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# Efficacy of bio-optimized extracts of turmeric and essential fennel oil on the quality of life in patients with irritable bowel syndrome

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## Abstract

**Background** The use of herbal products to treat irritable bowel syndrome (IBS), a disease that frequently affects the quality of life (QoL), is still under evaluation. This open pilot study assessed the efficacy of bio-optimized extracts of turmeric and essential fennel oil (Enterofytol®) in IBS patients.

**Methods** A total of 211 patients (14% diarrhea-predominant, IBS-D; 24% constipation-predominant, IBS-C; 62% mixed, IBS-M) were enrolled by general practitioners and completed questionnaires measuring symptom severity and QoL before and after Enterofytol®, two capsules b.i.d. for one month, followed by two capsules q.d. for another month.

**Results** IBS severity index and QoL were inversely related. A significant reduction in the severity index and an improvement in QoL were evident following treatment in all IBS subgroups. IBS-D patients showed the worst clinical picture at entry, with the highest IBS severity index and the lowest QoL score, compared with IBS-C and IBS-M subtypes. IBS-D patients, however, also showed the most pronounced response to therapy, considering both scores. The improvement in the IBS severity index was independent of age and sex.

**Conclusions** Results from this "real-life" study show that the combination of turmeric and essential fennel oil over two months improves both symptoms and QoL in IBS patients, irrespectively of age, sex, initial severity of symptoms and IBS-subtypes, suggesting a potential role for the natural treatment of IBS.

**Keywords** Abdominal pain, quality of life, irritable bowel syndrome, curcumin, turmeric, fennel essential oil

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## Introduction

Irritable bowel syndrome (IBS) is a chronic functional disease that significantly affects the quality of life (QoL) [1]. Conventional therapies often have poor outcomes and herbal products are currently being proposed as a useful alternative, although their efficacy is still under evaluation [2]. The combination of curcumin (derived from the turmeric herb *Curcuma longa*) and fennel essential oil improved symptoms and QoL in an Italian short-term double-blind, placebo-controlled multicenter study involving 120 IBS patients [2]. In that study a limited number of subjects (n=60) were randomized to nutraceuticals and enrolled in tertiary referral centers. A potential limitation in that context was the role of dietary habits in the modulation of symptoms [3], since results were collected in a geographical area where subjects consume a typical Mediterranean diet, which might have been responsible for their milder clinical presentation [4]. The aim of this study, therefore, was to verify the "real-life" efficacy of bio-optimized extracts of turmeric and essential oil of fennel in a larger group of IBS subjects diagnosed and recruited by general practitioners (GPs) in Belgium, a geographical area where dietary habits are quite different from those in southern Europe.

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Conflict of Interest: None

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## Patients and methods

### Patients

This observational, prospective, non-controlled, non-randomized pilot study was conducted in the setting of general practice between October 2015 and August 2016. Seventy GPs enrolled a total of 211 patients who fulfilled the Rome III criteria diagnostic criteria for IBS [5]. Exclusion criteria were the presence of "alarm" features (i.e., age of symptom onset after 50 years; rectal bleeding or melena; nocturnal diarrhea; progressive abdominal pain, unexplained weight loss; laboratory abnormalities with iron deficiency anemia, elevated C-reactive protein or fecal calprotectin; or family history of inflammatory bowel disease (IBD) or colorectal cancer). Also excluded were patients with IBD, anatomical gastrointestinal abnormalities, symptoms lasting for more than 10 years, gallstones, positive stool culture, drug or alcohol abuse, concomitant immunological, hematological or neoplastic disease, liver diseases, heart failure with New York Heart Association class III-IV, or a history of abdominal surgery in the previous six months. All subjects were fully informed about the aims of the protocol and had to sign a written informed consent document.

### Questionnaires and follow up

Patients were scheduled for three visits at time 0 (baseline), 30 and 60 days. At baseline, patients underwent a complete clinical examination and completed questionnaires related to IBS severity index, QoL, intestinal habits and the location of pain (see below). The evaluation of the IBS severity index was based on the answers to 4 questions [6] (Table 1). The final score was calculated by summing the scores for each answer. Since each response varied from 0-100, the final score ranged from 0-400 and was proportional to the severity of the syndrome (the higher the index, the greater the IBS severity). The features of intestinal habits depended on another 5 questions [6] (Table 2). Patients were also asked to mark all the locations where they felt abdominal pain on a body graph with the abdomen divided into 9 numbered quadrants. The number of pain locations was recorded for each patient. QoL was assessed according to a validated questionnaire (IBS QoL) [7] with scores ranging from 0-100 (the higher the score, the better the QoL). The IBS severity index, intestinal habits and locations of pain were checked at each time point, whereas the QoL was assessed at baseline and after 60 days.

### Treatment

After baseline evaluation, the therapy consisted of Enterofytol®, containing bio-optimized turmeric extract standardized to 42 mg of curcumin and 25 mg fennel essential oil (trans-anethole). For the first 30 days, the dose consisted of two capsules b.i.d., before meals. Patients were re-evaluated at day 30. The compliance of patients with therapy was checked by interview at the follow-up visits. All patients continued the follow up and were included in the analysis only if they confirmed that they were taking the treatment regularly on a daily basis. At day 30, if the compliance with treatment was adequate, the treatment was reduced to two capsules q.d. before a meal, for another 30 days. A final evaluation was performed at day 60. No other pharmacological treatment known to influence the gastrointestinal tract was allowed during the study. In addition, since the study aimed to evaluate the efficacy of the treatment in real life, patients were maintained on a free diet. The possible appearance of adverse events was monitored throughout the study.

**Table** 1 Assessment of irritable bowel syndrome severity index

| |
|---|
| (1) Are you currently suffering from abdominal pain (belly)? If yes, what is the intensity of your abdominal pain (from 0 = no pain to 100 = very intense pain), and what is the number of days during which you were in pain, over a period of 10 days (from 0-10)? |
| (2) Are you currently suffering from abdominal distension? If so, what is the intensity of your abdominal distension/tension (from 0 = no distension to 100 = very intense distension)? |
| (3) How satisfied are you with your intestinal habits (from 0 = very satisfied to 100 = very dissatisfied)? |
| (4) Indicate to what extent your irritable bowel syndrome affects, or interferes with, your life in general (from 0 = not at all, to 100 = totally)? |

Maximum possible score = 400

**Table 2** Assessment of features of intestinal habits in patients with irritable bowel syndrome

| |
|---|
| (1) What is the maximum number of times you pass stools (per day/week/month) and what is the minimum? |
| (2) Are your stools (1 = often, 2 = sometimes, 3 = never) normal, hard, very thin, in little chunks, soft, liquid? |
| (3) Do you sometimes (0 = no, 1 = yes) find mucus in your stools, find blood in your stools, have to hurry/rush to the toilet to pass stools, have to make efforts to pass stools, get the impression that you have not fully emptied your intestines after passing stools? |
| (4) Do you sometimes (0 = no, 1 = yes) find that your stools are more frequent and softer when you are in pain, find that this pain frequently fades after passing stools? |
| (5) Throughout the past year, how many weeks, approximately, have you been absent from work due to IBS (from 0 = no absence to 52 = complete absence), working while suffering from IBS (from 0 to 52 weeks) |

## Endpoints and sample size

The primary endpoints (outcome measures) in this study were the IBS severity index and the QoL score in the entire enrolled population. Any differences according to IBS subtype and effects on the number of pain locations were considered as secondary outcome measures. The sample size calculation was based on a two-sided test assessing the percentage change (Δ) in IBS severity index and QoL score from baseline to after 30 and 60 days of treatment. The null hypothesis of no change (Δ=0%) was challenged against the alternative hypothesis of a 15% drop from baseline after treatment (Δ=15%). The standard deviation (SD) of the distribution of percentage changes after treatment was set equal to 50%, the power to 90% and the significance level at 1% to account for multiple testing and preserve the overall 5% nominal level. Under these conditions, at least N=166 patients were required for the study.

### Statistical analysis

For quantitative variables, data were summarized as mean and SD. Frequency tables were used for categorical variables. To measure the association between two quantitative variables, the correlation coefficient was calculated and simple linear regression applied. Missing values were not replaced and calculations always used the maximum number of data available for each variable. For the calculation of the overall QoL score, patients with more than 50% unanswered questions were excluded. If less than 50% of the questions were unanswered, the score was calculated on the basis of the answers available and then rescaled to the total allowable 0-100 score. The significance of mean changes between visits was assessed using the paired Student's *t*-test. Linear mixed models were used to compare the time evolutions of IBS severity index and QoL score in IBS subtypes. Results were considered significant at the 5% critical level (P<0.05). All statistical calculations were performed using SAS (version 9.4) and R (version 3.2.2) software.

## Results

### Patient characteristics at entry

Patient characteristics at entry are presented in Table 3. All subjects who completed the study confirmed adequate compliance with treatment. Of the 211 IBS patients who entered the study, 205 (97%) had at least one follow-up visit.

The majority of patients (83%) reported medium intensity abdominal pain, while abdominal distension was present in 88% of patients. Enrolled subjects were generally dissatisfied with their intestinal habits and believed that IBS had a negative impact on their life. The majority of patients (74%) reported a feeling of not completely emptied intestine. Pain, when present, disappeared after passing stools in the majority of patients. IBS generated a mean of 1.5±6.2 weeks of absence from work and patients worked while suffering from IBS symptoms for about 5 months per year.

**Table 3** Characteristics of the 211 patients with symptoms of irritable bowel syndrome (IBS) at entry

| Characteristic | Descriptive statistics |
|---|---|
| Age (years) | 51 ± 17 |
| Females, N (%) | 148 (70) |
| Patients with abdominal pain (N, %) | 173 (83) |
| Pain intensity score (0-100) | 47 ± 27 |
| Number of days with pain in 10 days | 5.8 ± 3.0 |
| Patients with abdominal distension (N, %) | 186 (88) |
| Distension intensity score (0-100) | 50 ± 25 |
| Satisfaction with intestinal habits (0-100)[1] | 62 ± 20 |
| Maximum no. of evacuations/week | 20 ± 14 |
| Minimum no. of evacuations/week | 7.6 ± 7.1 |
| Mucus in stools (N, %) | 81 (38) |
| Rush to toilet (N, %) | 145 (69) |
| Efforts to pass stools (N, %) | 115 (55) |
| Not completely emptied intestine (N, %) | 157 (74) |
| Stools more frequent and softer when in pain (N, %) | 136 (65) |
| Pain fades after passing stools | 145 (69) |
| No. of weeks absent from work due to IBS | 1.5 ± 6.2 |
| No. of weeks working suffering from IBS | 20 ± 19 |
| IBS severity index (0-400) | 218 ± 73 |
| IBS QoL score (0-100)[2] | 60 ± 19 |
| No. of abdominal pain locations | 2.2 ± 1.5 |

Values are number of patients (%) or mean ± SD; [1]range 0 very satisfied - 100 very unsatisfied; [2]range 0 (IBS has no impact on QoL) - 100 (IBS has maximal impact on QoL)

*QoL, Quality of life*

According to the Rome III criteria [5], 30 patients were classified as diarrhea-predominant IBS (IBS-D, 14%, mean age 48.2±21.3 years, 12 male), 50 patients suffered from constipation-predominant IBS (IBS-C, 24%, 52.9±16.3 years, 17 male), and 131 had mixed IBS (IBS-M, 62%, 51.2±15.9 years, 34 male). The three subgroups were homogeneous with regard to age (P=0.52) and sex (P=0.22).

The IBS severity index differed significantly according to IBS subtypes, with IBS-D patients having the highest mean score (268±69.0), compared to IBS-C (221±62.3) and IBS-M (206±72.6) patients (P<0.0001). The IBS QoL score was lower in IBS-D patients (46.0±21.5) than in IBS-C (62.2±17.2) and IBS-M (62.7±17.0) subjects (P<0.0001). Overall, a negative correlation was observed between the IBS QoL score and the

IBS severity index (r=-0.71, P<0.0001) (Fig. 1), whereas the IBS severity index was positively correlated with the number of abdominal pain locations (r=0.42, P<0.0001).

### Treatment efficacy

In the whole group of patients, a significant reduction (29±23%) in the IBS severity index was achieved after 30 days of treatment, with a further significant reduction (17±35%) at the end of the follow up (P<0.0001, Fig. 2). The decline in IBS severity index followed the same path in the 3 IBS subtypes, being more pronounced in IBS-D patients (P=0.007, Fig. 2). At the end of the follow up (60 days), the three subgroups reached similar values (142±50.2, 132±68.1 and 113±63.6 for IBS-D, IBS-C and IBS-M, respectively, P=0.052). Until the end of the study no adverse event was reported in response to therapy.

Overall, the IBS QoL improved from baseline, reaching a mean increment of 31±40% during the 60 days (Fig. 3). The linear mixed modelling of data showed that the greatest increase was in the IBS-D patients (70.4±70.9%), as compared with the IBS-C (24.5±26.5%) and the IBS-M subjects (25.3±29.6%, P<0.0001). After 60 days of treatment, however, the QoL score remained significantly lower in the IBS-D subtype (63.9±17.9) than in IBS-C (74.0±14.3) and IBS-M (73.9±15.1) patients (P<0.0001, Fig. 3).

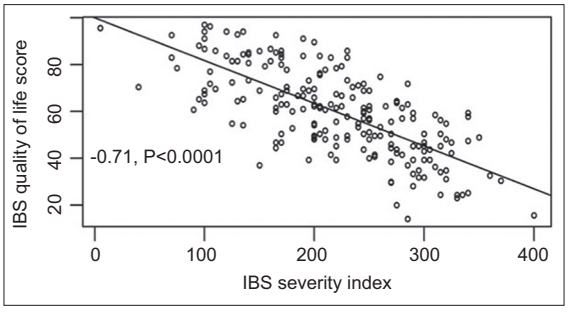


**Figure 1** Relationship between quality of life score and irritable bowel syndrome (IBS) severity index, at enrollment, in a group of 211 IBS patients

Overall, the number of different pain locations dropped from 2.2±1.5 at baseline to 1.6±1.3 and 1.2±1.1 after 30 and 60 days of treatment, respectively (P<0.0001). At the end of the follow up, in the whole group of subjects, the relationships between the IBS severity index and IBS QoL (r=-0.64, P<0.0001) and between the IBS severity index and the number of abdominal pain locations (r=0.34, P<0.0001) were still present.

Overall, the maximum number of weekly evacuations decreased from 20±14 at entry to 15±10 after 30 days (P<0.0001) and to 14±9 after 60 days of treatment (P<0.0001 vs. entry, P=0.0079 vs. 30 days). The minimum number of evacuations fell from 7.6±7.1 at entry to 6.6±5.2 after 30 days and to 5.9±3.5 after 60 days (P<0.0001).

Neither the age nor the sex of enrolled subjects influenced the observed variations in the IBS severity index, in the overall QoL or in the maximum and minimum number of evacuations per week. The reduction in the number of locations of abdominal pain was more pronounced with increasing age, but was not influenced by sex (data not shown).

## Discussion

The results of the present study confirm and expand previous observations about the positive effects of prolonged therapy with bio-optimized extracts of turmeric and essential oil of fennel in adult IBS patients. IBS depends on a complex panel of mechanisms that mainly include genetic [8] and psychosocial factors [9], altered gastrointestinal motility [1], visceral hypersensitivity [10,11], inflammation and hyperalgesia [12,13], and disordered intestinal microbiota [14]. Thus, the therapeutic approach to IBS requires tools that can potentially target the largest number of these elements. It has been previously shown *in vitro* that curcumin, the active component of turmeric (derived from the root of the plant *Curcuma longa*), displays therapeutic, preventive and anti-inflammatory activities through the modulation of a number of molecular targets (i.e., transcription factors, enzymes, cell cycle proteins, cytokines, receptors, cell surface adhesion molecules), influencing their gene expression [15].

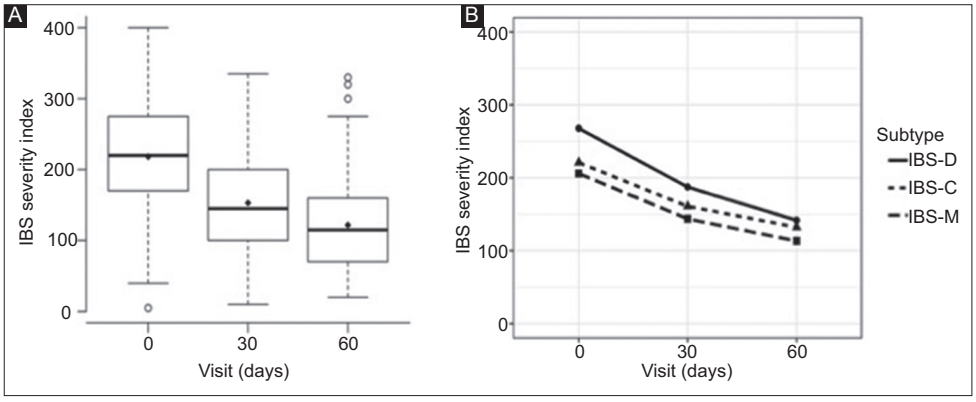


**Figure 2** (A) Irritable bowel syndrome (IBS) severity index at entry and after 30 and 60 days of therapy with bio-optimized extracts of turmeric and essential oil of fennel in 211 IBS patients. (B) Progressive decline in the IBS severity index during 60 days of therapy, according to IBS subtype *IBS-D, IBS diarrhea-predominant; IBS-C, IBS constipation-predominant; IBS-M, IBS mixed-type*

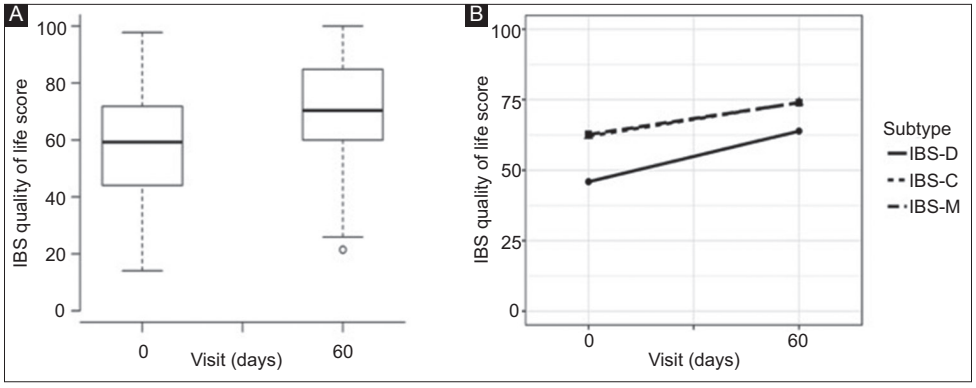


**Figure 3** (A) Irritable bowel syndrome (IBS) quality of life score at entry and after 60 days of therapy with bio-optimized extracts of turmeric and essential oil of fennel in 211 patients with IBS). (B) Variation in the IBS quality of life score during 60 days of therapy, according to IBS subtype *IBS-D, IBS diarrhea-predominant; IBS-C, IBS constipation-predominant; IBS-M, IBS mixed-type*

In particular, curcumin's anti-inflammatory and immune modulating properties mainly derive from the capacity to inhibit the expression of inducible nitric oxide synthase[16], nuclear factor kappa-light-chain-enhancer of activated B cells [16,17], cyclooxygenase-2 [18], microsomal prostaglandin E2 synthase-1 [19], lipoxygenase-5 [19], and many pro-inflammatory cytokines, such as interleukin (IL)-1, IL-2, IL-6, IL-8, IL-12 and tumor necrosis factor-α [20,21]. Curcumin has also been recently identified as a common NLRP3 inflammasome activation inhibitor [22], and is potentially able to downregulate mammalian target of rapamycin complex 1 signaling in the intestinal epithelium, with relevant implications for both tumorigenesis and inflammation [23]. These properties, together with a marked anti-apoptotic effect protecting intestinal cells from inflammatory damage [24,25] and a modulating effect on chronic intestinal inflammation that can reduce intestinal barrier dysfunction [26,27], led curcumin to be suggested as a treatment for several chronic diseases [27], including IBD [28]. Furthermore, because of its capacity to modulate cell signaling proteins and gene expression and to inhibit cell proliferation, invasion and angiogenesis [29], with favorable effects on colon cancer [30,31], the administration of curcumin has also been considered in cancer therapy [32].

In animal models of colitis, curcumin has been shown to reduce mucosal injuries [33-35] and is traditionally employed in oriental and western herbal medicine to treat abdominal pain and bloating. In humans, dietary turmeric is able to activate bowel motility and to favor carbohydrate colonic fermentation [36]. Furthermore, curcumin (72-144 mg daily for 8 weeks) has been shown to decrease the extent of abdominal pain and to improve QoL in IBS patients [37]. On the other hand, the main component of fennel seed oil, anethole, is potentially able to act positively on different pathogenic mechanisms of IBS, since it has antimicrobial activity [38] and anxiolytic effects [39] and is able to exert a relaxant effect on smooth muscle [40,41], possibly through potassium channel opening [41]. In a randomized, placebo-controlled trial in infants, fennel seed oil was able to significantly decrease the intensity of infantile colic without causing side effects [42]. This therapeutic effect has been confirmed by a recent systematic review of interventions in breast-fed infants [43]. The efficacy of fennel in reducing abdominal pain has also been suggested by a preliminary report involving adult IBS patients [44]. Taken together, these previous findings should justify the combination of the two herbal products as a possible and useful therapeutic tool in IBS patients. In fact, observations from an Italian multicenter study indicated that the nutraceutical combination of curcumin and fennel essential oil was able, during one month of therapy, to clearly improve both symptoms and QoL in IBS patients enrolled in tertiary clinical centers [2]. Data from the present series, derived from a larger number of patients, confirm these positive effects in a "real-life" context of subjects enrolled by GPs (thus not in specialized clinical centers) and in a different geographical area (Belgium). This last finding, in particular, seems relevant, since different dietary habits are strongly involved in the generation of symptoms in IBS patients [3] and, at least theoretically, the efficacy of pharmacologic approaches might be limited by an unfavorable diet. In this respect, it has to be underlined that low adherence to a Mediterranean diet (the typical diet in Italy) may trigger gastrointestinal symptoms in IBS patients [4]. Further insights into this topic may be found in the literature [3,45].

According to the results of the present study, the different cultural and dietary habits in the explored area (Belgium), as compared to a typical Italian context (Mediterranean diet), do not seem to limit the therapeutic efficacy of the combination of turmeric and essential oil of fennel in adult IBS patients. Furthermore, although it has been reported that IBS symptoms present more in women and in young adults, our data also show that the beneficial effects of the proposed therapy on symptom severity were independent of the enrolled subjects' age and sex. Within one month, starting therapy with the highest dosage (two capsules b.i.d.) led to a marked improvement in the severity of symptoms and in intestinal habits (i.e. frequency of normal evacuations, proportion of patients with mucus in stool, effort to pass stools, impression of empty intestine after evacuation, abdominal pain), significantly improving the patients' QoL. Notably, these positive therapeutic effects were also evident between 30 and 60 days with a lower dose of the nutraceutical combination (two capsules q.d.), during which further improvement was seen in both QoL and severity index.

The results of our study showed that IBS-D patients had the worst clinical picture at entry, with the highest IBS severity index

and the lowest QoL score as compared with the other two IBS subtypes. These results are in line with previous observations showing that IBS-D patients have more work absenteeism, more presenteeism, and greater overall work productivity loss than controls, pointing to the need for effective therapies in this subgroup of IBS subjects [46]. In the present series, however, IBS-D patients also showed the most pronounced response to therapy considering both scores, although at the end of the follow up the QoL remained lower, compared with the IBS-C and IBS-M subgroups. Further studies are needed in order to evaluate the possibility of a progressive clinical improvement following more prolonged treatment and/or higher dosage of the examined nutraceuticals.

Additional studies should also better explore the therapeutic effect of the proposed nutraceutical combination at lower doses (in particular in IBS-C and IBS-M subjects), and compared with a placebo-controlled group. This last feature is a limitation of the present study, since IBS patients may spontaneously enter remission periods over time, and it has been suggested that the positive response to placebo ranges from 40-50% in different trials [47]. Although this aspect could limit the value of the final results from the present series, our group has clearly shown in a previous series of IBS patients that the combination of curcumin and fennel essential oil, compared to placebo, has greater therapeutic efficacy on both IBS symptoms and QoL [2].

Since the present study was not designed to observe patients further after treatment withdrawal, studies should also be targeted to explore symptom recurrence after the suspension of therapy and, in view of previous results of beneficial effects in IBS patients of curcumin [37] and fennel seed oil [44] given separately, to assess if the association of these components is able to give better results than either component alone.

In conclusion, results from this "real-life" study show that the combination of curcumin and fennel essential oil might represent a useful therapeutic approach in IBS patients, given its beneficial effects on both symptoms and QoL, at least within the time range (i.e. 2 months) observed in this study. The effect occurs irrespectively of age, sex, initial severity of symptoms and IBS subtypes. Further clinical and experimental studies should be oriented to better explore the ultimate mechanisms of action of this nutraceutical combination.

**Summary Box**

**What is already known:**

- Irritable bowel syndrome (IBS) is a chronic functional disease that significantly affects patients' quality of life (QoL) and conventional therapies often have poor outcomes
- The efficacy of herbal products in IBS patients has not yet been fully determined
- Previous observations showed possible beneficial effects of the combination of curcumin and fennel essential oil on QoL in Italian IBS patients enrolled in a tertiary referral center

**What the new findings are:**

- In this "real-life" study, the combination of curcumin and fennel essential oil take during a 2-month period was associated with a significant reduction in the severity of symptoms and an improvement of QoL in IBS patients
- Patients with diarrhea-predominant IBS showed the worst clinical picture at entry, but also the most pronounced therapeutic effects
- The beneficial effects of this therapy on both symptoms and QoL were independent of age, sex, initial severity of symptoms and IBS subtypes

## References


1. Portincasa P, Moschetta A, Baldassarre G, Altomare DF, Palasciano G. Pan-enteric dysmotility, impaired quality of life and alexithymia in a large group of patients meeting ROME II criteria for irritable bowel syndrome. *World J Gastroenterol* 2003;**9**:2293-2299.
2. Portincasa P, Bonfrate L, Scribano ML, et al. Curcumin and fennel essential oil improve symptoms and quality of life in patients with irritable bowel syndrome. *J Gastrointestin Liver Dis* 2016;**25**:151-157.
3. Portincasa P, Bonfrate L, de Bari O, Lembo A, Ballou S. Irritable bowel syndrome and diet. *Gastroenterol Rep (Oxf)* 2017;**5**:11-19.
4. Zito FP, Polese B, Vozzella L, et al. Good adherence to Mediterranean diet can prevent gastrointestinal symptoms: A survey from Southern Italy. *World J Gastrointest Pharmacol Ther* 2016;**7**:564-571.
5. Longstreth GF, Thompson WG, Chey WD, Houghton LA, Mearin F, Spiller RC. Functional bowel disorders. *Gastroenterology* 2006;**130**:1480-1491.
6. Francis CY, Morris J, Whorwell PJ. The irritable bowel severity scoring system: a simple method of monitoring irritable bowel syndrome and its progress. *Aliment Pharmacol Ther* 1997;**11**:395-402.
7. Patrick DL, Drossman DA, Frederick IO, DiCesare J, Puder KL. Quality of life in persons with irritable bowel syndrome: development and validation of a new measure. *Dig Dis Sci* 1998:**43**:400-411.
8. Saito YA, Petersen GM, Locke GR 3rd, Talley NJ. The genetics of irritable bowel syndrome. *Clin Gastroenterol Hepatol* 2005;**3**:1057-1065.
9. Chang L. The role of stress on physiologic responses and clinical symptoms in irritable bowel syndrome. *Gastroenterology* 2011;**140**:761-765.
10. Zuo XL, Li YQ, Shi L, et al. Visceral hypersensitivity following cold water intake in subjects with irritable bowel syndrome. *J Gastroenterol* 2006;**41**:311-317.
11. Nozu T, Kudaira M, Kitamori S, Uehara A. Repetitive rectal painful distention induces rectal hypersensitivity in patients with irritable bowel syndrome. *J Gastroenterol* 2006;**41**:217-222.
12. Chadwick VS, Chen W, Shu D, et al. Activation of the mucosal immune system in irritable bowel syndrome. *Gastroenterology* 2002;**122**:1778-1783.

13. Liebregts T, Adam B, Bredack C, et al. Immune activation in patients with irritable bowel syndrome. *Gastroenterology* 2007;**132**:913-920.
14. Bonfrate L, Tack J, Grattagliano I, Cuomo R, Portincasa P. Microbiota in health and irritable bowel syndrome: current knowledge, perspectives and therapeutic options. *Scand J Gastroenterol* 2013;**48**:995-1009.
15. Shishodia S, Sethi G, Aggarwal BB. Curcumin: getting back to the roots. *Ann N Y Acad Sci* 2005;**1056**:206-217.
16. Venkataranganna MV, Rafiq M, Gopumadhavan S, Peer G, Babu UV, Mitra SK. NCB-02 (standardized Curcumin preparation) protects dinitrochlorobenzene- induced colitis through down-regulation of NFkappa-B and iNOS. *World J Gastroenterol* 2007;**13**:1103-1107.
17. Rajasekaran SA. Therapeutic potential of curcumin in gastrointestinal diseases. *World J Gastrointest Pathophysiol* 2011;**2**:1-14.
18. Plummer SM, Holloway KA, Manson MM, et al. Inhibition of cyclo-oxygenase 2 expression in colon cells by the chemopreventive agent curcumin involves inhibition of NF-kappaB activation via the NIK/IKK signalling complex. *Oncogene* 1999;**18**:6013-6020.
19. Koeberle A, Muñoz E, Appendino GB, et al. SAR studies on curcumin's pro-inflammatory targets: discovery of prenylated pyrazolocurcuminoids as potent and selective novel inhibitors of 5-lipoxygenase. *J Med Chem* 2014;**57**:5638-5648.
20. Baliga MS, Joseph N, Venkataranganna MV, Saxena A, Ponemone V, Fayad R. Curcumin, an active component of turmeric in the prevention and treatment of ulcerative colitis: preclinical and clinical observations. *Food Funct* 2012;**3**:1109-1117.
21. Hanai H, Sugimoto K. Curcumin has bright prospects for the treatment of inflammatory bowel disease. *Curr Pharm Des* 2009;**15**:2087-2094.
22. Yin H, Guo Q, Li X, et al. Curcumin suppresses IL-1beta secretion and prevents inflammation through inhibition of the NLRP3 inflammasome. *J Immunol* 2018;**200**:2835-2846.
23. Kaur H, He B, Zhang C, Rodriguez E, Hage DS, Moreau R. Piperine potentiates curcumin-mediated repression of mTORC1 signaling in human intestinal epithelial cells: implications for the inhibition of protein synthesis and TNFα signaling. *J Nutr Biochem* 2018;**57**:276-286.
24. Loganes C, Lega S, Bramuzzo M, et al. Curcumin anti-apoptotic action in a model of intestinal epithelial inflammatory damage. *Nutrients* 2017;**9**.
25. 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.
26. Wang J, Ghosh SS, Ghosh S. Curcumin improves intestinal barrier function: modulation of intracellular signaling, and organization of tight junctions. *Am J Physiol Cell Physiol* 2017;**312**:C438-C445.
27. Ghosh SS, He H, Wang J, Gehr TW, Ghosh S. Curcumin-mediated regulation of intestinal barrier function: The mechanism underlying its beneficial effects. *Tissue Barriers* 2018;**6**:e1425085.
28. Sreedhar R, Arumugam S, Thandavarayan RA, Karuppagounder V, Watanabe K. Curcumin as a therapeutic agent in the chemoprevention of inflammatory bowel disease. *Drug Discov Today* 2016;**21**:843-849.
29. Kunnumakkara AB, Anand P, Aggarwal BB. Curcumin inhibits proliferation, invasion, angiogenesis and metastasis of different cancers through interaction with multiple cell signaling proteins. *Cancer Lett* 2008;**269**:199-225.
30. Xu B, Yu L, Zhao LZ. Curcumin up regulates T helper 1 cells in patients with colon cancer. *Am J Transl Res* 2017;**9**:1866-1875.
31. Dasiram JD, Ganesan R, Kannan J, Kotteeswaran V, Sivalingam N. Curcumin inhibits growth potential by G1 cell cycle arrest and induces apoptosis in p53-mutated COLO 320DM human colon adenocarcinoma cells. *Biomed Pharmacother* 2017;**86**:373-380.
32. Li YH, Niu YB, Sun Y, et al. Role of phytochemicals in colorectal cancer prevention. *World J Gastroenterol* 2015;**21**:9262-9272.
33. Lubbad A, Oriowo MA, Khan I. Curcumin attenuates inflammation through inhibition of TLR-4 receptor in experimental colitis. *Mol Cell Biochem* 2009;**322**:127-135.
34. Billerey-Larmonier C, Uno JK, Larmonier N, et al. Protective effects of dietary curcumin in mouse model of chemically induced colitis are strain dependent. *Inflamm Bowel Dis* 2008;**14**:780-793.
35. Martelli L, Ragazzi E, di Mario F, et al. A potential role for the vanilloid receptor TRPV1 in the therapeutic effect of curcumin in dinitrobenzene sulphonic acid-induced colitis in mice. *Neurogastroenterol Motil* 2007;**19**:668-674.
36. Shimouchi A, Nose K, Takaoka M, Hayashi H, Kondo T. Effect of dietary turmeric on breath hydrogen. *Dig Dis Sci* 2009;**54**:1725-1729.
37. Bundy R, Walker AF, Middleton RW, Booth J. Turmeric extract may improve irritable bowel syndrome symptomology in otherwise healthy adults: a pilot study. *J Altern Complement Med* 2004;**10**:1015-1018.
38. Mota AS, Martins MR, Arantes S, et al. Antimicrobial activity and chemical composition of the essential oils of Portuguese *Foeniculum vulgare* fruits. *Nat Prod Commun* 2015;**10**:673-676.
39. Mesfin M, Asres K, Shibeshi W. Evaluation of anxiolytic activity of the essential oil of the aerial part of *Foeniculum vulgare* miller in mice. *BMC Complement Altern Med* 2014;**14**:310.
40. Ostad SN, Soodi M, Shariffzadeh M, Khorshidi N, Marzban H. The effect of fennel essential oil on uterine contraction as a model for dysmenorrhea, pharmacology and toxicology study. *J Ethnopharmacol* 2001;**76**:299-304.
41. Boskabady MH, Khatami A, Nazari A. Possible mechanism(s) for relaxant effects of *Foeniculum vulgare* on guinea pig tracheal chains. *Pharmazie* 2004;**59**:561-564.
42. Alexandrovich I, Rakovitskaya O, Kolmo E, Sidorova T, Shushunov S. The effect of fennel (*Foeniculum vulgare*) seed oil emulsion in infantile colic: a randomized, placebo-controlled study. *Altern Ther Health Med* 2003;**9**:58-61.
43. Harb T, Matsuyama M, David M, Hill RJ. Infant colic-what works: a systematic review of interventions for breast-fed infants. *J Pediatr Gastroenterol Nutr* 2016;**62**:668-686.
44. Amjad H, Jafary HA. Foeniculum vulgare therapy in irritable bowel syndrome. *Am J Gastroenterol* 2000;**95**:2491.
45. Portincasa P, Lembo A, De Bari O, et al. The role of dietary approach in irritable bowel syndrome. *Curr Med Chem* 2017 Apr 7 [Epub ahead of print]. doi: 10.2174/0929867324666170428102451.
46. Buono JL, Carson RT, Flores NM. Health-related quality of life, work productivity, and indirect costs among patients with irritable bowel syndrome with diarrhea. *Health Qual Life Outcomes* 2017;**15**:35.
47. Lu CL, Chang FY. Placebo effect in patients with irritable bowel syndrome. *J Gastroenterol Hepatol* 2011;**26** Suppl 3:116-118.