 ± 7.16
Anthropometric measure	
BMI, kg/m^2	27.60 ± 2.01
Evacuation	
Normal	9 (33%)
Constipation	7 (26%)
Diarrhea	11 (41%)
Blood tests	
Glycemia (mg/dL)	87.74 ± 13.56
AST (U/L)	19.60 ± 5.81
ALT (U/L)	21.04 ± 11,18
GGT (U/L)	21.41 ± 8.30
Creatinine (mg/dL)	0.79 ± 0.19

AST, aspartate transaminase; ALT, alanine transaminase; GGT, gamma glutamyl transferase

Results

A total of 27 patients (16 women and 11 men) were included in the study, with a mean (±SD) age of 65.22 (±7.16) years. Figure 1 shows the flow diagram for inclusion in the study, while Table 1 provides the baseline descriptive characteristics of patients. Thirteen patients required additional treatment with spasmolytic drugs and/or non-opioid analgesics, while 14 did not receive any additional medication. On day 11, 2 patients were also treated with an antibiotic (deviation from the protocol) due to worsening pain. Table 2 reports the frequencies of pain score after 10, 20, and 30 days of CBP supplementation and shows that it is efficacious within 10 days, subsequently maintaining its efficacy almost constant until the 30th day of intervention. After 30 days of CBP supplementation, 21 patients (77%) reported a pain intensity score lower or equal to 1. Only 1 patient (additionally treated with antibiotics) at the end of the observation period reported a pain score equal to 7. Table 3 reports the frequencies of GAE at the end of the study. Figures 2 and 3 respectively show the mean pain intensity score over time for (1) all the patients analyzed and (2) separately for the three different defecation groups (diarrhea, normal, and constipation). These plots suggest that CBP supplementation reduces the pain sensation over time and that this effect is more marked for patients with diarrhea and normal defecation as compared to those with constipation. In 18% of patients, the disappearance of symptoms (pain score ≤1) was observed before day 7, whereas symptoms disappeared between days 7 and 10 in 52% of patients and in 18% of patients after 10 days; for three patients, a pain score of >1 was observed. Figure 4 shows the boxplots of SPID over clinically relevant periods for all the patients and for each defecation group.

Figure 1. Flow diagram of the participants.



The primary endpoint was the change in intensity of lower abdominal pain during the 30 days of treatment. The global evaluation of the effect of CBP supplementation on lower abdominal pain intensity over time was analyzed using a CLMM. Table 4 shows the estimate (β), standard error, and *p* value of time on pain score.

Table 2. Frequencies of pain scores after 10 days, 20 days, and 30 days of supplementation.

Score	10 days	20 days	30 days
	Study group		
(*n*=27)			
0	5 (19%)	11 (41%)	12 (44%)
1	10 (37%)	4 (15%)	9 (33%)
2	4 (15%)	9 (33%)	2 (7%)
3	4 (15%)	–	2 (7%)
4	2 (7%)	–	1 (4%)[a]
5	–	1 (4%)[a]	–
6	–	1 (4%)	–
7	–	1 (4%)[a]	1 (4%)[a]
8	–	–	–
9	–	–	–

Study group (*n*=27).

[a]Patients additionally treated with antibiotics.

Table 3. Frequencies of global assessment of efficacy at the end of the study.

Variable	Frequency
Global assessment of efficacy	
Ineffective	2 (7%)
Moderately effective	7 (26%)
Effective	11 (41%)
Very effective	7 (26%)

The sensitivity analysis reported the results obtained excluding the two patients treated with additional antibiotics and then assessed the presence of significant interaction between time and defecation group, comparing the goodness-of-fit of the two models (interaction *versus* no interaction) via LRT (p=0.06). Given the small sample size and the low power of the interaction test, a p<0.10 can be considered as statistically significant. Thus, we explored the effect of time in each defecation group stratifying the data by groups and testing the effect of time separately within each group. Table 5 reports the estimate (β), standard error, and p value of the time on pain score separately for each patient group as defined by the different types of defecation. Coefficients of the CLMM are interpreted as log odds of being in the higher level of outcome *versus* the combined middle and low categories for a one-unit increase in time given all of the other variables in the model are held constant.

We then calculated SPIDs over clinically relevant periods and using the non-parametric Wilcoxon signed rank test we compared $SPID_{1–10}$ with $SPID_{11–20}$ (p<0.0001) and $SPID_{11–20}$ with $SPID_{21–30}$ (p=0.005). We observed a statistically significant decreasing trend in SPID over the three reference periods (β=–13.61, 95% CI 16.53 to –10.69; p<0.0001) by using a linear growth model. By fitting the spline model we observed a statistically significant decreasing linear trend from $SPD_{1–10}$ to $SPD_{11–20}$ (β=–24.04, 95% CI –28.90 to –19.18; p<0.0001) and a non-statistically significant decreasing linear trend from $SPD_{11–20}$ to $SPD_{21–30}$ (β=–3.18, 95% CI –8.04 to 1.67; p=0.19).

Accounting for secondary outcomes, complete pain relief (NRS ≤1) was reported by 89% of patients, with a median time to complete pain relief of 9.5 days. Thirteen patients required additional spasmolytic and analgesic therapy. As shown in Table 2, the GAE, assessed by each patient, was ranked as 'very effective' or 'effective', respectively, by 26% and 41% of patients, while 26% of patients described efficacy as 'moderately effective' and only 7% as 'ineffective.' The correlation between GAE at the end of the study and pain score at day 1 was calculated by Spearman rank-order both in the

Figure 2. Mean pain intensity score (and standard deviation) over time for all patients.

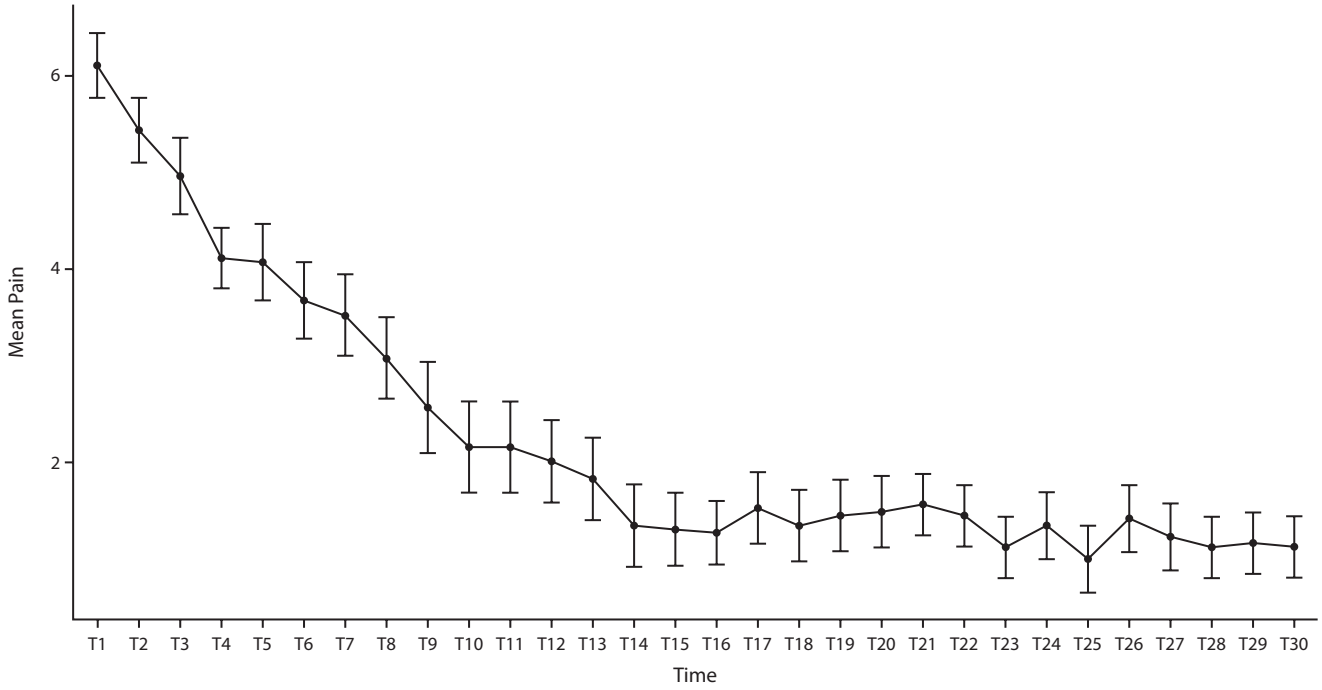


Figure 3. Comparison of mean pain intensity score over time by type of defecation.

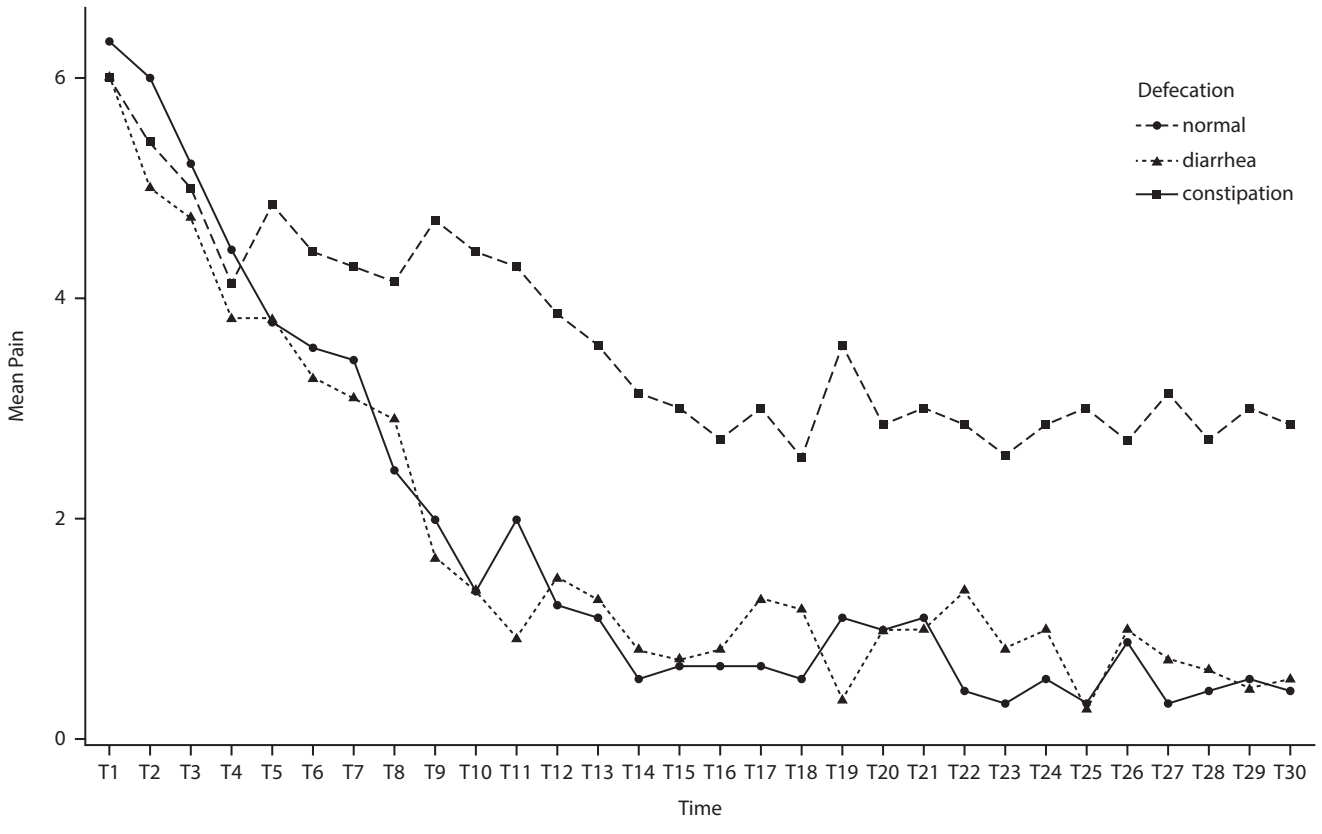


Figure 4. **Boxplots of the sum of pain intensity difference (SPID) over clinically relevant periods ($SPID_{1–10}$, $SPID_{11–20}$, $SPID_{21–30}$) for all patients and separately for each defecation group. The horizontal line within each box plot represents the median of SPID, while the first quartile marks one end of the box and the third quartile marks the other end of the box. The upper and lower vertical lines represent the maximum and the minimum value, respectively, while the dots outside the whiskers represent outlier ratings.**

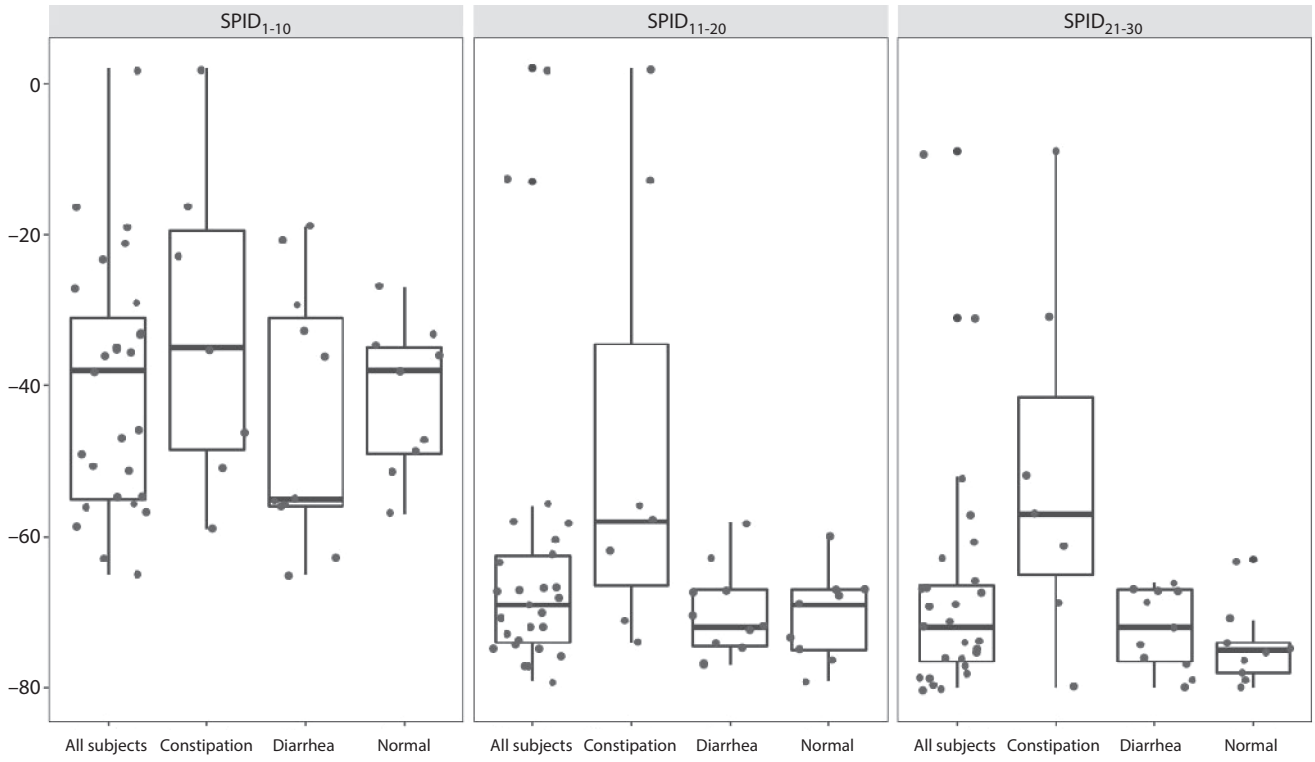


Table 4. **Results from the Cumulative Link Mixed Model investigating the effect of supplementation on abdominal pain in all included patients.**

	β	Standard error	*p* value	β[a]	Standard error[a]	*p* value[a]
Time	−0.24	0.03	<0.0001	−0.25	0.03	<0.0001

[a]Analysis performed excluding the two patients treated with additional antibiotics. All models were adjusted for sex, age, and additional drugs.

Table 5. **Results from the Cumulative Link Mixed Model investigating the effect of supplementation on abdominal pain in all included patients according to defecation type.**

Defecation	β	Standard error	*p* value	β[a]	Standard error[a]	*p* value[a]
Constipation	−0.18	0.07	0.01	−0.23	0.10	0.02
Diarrhea	−0.21	0.04	<0.0001	–	–	–
Normal	−0.30	0.04	<0.0001	–	–	–

[a]Analysis performed excluding the two patients treated with additional antibiotics. As these two patients belong to the group 'constipation', the analysis was repeated only for this group. All models were adjusted for sex, age, and additional drugs

entire sample (ρ=0.36, p=0.06) and separately in the three defecation groups (diarrhea: ρ=0.44, p=0.18; constipation: ρ=0.07, p=0.88; normal: ρ=0.25, p=0.51). An independent sample Kruskal–Wallis test showed no statistically significant differences between defecation group and GAE (p=0.46).

We created binary variables, assigning a value equal to 0 for GAE 1 and 2 and a value equal to 1 for GAE 3 or 4 and tested the association between defecation group (independent variable) and binary GAE (dependent variable) using a logistic model. No significant association between binary GAE and defecation groups was observed.

Discussion

For the first time, the potential use of a supplementation based on a food-grade lecithin formulation of CBP standardized extracts was investigated. This association in phytosome could represent an interesting alternative to the use of pharmacological therapies for the relief of SUDD symptoms and specifically of abdominal pain, thus avoiding the risk of unwanted effects and complications due to drug treatments. In fact, this study shows that the innovative formulation of this association is efficacious and safe in patients with SUDD.

This one-group longitudinal explanatory study shows that treatment of SUDD for 30 days with CBP is followed by a significant decrease in abdominal pain. The statistical analysis demonstrates that the result is significant regardless of the inclusion of the two cases who received additional antibiotics. This result is of relevant importance as abdominal pain is the most important symptom in SUDD and, to date, an optimal treatment for this symptom has not been identified. Similar results were obtained by Bafutto et al.,[38] who treated 12 patients with SUDD with 2 g of curcumin for 30 days with a significant reduction in abdominal pain intensity. Moreover, these authors showed a reduction in abdominal distension as well as a reduction in fecal calprotectin levels (neither of these parameters have been evaluated in the present study).

Additionally, as shown in Table 4, the bowel habit seems to influence the treatment response. Patients with normal bowel function or with diarrhea showed a highly significant result. We also observed a significant therapeutic effect and thus a decreasing pain trend in patients with constipation, although of a lesser magnitude (Figure 2).

The trend over time is also clear from the boxplots of SPID over three clinically relevant periods ($SPID_{1–10}$, $SPID_{21–20}$, $SPID_{31–30}$) for all patients and separately by defecation group (Figure 3). Nevertheless, the influence of bowel behavior has to be confirmed with controlled studies with a larger number of patients.

A statistically significant decreasing trend of SPID over the three time periods was observed by fitting a linear growth model (p<0.0001). When a spline model was activated dividing the data into two segments, the analysis showed a marked decreasing trend of abdominal pain in the first spline (up to the transition point, i.e. $SPID_{11–20}$), while the second spline showed a slight and non-statistically significant decrease. This linear mixed model demonstrates a marked effect of CBP supplementation on abdominal pain in patients with SUDD in the early stage of intervention and that it becomes almost stable, with an additional slight pain decrease, in the second half of the intervention. Indeed, in 18% of patients, the disappearance of symptoms (pain score ≤1) was observed before day 7, whereas symptoms disappeared in 52% of patients between days 7 and 10, and in 18% of patients after day 10; a pain score ≤1 was not observed in 12% of patients. The median time to complete pain relief was 9.5 days, which is similar to the results of Kruis et al.[32] after treatment of SUDD pain with mesalazine (8.0 days).

The GAE based on a subjective judgment of patients at the end of the study was favorable and in line with the results of the statistical analysis. Indeed, 26% of patients stated that the treatment was very effective (absence of symptoms), 41% had a marked improvement of symptoms, 26% had a slight improvement, and only 7% reported treatment to be ineffective.

In order to understand the potential mechanisms of action of CBP supplementation in patients with SUDD, a careful analysis of the etiology of SUDD symptoms is required. Although the pathogenesis of symptoms is not completely understood, low-grade colonic mucosal inflammation could represent the major factor.[7] Low-grade inflammation, followed by abnormal activation of intrinsic effects and extrinsic afferent primary neurons, associated with neural and muscle dysfunction, could represent the basic pathogenic aspect of SUDD.[39]

The efficacy of the supplementation with CBP on pain relief in patients with SUDD may be due to various reasons. The anti-inflammatory effect of both curcumin and boswellia extracts must be underlined, as it could play a major role for the relief of SUDD. Curcumin is a compound mostly known for its anti-inflammatory effect[40,41] and extracts of *B. serrata* resin have also been shown to have anti-inflammatory activity.[40–42]

The efficacy of Boswellia extracts in the treatment of SUDD symptoms was previously hypothesized by Tursi et al.,[42] who positively treated a group of patients with an association of natural active ingredients, including *B. serrata*, inulin, niacin, cranberry, vitamins B1, B2, B6 and B12, zinc, and folic acid. The anti-inflammatory effect of the association of curcumin and boswellia extracts supplemented as CBP would mimic the anti-inflammatory activity revealed for mesalazine that has been shown to be better than placebo in reducing symptoms in patients with SUDD.[43]

Furthermore, recent studies have demonstrated alterations of gut microbiota in patients with diverticular disease.[44] Probiotics and poorly absorbable antibiotics, such as rifaximin, have been described as potential effective therapies in SUDD due to their eubiotic effects.[45–47] The potential of curcumin in the relief of SUDD may not only rely on its anti-inflammatory effect but also on its effect on microbiota.[48] *In vitro*, animal, and human studies investigating the effects of curcumin on intestinal microbiota, intestinal permeability, gut inflammation, and oxidative stress have shown several changes that could positively influence SUDD

symptoms as well as many other intestinal diseases.[49] Curcumin may favor the growth, proliferation, or survival of beneficial components of the gut microbiota. In fact, curcumin significantly modifies the ratio between beneficial and pathogenic microbiota by increasing the presence of *Bifidobacteria*, *Lactobacilli*, and butyrate-producing bacteria and by reducing the abundance of *Prevotellaceae*, *Coriobacteriaceae*, *Enterobacteria*, and *Enterococci*.[48] Curcumin-supplemented animals showed fewer pro-inflammatory *Enterobacteria* and *Enterococci* and higher anti-inflammatory *Bifidobacteria* and *Lactobacilli* loads.[50] Moreover, curcumin undergoes enzymatic modifications by bacteria, forming pharmacologically more active metabolites than curcumin itself.[51] This has also been recently reported for its phytosome formulation, which showed beneficial effects with a more efficient biotransformation of curcuminoids by human microbiota and a higher production of colonic metabolites, without altering the natural profile of curcumin metabolites.[52]

B. serrata also has bactericidal properties due to the presence of boswellic acids and various aromatic compounds.[53,54] Ismail et al.[55] showed that total bacteria count, *Escherichia coli*, and *Salmonella* populations were lower in the cecum of rabbits supplemented with boswellia as compared to the control group. In addition, studies with probiotics showed positive results in terms of strain variability in different growth conditions, reporting no negative interactions between probiotics and a boswellia formulated phytosome.[56]

Moreover, *B. serrata* preserves the intestinal epithelial barrier from oxidative and inflammatory damage.[57] This could be an important benefit when combined with curcumin, which could also act as an antinociceptive agent. In an ulcerative colitis rat model, the oral supplementation of curcumin reduces visceral hyperalgesia.[58] The analgesic effect could be partially due to the downregulation of the colonic expression and phosphorylation of TRPV1 on the afferent fibers projected from peptidergic and non-peptidergic nociceptive neurons of dorsal root ganglion as demonstrated by Zhi et al.[59]

In our study, compliance was very good as we did not observe drop out and all patients took the planned tablets of CBP. Moreover, the supplement appeared safe; no adverse event was reported and laboratory analysis of urine and serum samples at the end of the study did not show abnormalities. Only two cases showed an increase in pain during the study for which therapy with antibiotics was added, yet both patients completed the study with proper CBP pill intake until day 30.

A limitation of this study is the lack of a randomized control group, which does not allow us to draw causal conclusions on the effect of the treatment on the outcome analyzed. Despite this limitation, the study has offered the opportunity to compare the difference between pre- and post-treatment measurements, thus investigating the potential effect of CBP supplementation. This is a pilot study planned in order to evaluate the potential efficacy of this treatment as well as the safety of this formulation as, to date, no study has been conducted to assess the association of curcumin and boswellia in patients with SUDD. The absence of a control group is a major limitation of the study; however, the positive results obtained in terms of the potential effectiveness of this treatment in patients with SUDD as well as its safety, based on the absence of relevant side effects, should be considered very promising. Another limitation of this study is the absence of fecal calprotectin assessment and of serum C-reactive protein that may improve the clinical diagnosis of SUDD and allow a more complete evaluation of the effect of the therapeutic intervention. Furthermore, patients self-reported their pain and symptoms and there was no placebo in the study; therefore, the results could be influenced by a bias or confounding effect of patient perception. Nevertheless, the promising results of this study are useful in informing the scientific community about this new and safe potential therapeutic approach and stimulate the realization of controlled studies.

Conclusions

The treatment of SUDD symptoms is still a matter of debate despite probiotics, rifaximin, and mesalazine having been suggested as therapeutic options.[8] This clinical study indicates that the innovative association of curcumin and boswellia extracts in a food-grade phytosome delivery system may be useful for the relief of SUDD abdominal pain. However, additional and controlled studies need to be performed in order to obtain final conclusions.

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References

1. Bugiantella W, Rondelli F, Longaroni M, Mariani E, Sanguinetti A, Avenia N. Left colon acute diverticulitis: an update on diagnosis, treatment and prevention. *Int J Surg*. 2015;13:157–164. https://doi.org/10.1016/j.ijsu.2014.12.012
2. Shahedi K, Fuller G, Bolus R, et al. Long-term risk of acute diverticulitis among patients with incidental diverticulosis found during colonoscopy. *Clin Gastroenterol Hepatol*. 2013;11(12):1609–1613. https://doi.org/10.1016/j.cgh.2013.06.020
3. Cuomo R, Barbara G, Pace F, et al. Italian consensus conference for colonic diverticulosis and diverticular disease. *United Eur Gastroenterol J*. 2014;2(5):413–442. https://doi.org/10.1177/2050640614547068
4. Tursi A, Papa A, Danese S. Review article: the pathophysiology and medical management of diverticulosis and diverticular disease of the colon. *Aliment Pharmacol Ther*. 2015;42(6):664–684. https://doi.org/10.1111/apt.13322
5. Tursi A. Diverticular disease: a therapeutic overview. *World J Gastrointest Pharmacol Ther*. 2010;1(1):27–35. https://doi.org/10.4292/wjgpt.v1.i1.27
6. Tursi A. Irritable bowel syndrome and diverticular disease: association or misdiagnosis. *Am J Gastroenterol*. 2010;105(10):2293. https://doi.org/10.1038/ajg.2010.198
7. Tursi A. Diverticular disease of the colon and irritable bowel syndrome: it is time to differentiate. *Am J Gastroenterol*. 2015;110(5):774–775. https://doi.org/10.1038/ajg.2015.78
8. Carabotti M, Annibale B. Treatment of diverticular disease: an update on latest evidence and clinical implications. *Drugs Context*. 2018;7:212526. https://doi.org/10.7573/dic.212526
9. Tursi A, Picchio M, Elisei W, Di Mario F, Scarpignato C, Brandimarte G. Current management of patients with diverticulosis and diverticular disease: a survey from the 2nd International Symposium on Diverticular Disease. *J Clin Gastroenterol*. 2016;50(Suppl 1):S97–S100. https://doi.org/10.1097/MCG.0000000000000645
10. Tursi A. New physiopathological and therapeutic approaches to diverticular disease: an update. *Expert Opin Pharmacother*. 2014;15(7):1005–1017. https://doi.org/10.1517/14656566.2014.903922
11. Picchio M, Elisei W, Tursi A. Mesalazine to treat symptomatic uncomplicated diverticular disease and to prevent acute diverticulitis occurrence. A systematic review with meta-analysis of randomized, placebo-controlled trials. *J Gastrointestin Liver Dis*. 2018;27(3):291–297. https://doi.org/10.15403/jgld.2014.1121.273.pic
12. Perrone D, Ardito F, Giannatempo G, et al. Biological and therapeutic activities, and anticancer properties of curcumin (Review). *Exp Ther Med*. 2015;10(5):1615–1623. https://doi.org/10.3892/etm.2015.2749
13. Tabrizi R, Vakili S, Akbari M, et al. The effects of curcumin-containing supplements on biomarkers of inflammation and oxidative stress: a systematic review and meta-analysis of randomized controlled trials. *Phyther Res*. 2019;33(2):253–262. https://doi.org/10.1002/ptr.6226
14. Tursi A, Elisei W, Brandimarte G, et al. Musosal tumour necrosis factor α in diverticular disease of the colon is overexpressed with disease severity. *Color Dis*. 2012;14(5):e258–63. https://doi.org/10.1111/j.1463-1318.2012.02926.x
15. Tursi A, Elisei W, Giorgetti GM, et al. Expression of basic fibroblastic growth factor, syndecan 1 and tumour necrosis factor α in resected acute colonic diverticulitis. *Colorectal Dis*. 2014;16(3):O98–103. https://doi.org/10.1111/codi.12504
16. Cuomo J, Appendino G, Dern AS, et al. Comparative absorption of a standardized curcuminoid mixture and its lecithin formulation. *J Nat Prod*. 2011;74(4):664–669. https://doi.org/10.1021/np1007262

17. Asher GN, Xie Y, Moaddel R, et al. Randomized pharmacokinetic crossover study comparing 2 curcumin preparations in plasma and rectal tissue of healthy human volunteers. *J Clin Pharmacol*. 2017;57(2):185–193. https://doi.org/10.1002/jcph.806
18. Szymanski MC, Gillum TL, Gould LM, Morin DS, Kuennen MR. Short-term dietary curcumin supplementation reduces gastrointestinal barrier damage and physiological strain responses during exertional heat stress. *J Appl Physiol*. 2018;124(2): 330–340. https://doi.org/10.1152/japplphysiol.00515.2017
19. Siddiqui MZ. *Boswellia serrata*, a potential antiinflammatory agent: an overview. *Indian J Pharm Sci*. 2011;73(3):255–261. https://doi.org/10.4103/0250-474X.93507
20. Abdel-Tawab M, Werz O, Schubert-Zsilavecz M. *Boswellia serrata*: An overall assessment of in vitro, preclinical, pharmacokinetic and clinical data. *Clin Pharmacokinet*. 2011;50(6):349–369. https://doi.org/10.2165/11586800-000000000-00000
21. Banno N, Akihisa T, Yasukawa K, et al. Anti-inflammatory activities of the triterpene acids from the resin of *Boswellia carteri*. *J Ethnopharmacol*. 2006;107(2):249–253. https://doi.org/10.1016/j.jep.2006.03.006
22. Poeckel D, Werz O. Boswellic acids: biological actions and molecular targets. *Curr Med Chem*. 2006;13(28):3359–3369. https://doi.org/10.2174/092986706779010333
23. Riva A, Morazzoni P, Artaria C, et al. A single-dose, randomized, cross-over, two-way, open-label study for comparing the absorption of boswellic acids and its lecithin formulation. *Phytomedicine*. 2016;23(12):1375–1382. https://doi.org/10.1016/j.phymed.2016.07.009
24. Pellegrini L, Milano E, Franceschi F, et al. Managing ulcerative colitis in remission phase: usefulness of Casperome®, an innovative lecithin-based delivery system of *Boswellia serrata* extract. *Eur Rev Med Pharmacol Sci*. 2016;20(12):2695–2700.
25. Belacaro G, Gizzi G, Pellegrini L, et al. Supplementation with a lecithin-based delivery form of *Boswellia serrata* extract (Casperome®) controls symptoms of mild irritable bowel syndrome - PubMed. *Eur Rev Med Pharmacol Sci*. 2017;21(9): 2249–2254.
26. Riva A, Giacomelli L, Totogni S, et al. Oral administration of a lecithin-based delivery form of boswellic acids (Casperome®) for the prevention of symptoms of irritable bowel syndrome: a randomized clinical study. *Minerva Gastroenterol Dietol*. 2019;65(1):30–35. https://doi.org/10.23736/S1121-421X.18.02530-8
27. Governa P, Marchi M, Cocetta V, et al. Effects of *Boswellia serrata* roxb. and *Curcuma longa* L. in an in vitro intestinal inflammation model using immune cells and caco-2. *Pharmaceuticals*. 2018;11(4). https://doi.org/10.3390/ph11040126
28. Kizhakkedath R. Clinical evaluation of a formulation containing *Curcuma longa* and *Boswellia serrata* extracts in the management of knee osteoarthritis. *Mol Med Rep*. 2013;8(5):1542–1548. https://doi.org/10.3892/mmr.2013.1661
29. Belcaro G, Cesarone MR, Dugall M, et al. Efficacy and safety of Meriva®, a curcumin-phosphatidylcholine complex, during extended administration in osteoarthritis patients. *Altern Med Rev*. 2010;15(4):337–344.
30. El Sherif FA, Othman AH, Abd El-Rahman AM, Taha O. Effect of adding intrathecal morphine to a multimodal analgesic regimen for postoperative pain management after laparoscopic bariatric surgery: a prospective, double-blind, randomized controlled trial. *Br J Pain*. 2016;10(4):209–216. https://doi.org/10.1177/2049463716668904
31. Brodribb AJM. Treatment of symptomatic diverticular disease with a high-fibre diet. *Lancet*. 1977;309(8013):664–666. https://doi.org/10.1016/S0140-6736(77)92112-2
32. Kruis W, Meier E, Schumacher M, Mickisch O, Greinwald R, Mueller R. Randomised clinical trial: Mesalazine (Salofalk granules) for uncomplicated diverticular disease of the colon - A placebo-controlled study. *Aliment Pharmacol Ther*. 2013;37(7):680–690. https://doi.org/10.1111/apt.12248
33. Green P, MacLeod CJ. SIMR : an R package for power analysis of generalized linear mixed models by simulation. *Methods Ecol Evol*. 2016;7(4):493–498. https://doi.org/10.1111/2041-210X.12504
34. Package "simr." Power analysis for generalised linear mixed models by simulation. https://cran.r-project.org/web/packages/simr/index.html
35. Agresti A. Modelling ordered categorical data: recent advances and future challenges. *Stat Med*. 1999;18(17–18):2191–2207. https://doi.org/10.1002/(sici)1097-0258(19990915/30)18:17/18<2191::aid-sim249>3.0.co;2-m
36. Agresti A. *Categorical Data Analysis*. Hoboken, NJ: Wiley; 2002.
37. R Core Team. *R: A Language and Environment for Statistical Computing*; 2017. https://www.gbif.org/tool/81287/r-a-language-and-environment-for-statistical-computing. Accessed June 4, 2019.
38. Bafutto M, Cherubin D, Cruvinel Dionis MV, de Franco Alcântara PH, De Oliveira EC, Joffre Rezende F. Evaluation showed of curcumin in the treatment of symptomatic uncomplicated diverticular disease. *J Gastrointest Liver Dis*. 19AD;28(4):67–68.
39. Scarpignato C, Barbara G, Lanas A, Strate LL. Management of colonic diverticular disease in the third millennium: Highlights from a symposium held during the United European Gastroenterology Week 2017. *Therap Adv Gastroenterol*. 2018;11:1756284818771305. https://doi.org/10.1177/1756284818771305
40. Iqbal M, Sharma SD, Okazaki Y, Fujisawa M, Okada S. Dietary supplementation of curcumin enhances antioxidant and phase II metabolizing enzymes in ddY male mice: possible role in protection against chemical carcinogenesis and toxicity. *Pharmacol Toxicol*. 2003;92(1):33–38. https://doi.org/10.1034/j.1600-0773.2003.920106.x

41. Jurenka JS. Anti-inflammatory properties of curcumin, a major constituent of *Curcuma longa*: a review of preclinical and clinical research. *Altern Med Rev*. 2009;14(2):141–153.
42. Tursi A, Brandimarte G, Mario F Di, Elisei W, Picchio M. Efficacy and safety of a new nutraceutical formulation in managing patients with symptomatic uncomplicated diverticular disease: a 12-month, prospective, pilot study. *J Gastrointest Liver Dis*. 2018;27(2):201–205. https://doi.org/10.15403/jgld.2014.1121.272.fef
43. Picchio M, Elisei W, Brandimarte G, et al. Mesalazine for the treatment of symptomatic uncomplicated diverticular disease of the colon and for primary prevention of diverticulitis: a systematic review of randomized clinical trials. *J Clin Gastroenterol*. 2016;50:S64–S69. https://doi.org/10.1097/MCG.0000000000000669
44. Lopetuso LR, Petito V, Graziani C, et al. Gut microbiota in health, diverticular disease, irritable bowel syndrome, and inflammatory bowel diseases: time for microbial marker of gastrointestinal disorders. *Dig Dis*. 2017;36(1):56–65. https://doi.org/10.1159/000477205
45. Cuomo R, Barbara G, Annibale B. Rifaximin and diverticular disease: position paper of the Italian Society of Gastroenterology (SIGE). *Dig Liver Dis*. 2017;49(6):595–603. https://doi.org/10.1016/j.dld.2017.01.164
46. Ponziani FR, Zocco MA, D'Aversa F, Pompili M, Gasbarrini A. Eubiotic properties of rifaximin: Disruption of the traditional concepts in gut microbiota modulation. *World J Gastroenterol*. 2017;23(25):4491–4499. https://doi.org/10.3748/wjg.v23.i25.4491
47. Lahner E, Bellisario C, Hassan C, Zullo A, Esposito G, Annibale B. Probiotics in the treatment of diverticular disease. A systematic review. *J Gastrointest Liver Dis*. 2016;25(1):79–86. https://doi.org/10.15403/jgld.2014.1121.251.srw
48. Shen L, Ji HF. Bidirectional interactions between dietary curcumin and gut microbiota. *Crit Rev Food Sci Nutr*. 2019;59(18):2896–2902. https://doi.org/10.1080/10408398.2018.1478388
49. Lopresti AL. The problem of curcumin and its bioavailability: could its gastrointestinal influence contribute to its overall health-enhancing effects? *Adv Nutr*. 2018;9(1):41–50. https://doi.org/10.1093/advances/nmx011
50. Bereswill S, Muñoz M, Fischer A, et al. Anti-inflammatory effects of resveratrol, curcumin and simvastatin in acute small intestinal inflammation. *PLoS One*. 2010;5(12):e15099. https://doi.org/10.1371/journal.pone.0015099
51. Pluta R, Januszewski S, Ułamek-Kozioł M. Mutual two-way interactions of curcumin and gut microbiota. *Int J Mol Sci*. 2020;21(3). https://doi.org/10.3390/ijms21031055
52. Bresciani L, Favari C, Calani L, et al. The effect of formulation of curcuminoids on their metabolism by human colonic microbiota. *Molecules*. 2020;25(4). https://doi.org/10.3390/molecules25040940
53. Kiczorowska B, Samolińska W, Ridha Mustafa Al-Yasiry A, Kowalczyk-Pecka D. Effect of *Boswellia serrata* dietary supplementation on growth performance, gastrointestinal microflora, and morphology of broilers. *Anim Sci*. 2016;16(3):835–849. https://doi.org/10.1515/aoas-2016-0007
54. Kiczorowska B, Al-Yasiry A, Science WS-L, 2016 U. The effect of dietary supplementation of the broiler chicken diet with *Boswellia serrata* resin on growth performance, digestibility, and gastrointestinal. *Livest Sci*. 2016;191:117–124. https://www.sciencedirect.com/science/article/pii/S1871141316301706. Accessed March 20, 2020.
55. Ismail IE, Abdelnour SA, Shehata SA, et al. Effect of dietary *Boswellia serrata* resin on growth performance, blood biochemistry, and cecal microbiota of growing rabbits. *Front Vet Sci*. 2019;6:471. https://doi.org/10.3389/fvets.2019.00471
56. Allegrini P, Berlanda D, Donzelli F, Riva A. *Boswellia serrata* fitosoma – Studio in vitro di interazione con probiotici commerciali. *L'integratore Nutr*. 2018;21(4). https://www.ceceditore.com/negozio/riviste/lintegratore-nutrizionale/lintegratore-nutrizionale-4-2018-pdf/
57. Catanzaro D, Rancan S, Orso G, et al. *Boswellia serrata* preserves intestinal epithelial barrier from oxidative and inflammatory damage. *PLoS One*. 2015;10(5):e0125375. https://doi.org/10.1371/journal.pone.0125375
58. Yang M, Wang J, Yang C, Han H, Rong W, Zhang G. Oral administration of curcumin attenuates visceral hyperalgesia through inhibiting phosphorylation of TRPV1 in rat model of ulcerative colitis. *Mol Pain*. 2017;13:1744806917726416. https://doi.org/10.1177/1744806917726416
59. Zhi L, Dong L, Kong D, et al. Curcumin acts via transient receptor potential vanilloid-1 receptors to inhibit gut nociception and reverses visceral hyperalgesia. *Neurogastroenterol Motil*. 2013;25(6):e429–40. https://doi.org/10.1111/nmo.12145