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Curcumin and Fennel Essential Oil Improve Symptoms and Quality of Life in Patients with Irritable Bowel Syndrome

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ABSTRACT

Background & Aims: Irritable Bowel Syndrome (IBS) patients still require effective treatment. The anti-inflammatory property of curcumin and the antispasmodic and carminative effect of fennel suggests that combination of these nutraceutical compounds would be useful in functional bowel disorders including IBS. We assessed the efficacy and tolerability of a combination of curcumin and fennel essential oil (CU-FEO) in IBS symptoms relief.
Methods: 121 patients with mild-to-moderate symptoms of IBS defined by an Irritable Bowel Syndrome-symptom severity score (IBS-SSS) 100-300 and abdominal pain score 30-70 on a 100 mm Visual Analogue Scale (VAS), were randomly assigned to CU-FEO or placebo (2 capsules b.d. for 30 days). Primary endpoint was the mean decrease of IBS-SSS at the end of the treatment corrected for the mean baseline score (relative decrease). The impact of the treatment on quality of life was assessed through IBS-QoL questionnaire.
Results: CU-FEO was safe, well-tolerated and induced symptom relief in patients with IBS; a significant decrease in the mean relative IBS-SSS was observed after 30 days of treatment (50.05 ± 28.85% vs 26.12 ± 30.62%, $P<0.001$). This result matched the reduction of abdominal pain and all the other symptoms of IBS-SSS. The percentage of symptom-free patients was significantly higher in the CU-FEO than in the placebo group (25.9% vs. 6.8%, $P = 0.005$). All domains of IBS-QoL improved consistently.
Conclusion: CU-FEO significantly improved symptoms and quality of life in IBS patients over 30 days.

Key words: abdominal pain – bloating – irritable bowel syndrome – randomized placebo-controlled study.

Abbreviations: AEs: adverse events; CU-FEO: Curcumin-Fennel Essential Oil; GI: gastrointestinal; IBS: irritable bowel syndrome; IBS-D: irritable bowel syndrome-diarrhea; IBS-C: irritable bowel syndrome-constipation; IBS-SSS: Irritable Bowel Syndrome - symptom severity score; NF-kB: nuclear factor-κB; QoL: quality of life; UC: ulcerative colitis; VAS, Visual Analogue Scale.

INTRODUCTION

Irritable bowel syndrome (IBS) is a frequent functional gastrointestinal disorder and one of the most common diagnoses for gastroenterologists and family practitioners. Cardinal symptoms of IBS are episodes of abdominal pain, bloating, and altered bowel habits in the absence of organic abnormalities. Quality of life (QoL) can be strongly affected in IBS patients leading to poor work productivity, and high access to medical health care [1].

Definitive treatment options are still missing in IBS patients with either diarrhea or constipation and might include from time to time dietary modification, laxatives, lubiproston, linaclotide, antidiarrhoeals, alosetron, rifaximin, eluxadoline [2-5].

Further therapies including herbal products have been evaluated in IBS patients but their ultimate role remains elusive [6, 7]. Curcumin-Fennel Essential Oil (CU-FEO) is a nutraceutical product consisting of a combination of two phytonutrients: curcumin, derived from the rhizome (turmeric) of the herb Curcuma longa and fennel essential oil.

In vitro, curcumin displays an anti-inflammatory activity [8], while in the animal model of colitis curcumin reduces mucosal injuries [9-15]. Mechanisms include the modulation of I-kappa B kinase activity, driven by inhibition of nuclear factor-κB (NF-kB) and pro-inflammatory cytokines (tumor necrosis

factor alfa, interleukin 1β and 6) [16-19]. Turmeric (Curcuma longa) has been traditionally used in Indian, Chinese, and Western herbal medicine for managing abdominal pain, and abdominal bloating.

A potential role for curcumin in bowel disorders is supported by a randomized, double blind placebo-controlled study in ulcerative colitis (UC) patients: curcumin (2 g/day) plus sulfasalazine or mesalamine for 6 months, improved the Clinical Activity Index, the endoscopic score and prevented acute UC flares [20]. In a small group of IBS patients [21], curcumin (72 mg or 144 mg given daily for 8 weeks) decreased abdominal pain intensity and improved quality of life.

Anethole, the major component of fennel oil seeds, is chemically similar to the neurotransmitter dopamine, and has a relaxant effect on intestinal smooth muscle, isolated rat uterus [22], and guinea pig trachea rings [23]. In a pilot study on IBS patients, the fennel reduced abdominal pain, a mechanism likely mediated by the anethole-dependent relaxation of intestinal smooth muscle [24].

A major problem related to curcumin efficacy is the low bioavailability due to poor absorption and extensive intestinal metabolism [25, 26]. However, this novel formulation of CU-FEO associates curcumin with an emulsifier that improves the solubility of curcumin in biologic fluids and provides up to 50-fold increase in the bioavailability, if compared with other unformulated curcuminoid mixtures [27].

Based on the effects of curcumin and FEO on bowel symptoms and the emerging role of intestinal inflammation and immune activation in functional bowel diseases including IBS [28], the present study has been designed to verify whether a highly bioavailable combination of curcumin and FEO could effectively ameliorate symptoms and QoL in patients with IBS.

METHODS

Subjects

A total of 121 consecutive patients (M:F = 44:77) with a Rome III diagnosis of IBS (IBS-D subjects 62%, IBS-C subjects 38%) [29] were consecutively recruited within a randomized, double-blind, placebo-controlled trial involving five Italian centers from October 2012 to May 2013. The protocol was approved by the Ethics Committees of each participating center, and all patients gave full written informed consent.

IBS patients of both sexes, ≥18 and ≤ 60 years old were randomized at baseline visit to receive two capsules of either CU-FEO (Curcuma longa L. 42 mg and Foeniculum vulgare Miller Oil 17.5 mg, each capsule kindly provided by Alfa Wassermann S.p.A., Italy) or placebo BID for 30 days under fasting conditions, according to a pre-defined randomisation list, prepared using permuted blocks of size 4 (Fig. 1). The active treatment was undistinguishable from placebo by physical and organoleptic characteristics.

At the baseline visit, the eligible patients had an Irritable Bowel Syndrome Symptom Severity Score (IBS-SSS) ≥ 100 to ≤ 300 points, an abdominal pain / discomfort ≥ 30 and ≤ 70 (measured on a 100 mm VAS) for at least 3 days in the 10 days preceding the enrolment, and at least one of the following symptoms: abdominal distension and dissatisfaction with bowel habits.

Baseline characteristics of the randomized groups according to treatment, sex, age, severity of disease, dissatisfaction with bowel habits, and QoL are reported in Table I.

Exclusion criteria were the presence of inflammatory bowel disease, structural abnormality of the gastrointestinal (GI) tract, GI symptoms lasting for more than 10 years, abdominal surgery within the previous 6 months, biliary duct obstructions, gallstones, positive stool culture for common pathogenic bacteria, drug or alcohol abuse, mental illness, concomitant immunological, haematological or neoplastic disease, severe hepatic insufficiency (i.e., Child-Pugh class C), and severe heart failure (NYHA class III-IV).

Nonsteroidal anti-inflammatory drugs, anticoagulants, antibiotics, fibers or probiotics were not permitted during the two weeks before baseline and throughout the study. Concomitant treatments (i.e. antispasmodic, antiflatulents, triptans, anticholinergics, motility regulating drugs and osmotic laxative, antidepressant or anxiolytic drugs) were allowed at stable doses in the four weeks before randomization and during the whole study. The consumption of such drugs was controlled, minimal and comparable between the two groups at each time point of the study (day 0, 10, 20 and 30). Paracetamol was allowed for no more than three consecutive days. Subjects were asked to maintain their diet for the entire study period.

Study design and procedures

Patients were evaluated at baseline (day 0) and on day 10, 20 and at the end of the study (day 30). At each time point, appropriate questionnaires were completed.

All IBS patients filled the IBS-SSS, developed and validated by Francis et al. [30]. The questionnaire is composed of: 1) two items concerning the presence of abdominal pain and bloating (response yes or no); 2) four visual analogue scales measuring intensity of pain, bloating, relief following defecation, and impact of symptoms on general quality of life; 3) an item on the number of days of suffering during the preceding 10 days. The IBS-SSS questionnaire produces a quantitative score ranging from 0 to 500 for estimation of symptom severity, i.e., symptom remission, if the score is lower than 75, mild symptoms with a score ≥75 and <175, moderate symptoms with a score ≥175 and ≤300 and severe symptoms with scores >300 [30].

The IBS QoL questionnaire [31] was used as a self-reported measure to assess the impact of the treatment on QoL and completed at baseline and at the end of treatment.

Adverse events were carefully evaluated as onset of symptoms, duration and intensity.

Efficacy endpoints

The primary study endpoint was the relative decrease of IBS-SSS [100*(value at post-baseline - value at day 0)/value at day 0]. Secondary endpoints included the absolute change of IBS-SSS [(value at post-baseline day - value at day 0)/value at day 0]; the rate of patients on symptom remission (i.e., IBS-SSS <75); the rate of patients with ≥50% decrease of abdominal pain score compared to baseline; the relative decrease of abdominal pain score; the absolute change of bowel distension and dissatisfaction with bowel habit scores and interference on life at each time-point (baseline, day 10, day 20, final visit at day 30), and the improvement in QoL.

Safety evaluations

Adverse events (AEs) were monitored throughout the study. The duration and intensity of each event were recorded by the investigator, together with its relationship to the study product, and its outcome and seriousness.

Statistical analysis

Data are expressed as mean ± standard deviation (SD), range and percentage. The full analysis included all randomized patients who received at least one dose of investigational product and with at least one post-baseline efficacy assessment. Safety sets of data included all patients randomized who received at least one dose of the investigational product. At each time point, the absolute and relative change from baseline (day 0) for the IBS-SSS Total Score, each single items of IBS-SSS were compared between treatment groups by a paired *t*-test and a mixed model for repeated measures. The number of patients with an absolute IBS-SSS Total Score lower than 75 days at day 30 and the number of patients with a decrease of the relative change from baseline in the IBS-SSS abdominal pain higher than 50% at day 30 were compared between treatments by means of the Chi-square test.

IBS-QoL Total Score and the eight domains were reported at day 0 and day 30 by descriptive statistics. At day 30, the change from baseline was summarised by a treatment group by means of descriptive statistics, and a paired *t*-test was performed within each treatment group. Comparison between treatment groups on the IBS-QoL Total Score and the eight domains were performed with an ANCOVA model with change from baseline as a dependent variable, treatment as fixed effect and baseline value (Day 0) as a covariate. The percentage of patients who were affected by AEs and AEs leading to discontinuation were summarized by the treatment group.

The determination of sample size was carefully performed by a senior biostatistician. The processes and the conduction of the statistical analyses for the clinical trial were based on the ICH E9 "Statistical Principles for Clinical Trials" and on the Standard Operating Procedures of CROS NT s.r.l. A sample size of at least 110 patients (55 evaluable patients per group) was expected to detect a difference of 50 points between the decrease of IBS-SS in the Curcumin-Fennel group and placebo treatments, with a 90% power and a 2-tailed significance level of 0.05, starting from an expected baseline mean value of 180 with a standard deviation of ±80. Assuming a rate of not able to be evaluated patients of approx 10%, up to 120 participants were randomized.

RESULTS

The study flow-chart is depicted in Fig. 1. Two patients (1.7%, one in each treatment arm) were excluded from the safety analysis, because they did not take the study product; another two patients (1.7%, one in each arm) were excluded from the efficacy analysis, because they withdrew their consent before the assessment of any post-baseline efficacy parameter. One patient in the placebo group withdrew from the study after 10 days of treatment due to worsening of gastro-oesophageal reflux and the last non missing post baseline IBS-SSS was carried forward.

Thus, the final analysis was conducted on 116 IBS patients.

Baseline characteristics including age, sex, severity of disease, and IBS-SSS were comparable between groups (Table I). Namely, the patients were primarily female with an average age of 40 and a moderate symptom severity (IBS-SSS ranging from 143 to 300 and abdominal pain symptoms from 30 to 75). The overall baseline IBS-QoL was comparable between the two treatment groups (52.1±20.8 and 53.3±20 in CU-FEO and placebo group, respectively).

Overall, three patients received concomitant permitted medications maintained at a stable dose throughout the study (i.e., omeprazole or esomeprazole for gastroesophageal reflux disease).

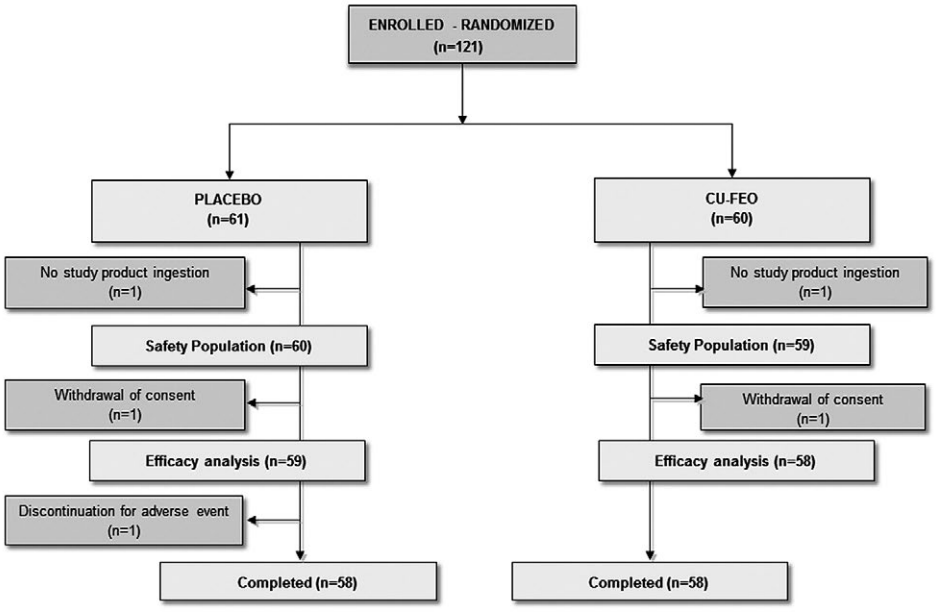

Fig. 1. Study flow chart. After the enrolment, 121 subjects were randomized to placebo and Curcumin-Fennel Essential Oil (CU-FEO). The number of patients that completed the study was 116 (see text for details).

Table I. Baseline characteristics of the study groups

	Placebo (n=58)	CU-FEO (n=58)
Age, years	39.4	41.5
Range	18-66	20-65
Females, n (%)	36 (61.0%)	41 (70.7%)
Mild disease, n (%)	2 (3.4%)	3 (5.2%)
Moderate disease, n (%)	57 (96.6%)	55 (94.8%)
IBS-SSS	263.2 ± 34.4	255.7 ± 39.9
a. Abdominal pain	51.2 ± 13.3	48.9 ± 12.4
b. Number of days without pain	5.8 ± 1.7	6.0 ± 1.8
c. Abdominal distension	51.5 ± 16.5	52.7 ± 13.8
d. Dissatisfaction with bowel habit	61.6 ± 18.5	56.2 ± 18.4
e. Interference with QoL	57.9 ± 16.8	58.0 ± 14.1
IBS-QoL	53.3 ± 20.0	52.1 ± 20.8

IBS-SSS: IBS-symptom severity score; QoL: quality of life
Data are mean ± SD. Differences between groups are not significant (*t*-test, P-value = 0.316).

Efficacy endpoints

Compared with baseline (see Table I), the mean IBS-SSS decreased from 255.7±39.9 to 127.8±77.4 (range 0 – 300) at day 30 with CU-FEO and from 263.2±34.4 to 195.5±88.0 (range 25 - 345) with placebo (Fig. 2A), with a relative decrease significantly greater and almost double with CU-FEO compared with placebo (50.05±28.85% vs. -26.12±30.62%, respectively; P < 0.001), and the adjusted mean difference between treatment at day 30 of -24.04% (95% CI: -35.08; -13.00) (Fig. 2B). Patients on CU-FEO achieved a higher and statistically significant level of complete symptoms free rate (i.e., IBS-SSS <75 points) at day 30, compared to placebo [25.9% (15/58) vs. 6.8% (4/59); P=0.005]. The reduction in the mean IBS-SSS was associated with a statistically significant improvement of all the single items of the IBS-SSS at day 30. Abdominal pain severity had a larger decrease in the CU-FEO group compared to the placebo group (P<0.001) (Fig. 3), with a trend that was already evident at day 10 and became statistically significant at day 20 (P=0.006). Also, a reduction of more than 50% of abdominal pain symptom score from baseline to day 30 was observed: 63.8% (37/58) vs. 27.1% (16/59) (P<0.001) in the CU-FEO and the placebo group, respectively.

Absolute changes from baseline concerning abdominal distension, dissatisfaction with bowel habit, interference with QoL, and number of days in the last 10 days with pain are reported in Table II. The adjusted mean of difference for abdominal distension was already significant at day 10 (P < 0.001), while other parameters improved significantly between day 20 and 30 (0.05<P<0.001).

After 30 days, at the end of treatment, the IBS-QoL total score was significantly greater in the CU-FEO than in placebo group (17.4±19.2 vs. 7.7±18.0, respectively; P = 0.003) with an adjusted mean difference between groups of 9.19 (95% CI: 3.13, 15.25). CU-FEO treatment was associated with a statistically significant improvement in each domain of the IBS-QoL. Individual domains of dysphoria (P= 0.002), interference with activity (P= 0.008), body image (P= 0.003) and food avoidance (P= 0.010) showed the most relevant improvement with CU-FEO.

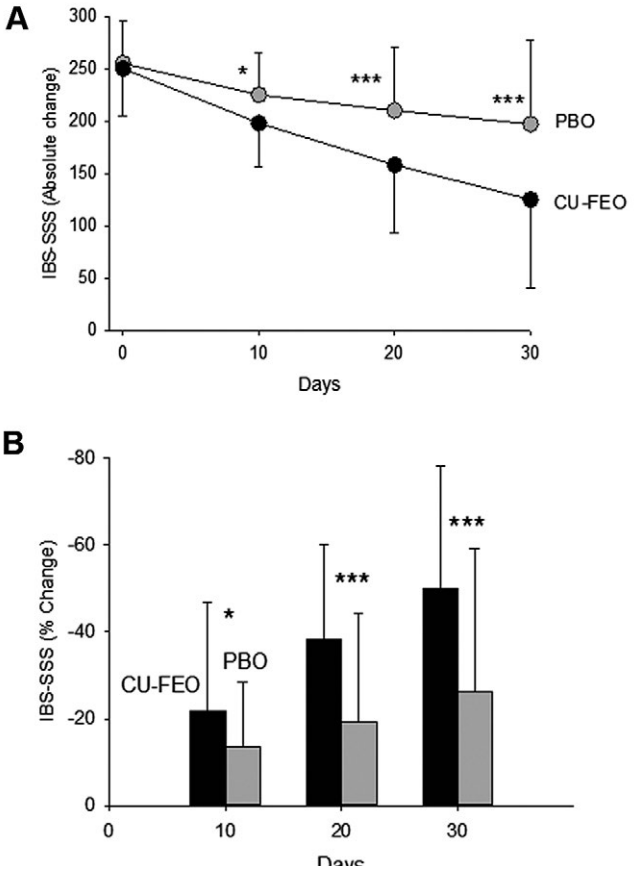

Fig. 2. Absolute (A) and relative (B) time-dependent changes from baseline of IBS-SSS in CU-FEO and Placebo (PBO) treatment groups. Data are mean±SD. Asteriks (*) indicate significant differences between groups at each time point (***P < 0.001; *P < 0.05).

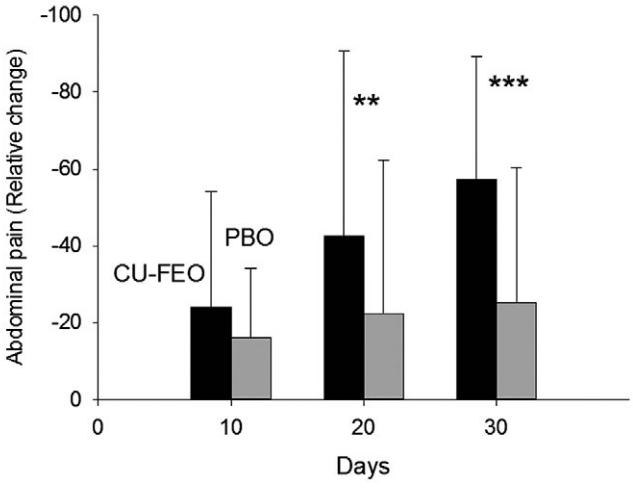

Fig. 3. Relative time-dependent change from baseline of abdominal pain severity in the treatment groups. Data are mean ± SD. Statistical significance between treatment groups was calculated by a mixed model for repeated measures. Asteriks (*) indicate significant differences between groups at each time point (***P < 0.001; **P < 0.01).

Safety

Safety data were obtained from all patients up to 30 days. During the treatment period, no serious AE was recorded. The following AEs were recorded but not related to treatments: nausea (3.4% in placebo), headache (1.7% in CU-FEO) with no differences between the two treatment groups.

Table II. Absolute change from baseline at each time-point in abdominal distension, dissatisfaction with bowel habit, interference with quality of life, number of days in the last 10 days with pain

		IBS-SSS parameters [mean (SD)]			
Time point	Treatment	Abdominal distension	Dissatisfaction with bowel habit	Interference with quality of life	N. of days in the last 10 days with abdominal pain
Baseline	CU-FEO	52.7 (13.8)	56.2 (18.4)	58.0 (14.1)	6.0 (1.8)
	Placebo	51.5 (16.5)	61.6 (18.5)	57.9 (16.8)	5.8 (1.7)
Day 10	CU-FEO	38.3 (15.1)	47.5 (19.2)	47.7 (16.2)	7.2 (2.2)
	Placebo	48.1 (18.3)	51.0 (19.9)	52.1 (18.0)	6.6 (2.3)
	Treatment difference	-10.4 (-16.0; -4.8)	-0.4 (-6.5; 5.7)	-4.4 (-10.2; 1.5)	0.4 (-0.3; 1.1)
	P	<0.001	NS	NS	NS
Day 20	CU-FEO	30.9 (15.5)	40.8 (18.9)	39.9 (16.6)	8.0 (2.0)
	Placebo	44.1 (21.7)	48.6 (18.9)	48.4 (19.7)	7.0 (2.3)
	Treatment difference	-14.2 (-20.7; -7.8)	-5.0 (-10.8; 0.8)	-8.9 (-15.5; -2.4)	1.0 (0.3; 1.7)
	P	<0.001	NS	0.008	0.007
Day 30	CU-FEO	25.3 (18.1)	36.0 (19.6)	32.0 (19.3)	8.6 (1.6)
	Placebo	39.5 (23.1)	45.6 (21.7)	45.6 (21.5)	7.2 (2.3)
	Treatment difference	-15.3 (-22.5; -8.0)	-6.9 (-13.6; -0.2)	-14.0 (-21.2; -6.8)	1.3 (0.6; 2.0)
	P	<0.001	0.042	<0.001	<0.001

Data are adjusted mean of treatment difference (95%CI) on the Full Analysis Set. Better effect is indicated by greater negative difference.

DISCUSSION

In this placebo-controlled study on patients with IBS, the novel nutraceutical combination of curcumin extract and fennel essential oil was highly effective in achieving consistent relief of GI symptoms. The beneficial effect of CU-FEO over placebo was confirmed by significant changes in IBS-SSS as well as in each total score component. Abdominal pain, the most difficult symptom to treat in IBS patients [32] improved with CU-FEO, as demonstrated by a progressive decrease in intensity and a greater proportion of patients reporting ≥50% reduction in abdominal pain. Furthermore, the improvement of IBS-SSS, abdominal pain, and the other bowel symptoms was observed from the first 10 days and throughout the entire treatment period.

The results achieved by CU-FEO in improving QoL and all related domains point to the therapeutic value of this combination. Indeed, IBS causes substantial impairment in health-related QoL and also patients suffering of IBS have increased use of health resources and a reduced work productivity [33].

Furthermore the results from this study indicate that CU-FEO has a good safety profile, as only one single AE was reported in patients receiving CU-FEO.

The patient population included in the trial could be described as mainly female subjects, suffering from abdominal pain and bowel distension and altered bowel habits over at least the previous six months in the absence of any detectable organic disease.

Although the ultimate mechanism of action of CU-FEO in IBS patients remains elusive, the significant improvement in bowel symptoms that was observed in this study could be explained by distinct evidences. Curcumin itself has been shown to have anti-inflammatory properties mediated by suppression of cytokines production (interferon-γ, interleukins and tumor necrosis factor), inhibition of the inducible nitric oxide synthase, as well as NF-κB [34].

Moreover, a pleiotropic effect for curcumin has been advocated and might involve antineoplastic and anticlastogenic properties by interacting with signal transduction and scavenging of free radicals at various levels in the body [35-37]. In this respect, the present and other formulations [38, 39] containing curcumin might further improve its bioavailability and intracellular uptake ability.

The beneficial effect of CU-FEO in this study could be important if one considers the role of intestinal inflammation and immune activation in patients with functional gut disorders. Indeed, the exposure to intestinal infections and psychological stress has been reported as a key contributing factor via the neuroendocrine interaction [28]. In addition, dietary turmeric was suggested to have a role in the activation of bowel motility and carbohydrate colonic fermentation [40] and both FEO [22] and curcumin [41] have a myorelaxant effect.

A noteworthy result of this trial is the response of patients to the placebo, that induced amelioration of symptoms over time. This is a rather expected finding in IBS, as patients can enter spontaneous remission over time; also, placebo response ranges 40-50% in different clinical trials [42]. In this regard a treatment-free follow-up would have ascertained a carry-over effect of the treatment and the persistence of symptom improvement compared to the placebo.

Currently available therapeutical options for IBS include dietary restrictions, fibre supplementation, antidiarrhoeals, smooth muscle relaxants, prokinetics, antidepressant or anxiolytic treatment and psychotherapy. Irritable bowel syndrome is often refractory to these treatments and for several classes of drugs no clear benefits have been observed in randomized clinical trials.

The present study has some limitations and caution should be taken when broadening the results obtained: the relatively small sample of patients and the short-term of the treatment are obvoius limitations of the study. Treatment-free periods, as well as recurrent treatments with CU-FEO need to be considered in future studies. Furthermore, our results need to be supported by larger randomized controlled trials evaluating the effect of CU-FEO on each IBS subtype (diarrhea, constipation and mixed).

CONCLUSION

The present study shows that the administration of a 30-day course of a novel oral combination of two nutraceutical compounds, namely curcumin and fennel oil, results in early and consistent symptomatic relief in IBS patients with both subtypes. The benefit is achieved without safety and tolerability concerns. Further studies should target subpopulations of IBS patients while identifying the ideal treatment periods.

Conflicts of interest: P.Portincasa, D.Festi and A.Gasbarrini served as speakers for and received research funding from Alfa Wassermann. No conflicts of interest for the other authors.

Authors' contributions: Data were collected and analyzed by CROS NT. P.P. and L.B. wrote the draft and the final version of the manuscript. All authors contributed to the clinical study and critically reviewed the manuscript. The corresponding author, also guarantor of the article (P.P.), had full access to all the data and takes full responsibility for the veracity of the data and statistical analysis.

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