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Curcumin as an Aid to Improve Symptoms of Inflammatory or Irritable Bowel Diseases

Sarah Orscheln

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Abstract

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Irritable Bowel Syndrome (IBS) is one of the most common diagnoses in gastroenterology practices in the North American hemisphere. IBS shares many of the same symptoms as IBD and despite growing research and compelling data, it's still unclear if there are genetic components and mucosal changes to explore.

Patients are becoming increasingly interested in how to maintain their remission or reverse the disease processes through diet and lifestyle changes. Current research focused on the chemical compound curcumin, found in the Turmeric rhizome, may hold the keys to maintaining remission in mild to moderate ulcerative colitis (UC). Through systematic literature review this article aims to explore existing research regarding natural food-based compounds, namely curcumin, and the potential benefits for patients with IBD and IBS diagnoses.

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curcumin, turmeric, irritable bowel disease, inflammatory bowel disease, crohn's, ulcerative colitis

Curcumin as an Aid to Improve Symptoms of Inflammatory or Irritable Bowel Diseases

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Clinical Graduate Project Coordinator: Annjanette Sommers, PA-C, MS

Biography

Following a successful run at journalism and television production in Los Angeles and New York City, Sarah moved to her Midwestern hometown in 2011 to pursue a career in medicine. Her past as an NCAA Division 1 college athlete led to a job as Community Outreach Director at a local gym where she enjoyed building and implementing lifestyle, nutrition and wellness programs for members. She volunteered at Kansas City CARE clinic, one of the largest free clinics in the country, and had the privilege of providing healthcare and aid in countries such as Haiti, Guatemala and Jamaica. Sarah moved to Oregon in 2016 following her acceptance into Pacific University School of Physician Assistant Studies and is looking forward to a long career serving others.

Abstract

Background: Inflammatory bowel disease (IBD) is a poorly understood process that affects over a million people in the United States alone. The disease typically manifests as recurrent flares of abdominal pain and bloody diarrhea along with periods of remission. Standard therapy has focused around maintenance and remission, rather than a cure. These lifelong diagnoses carry devastating consequences for patients. Modern medical therapy consists primarily of steroids, aminosalicylate anti-inflammatories and immunomodulators.

Irritable Bowel Syndrome (IBS) is one of the most common diagnoses in gastroenterology practices in the North American hemisphere. IBS shares many of the same symptoms as IBD and despite growing research and compelling data, it's still unclear if there are genetic components and mucosal changes to explore.

Patients are becoming increasingly interested in how to maintain their remission or reverse the disease processes through diet and lifestyle changes. Current research focused on the chemical compound curcumin, found in the Turmeric rhizome, may hold the keys to maintaining remission in mild to moderate ulcerative colitis (UC). Through systematic literature review this article aims to explore existing research regarding natural food-based compounds, namely curcumin, and the potential benefits for patients with IBD and IBS diagnoses.

Methods: An exhaustive search of available medical literature using the following databases: MEDLINE-PubMed, CINAHL-EBSCO Host and Web of Science was performed using the keywords "inflammatory bowel disease" and "curcumin." Randomized controlled trials (RCTs) were selected and inclusion criteria required studies from the past 5 years. Studies were assessed for quality using GRADE criteria.

Results: An extensive review of the studies concluded that there was no harm in using curcumin as add on therapy for IBD and while one study showed inconclusive improvement in inducing remission of patients with mild to moderate UC, the other showed improvement for patients suffering from IBS, which is characterized by the lack of inflammatory process but presence of unexplained cramping, gastrointestinal (GI) distress and either constipation or diarrhea. Many, if not all, of the symptoms of IBS are present in patients suffering from Inflammatory Bowel Diseases. The strongest support for alternative IBD therapy regarding curcumin is for remission maintenance in people with mild to moderate UC.

Conclusion: Although there is not enough current evidence to conclude that curcumin alone can induce or maintain remission in IBD patients; with the current available data it appears that there may be symptomatic relief along with negligible risk for patients looking outside of standard maintenance therapies.

Keywords: Inflammatory Bowel Disease, Irritable Bowel Syndrome, Crohn's Disease, Crohns, Ulcerative Colitis, UC, Curcumin, Curcuminoid, Turmeric, Curcuma longa, Flares, Colon Cancer, Indian, Curry, Gastrointestinal, Mesalamine

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List of Abbreviations

UC	Ulcerative Colitis
CD	Crohn's Disease
IBD	Inflammatory Bowel Disease
IBS	Irritable Bowel Syndrome
GI	Gastrointestinal
QOL	Quality of Life
6-MP	Azathioprine, 6 Mercaptopurine
TNF-alpha	Tissue Necrosis Factor Alpha
MPO	Myeloperoxidase
NO	Nitric Oxide
RCT	Randomized Controlled Trial
COX 1 and 2	Cycloxygenase 1 and 2
LOX	Lipoxygenase
NF-kB	Nuclear factor kappa-light-chain-enhancer
MAPK ERK	Kinases
CU-FEO	Curcumin-Fennel Essential Oil
PLGA	Poly(lactic-co-glycolic acid)
IBS-SSS	Irritable Bowel Symptom Severity Score
VAS	Visual Analogue Scale
UCDAI	Ulcerative Colitis and Disease Activity Index

Curcumin as an Aid to Improve Symptoms of Inflammatory or Irritable Bowel Diseases

BACKGROUND

It is known that curcumin (diferuloyl methane), a compound found in the *Curcuma Longa* or turmeric plant, possesses anti-inflammatory properties that have been shown to alleviate some of the symptomatology associated with Inflammatory Bowel Disease (IBD), specifically when maintaining remission in mild to moderate Ulcerative Colitis (UC).[1,2] IBD is a broad term used to describe vaguely understood autoimmune inflammation of the gastrointestinal (GI) tract. The 2 diseases associated with IBD are Crohn's disease (CD) (effecting any or all of the small and large bowel) or Ulcerative Colitis (UC) (disease isolated to the colon and rectum).[3]

Irritable Bowel Syndrome (IBS) is associated with many of the same indicia as diseases like UC and CD, but it lacks drastic changes to the colonic mucosa and is recognized as a motility disorder that causes bloating and flatulence, along with constipation, diarrhea or mixed IBS.[4] The differences and similarities between IBS and IBD have been studied since the late 1970s, early 1980s.[5] IBS accounts for as much as half of GI visits in the US and is more common than IBD.[6] While the pathophysiology of IBS and IBD have traditionally been viewed as separate conditions; It's frivolous to overlook the reality that an IBD patient in remission will often experience IBS symptoms.[7] There is evidence citing that IBS colonic mucosa does have an element of low-grade inflammation.[8] For this reason, both the Portincasa et al[9] and Singla et al[10] studies were chosen as the RCTs to evaluate the effectiveness of the curcumin compound on IBD symptomatology. A difference to be noted between IBD and IBS is that a diagnosis of IBS has not shown to increase the risk of mortality or colon cancer; a diagnosis of IBD, likely due to chronic states of inflammation, does have increased morbidity and mortality risks.[11]

UC is a debilitating, lifelong, relapsing-remitting IBD that afflicts millions of individuals throughout the world and produces symptoms that impair quality of life (QOL) and the ability to function.[12] As previously mentioned, while IBS and IBD are very different disease states (one does not lead to the other), some of the physical manifestations are similar and both have shown some benefit from curcumin therapy in the form of symptomatic relief.

Symptoms of IBD and IBS include some form of chronic or persistent abdominal cramping, pain, diarrhea, constipation, mucus in the stool, gassiness and/or constipation alternating with diarrhea. Symptoms specific to IBD include anemia, abdominal pain and cramping, weight loss, fever and bloody diarrhea. A comparison of IBD and IBS is found in Table 1.[13,14,15,16]

The prevalence of IBD in the United States varies by geographical region and is more predominant in more industrialized nations.[17] CD and UC carry large burdens on the healthcare system. Frequent lapses in remission, despite long-term medical therapies, account for a large number of hospitalizations.[2] Accepted therapies for UC patients are long-term mesalamine or sulfasalazine (5-ASA) protocols with corticosteroids for flares, possible immunosuppressive monoclonal antibody agents and azathioprine (6-MP). Initially effective, most agents fail over time and the patient must graduate up to a stronger or different treatment options.[2] Each of these medications comes with an extensive list of adverse effects, ranging from Cushing's syndrome from long-term steroid use to lymphoma and pancreatitis from 6-MP.[18] If treatments continue to fail without remission, surgery becomes inevitable. Current research is targeted at finding a compound to induce and/or maintain remission. Curcumin may have a protective role in IBD through modulation of the release of interleukin 6 (IL-6), tissue necrosis factor-alpha (TNF alpha), myeloperoxidase (MPO) and nitric oxide.[2]

The Lang et al study found that in patients with mild to moderate UC, curcumin, in addition to mesalamine therapy, was statistically superior at inducing remission compared to patients on mesalamine alone.[19]

Along with anti-inflammatory properties, curcumin has been studied for its antioxidant properties and the potential to influence signaling pathways like the kinases (MAPK, ERK), cycloxygenase 1 and 2 (COX-1 and COX-2), lipoxygenase (LOX) and inhibiting the transcription factor nuclear factor kappl-light-chain-enhancer (NF-kB).[20]

There is varying research in regards to the bioavailability of curcumin, choice of delivery method and its efficacy against IBD, IBS and colon cancer cells.

It cannot be determined what method of drug delivery, if any, might induce remission for IBD patients. There is evidence that curcumin may help to maintain remission for UC patients and relieve symptomatology for IBS patients.[2]

A major hurdle for scientists has been finding ways to make the curcumin compound bioavailable and pharmacologically effective against targeted cells. The polyphenol has a rapid metabolism, is photosensitive and water-soluble.[21] It's been discovered that when conjugated with poly(lactic-co-glycolic acid) (PLGA), curcumin becomes a sustainable compound with anti-proliferative activity and apoptosis in human CC cells.[22]

With IBD numbers on the rise in industrialized nations, it's not surprising that colon cancer or large bowel cancer is more common as well.[17,23] India, categorized by some experts as an industrialized nation, has drastically lower incidence rates of colon cancer than the United States.[24] This phenomenon is more prevalent in rural areas and is attributed to a traditional diet consisting of starches and curcumin used in Indian cooking.[23]

With a number of drugs on the market to treat IBS and IBD, but none that are sufficient in curing the symptoms, or inducing/maintaining remission, (especially barring adverse effects), the question remains: *Can Curcumin aid in improving symptoms in patients with mild to moderate IBD or IBS?*

METHODS

An exhaustive literature search was done using MEDLINE-PubMed, CINAHL-EBSCO host and Web of Science using the keywords: "inflammatory bowel disease" and "curcumin." Both key terms were then limited to Randomized Control Studies and restricted to English language. Further filters included human only and studies published within the last 5 years. Studies were assessed using GRADE criteria.[25]

RESULTS

The initial search using MEDLINE-PubMed yielded 32 articles. CINHAL-EBSCO yielded 3 articles and Web of Science yielded 56 for a total of 91 search results. Using PICO for inclusion and exclusion criteria, it was narrowed down to 2 randomized control studies[9,10] (See Table 2).

Portincasa et al

Study Description –The first of 2 randomized placebo-controlled studies was published in 2016 in the Journal of Gastrointestinal Liver Disease, examining 121 patients with mild-to-moderate IBS symptoms defined by the Irritable Bowel Syndrome Symptom Severity Score (IBS-SSS) and a Visual Analogue Scale (VAS). Patients >18 years old and <60 years old were recruited within a randomized, double-blind, placebo-controlled trial involving 5 different centers in Italy. All patients were given a Rome III diagnosis of IBS (62% were IBS-Diarrhea subjects and 38% were IBS-Constipation subjects). Patients received 2 capsules of either

Curcumin 42 mg and Fennel essential oil 25 mg (CU-FEO) or placebo under fasting conditions. Patients had to have an IBS-SSS between 100-300 points for at least 3 of 10 days preceding enrollment, plus the symptom of abdominal distention or dissatisfaction of bowel habits.

Patients with IBD, structural abnormalities of the GI tract, history of alcohol or drug abuse, positive stool cultures for pathogenic bacteria, moderate to severe liver or heart disease, biliary tract obstruction, previous surgeries in the last 6 months, mental illness or other immunological, hematological or neoplastic diseases were excluded.

The study screened and forbade use of non-steroidal anti-inflammatories, anticoagulants, antibiotics, fibers and prebiotics two weeks prior to, and throughout the duration of the trial. In a controlled and detailed fashion, the study allowed patients to use antispasmodics, motility regulating drugs, laxatives, anti-depressant and anti-anxiolytics. Acetaminophen could be used, but no longer than three consecutive days. The consumption of concomitant drugs was reportedly: controlled, minimal and comparable[9] between the two groups at each point in the study.

Participants were evaluated and given a validated IBS-SSS questionnaire, along with a QOL questionnaire four times throughout the study; day 0 (or baseline), day 10, day 20 and day 30 (the end of the study). Scoring of the two questionnaires were statistically combined and compared between the two groups of participants.

The baseline characteristics for the study groups included: age, sex, severity of disease (mild vs. moderate), IBS-SSS (evaluating: abdominal pain, number of days without pain, abdominal distension, dissatisfaction with bowel habit and interference with QOL) and a combined IBS-QOL score.

Study Results –Out of the 121 patient participants who began the study, 116 finished. 2 (one placebo and one non-placebo) were excluded because they didn't take the product, 2 (one placebo and one non-placebo) withdrew consent before they could be assessed post-baseline, and one patient from the placebo group withdrew consent due to worsening esophageal reflux like symptoms 10 days into placebo treatment.

Overall, this study shows that curcumin-fennel (CU-FEO) significantly improved symptoms and QOL in IBS patients.[9] (see Figure 1). Patients with IBS were given oral CU-FEO in capsule form for 30 days. Patients were evaluated via questionnaire at baseline (day 0), days 10, 20 and 30. Fennel essential oil was used along with the curcumin due to its known carminative effects. The study found significant improvement in overall QOL of subjects using CU-FEO versus placebo.[9]

Between the two groups, placebo and non-placebo, baseline characteristics showed mainly female participants with an average age of 40 and an IBS-SSS ranging from 143-300. 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).[9]

There was a statistically relevant decrease in the mean IBS-SSS scores. Compared to baseline, patients who took the CU-FEO decreased from 255.7±39.9 to 127.8±77.4 (range 0 – 300) by day 30. While the placebo group saw some improvement 263.2±34.4 to 195.5±88.0 (range 25 - 345), the relative decrease was significantly greater and almost double with CU-FEO compared to placebo at day 30 (the end of the trial).

Patients taking CU-FEO achieved higher and statistically significant levels of complete symptom free relief and a greater than 50% reduction in abdominal pain symptom score compared to placebo groups.

Statistically the CU-FEO group saw significant improvement by day 10 in the abdominal distension category by 10, and the others followed by days 20 and 30. At the end of treatment, 30 days, 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).[9]

Singla et al

A systematic review from the Cochrane Database published in 2012 found that there is evidence that it may be helpful to add oral curcumin therapy to 5-ASA in patients with mild to moderate colitis in order to maintain remission.[2] The Singla et al study aimed to further investigate and support this evidence.

Study Description –The Singla et al study, targeted at mild-to-moderate distal UC, used a curcumin enema delivery method in adjunct with patients' currently dosed oral 5-ASA. Disease activity was assessed during individualized visits at weeks 0, 4 and 8.

Participants were all >18 years of age, had mild-to-moderate distal UC based on the Ulcerative Colitis Disease Activity Index (UCDAI) score,[26] had 25 cm of diseased colon from the anal verge and were on a stable dose of Mesalamine therapy for more than 8 weeks.

Individual scores were added to the 4 parameters included in UCDAI which are: bowel frequency, rectal bleeding, endoscopic exam and physician's rating of severity. Patients were asked about rectal bleeding and stool frequency and given scores in regards to his or her reported symptoms over the past 7 days. These criteria were assessed and scored at weeks 0, 4 and 8.

Exclusions were made for patients who had used rectal steroids or rectal 5-ASA in the 4 weeks preceding the trial. Patients with severe UC based on the UCDAI score and those who's 5-ASA therapy was either initiated in the last 3 months or adjusted in the preceding 8 weeks

were not included. Patients with recent hospital stays, steroid injections or initiations those on investigational medicines, along with those patients with significant hepatic, renal, endocrine, respiratory and cardiovascular disease were excluded.

Patients were given either placebo enemas or enemas with 140 mg of NCB-02 (the standardized extract of Curcuma Longa) dissolved in 20 ml of water. The composition was 72% curcumin, 18.08% demethoxy curcumin and 9.42% bis-demethoxy curcumin.[10] All patients also received 800 mg oral mesalamine twice daily for the duration of the study.

Study Results – 45 patients met inclusion criteria and consented for this study and were randomized. 23 received NCB-02, 22 received placebo. Only 14 patients in the NCB-02 group and 16 in the placebo group finished the study. In the NCB-02 group, 5 had worsening symptoms and 4 were lost during follow-up evaluation. In the placebo group, 4 patients had worsening symptoms and had to drop out, and 2 were lost during follow-up.

Although the mesalamine use and age and sex were comparable in the two groups, the NCB-02 group had a significantly higher number of patients who had been treated with steroids in the past, as well as the duration of the disease compared to placebo groups.

While more patients receiving the curcumin NCB-02 enema (than the placebo group) improved after 8 weeks, the difference was not statistically significant. At the end of the trial, the NCB-02 group saw a higher response to treatment. More patients were in remission in the NCB-02 group than in the placebo group, and a higher number of patients received proved endoscopic disease activity scores in the NCB-02 group than the placebo.

The methodologies and improved outcomes appear promising, but further studies with more participants need to be done on the subject.[10]

DISCUSSION

Providers should not hesitate to recommend the addition of curcumin, in plant or essential oil form, for patients suffering from IBD or IBS. If curcumin additive is not tolerated it should be discontinued immediately as any positive therapeutic effect is outweighed by adverse reaction(s). The current research is not sufficient to suggest that curcumin will induce remission for a patient, but it is promising that CU-FEO may reduce IBS symptoms and oral curcumin can aid in maintaining remission and/or lessening flares for IBD patients.[9,2,19]

Neither of the studies addressed Crohn's disease, found under the IBD umbrella. In a pilot study done in 2005[27] patients with Crohn's and distal UC, or proctitis were given curcumin to test its anti-inflammatory processes. 4 out of the 5 Crohn's patients and 5 out of the 5 proctitis patients showed some form of relief. The point is there is promising reason to believe that the anti-inflammatory, anti-oxidative and analgesic properties found in the turmeric rhizome of the *Cucuma Longa* plant must continue to be studied in different populations.

None of these studies does an adequate job addressing the subject of curcumin's bioavailability. Curcumin has a rapid plasma clearance and conjugation. If the curcumin is not bioavailable, the patient will not be able to appreciate its systemic effects. Oral curcuminoids can be combined with the alkaloid piperine (found in black pepper) in order to be adequately absorbed and considered bioavailable.[28]

Adding turmeric (the rhizome containing curcumin compounds) to the diet may introduce anti-inflammatory, anti-oxidative properties to combat colon cancer.[29] While there is no direct evidence citing turmeric or curry-based foods as colon-protective anti-cancer therapy, there is no harm in following in the footsteps of countries like pre-industrialized India. Before rising obesity

rates, and diets rich in fruits and vegetables became unpopular, India touted one of the lowest colorectal cancer rates in the world.[30]

Important flaws to note are the small trial sizes and the vague nature of this clinical question. Providers cannot be confident in this limited amount of research that curcumin alone induces or maintains remission of IBD. While it may aid relief of symptoms there is still much to be answered.

Method of delivery needs to be further explored by future research, particularly in human subjects. Should providers be suggesting Turmeric Enemas to their patients? Not at this time. As previously mentioned, there will likely never be an RCT where patients stop the use of remission therapy and take turmeric alone, making this a difficult subject to research.

CONCLUSION

While there seems to be some favorable evidence that curcumin can aid in the relief of IBD and IBS symptomatology, the current research is minimal and needs to be added upon. Focus on lifestyle changes, particularly diet and exercise, is the current recommendation for add-on therapy and there is no harm in the addition of low-cost, easily accessible alternatives like turmeric for patient treatment plans. In summation, curcumin in your diet can't hurt, but it may help. In a Westernized culture where obesity, weakly understood autoimmune processes and cancer are on the rise, research must expand and continue for the betterment of medical efficacy and treatment plans worldwide.

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Table 1: Comparison of UC, CD and IBS	Ulcerative Colitis	Both CD & UC	Crohn's disease	Both IBD & IBS	Irritable Bowel Syndrome
Epidemiology					
Sex Ratio (M:F)	1:1		2:1		More prevalent in women than men
Nicotine	May be protective		Can Precipitate CD	*	Risk factor for developing IBS[14]
Genetic Components	Yes	*	Yes	*	Some Familial Tendency[13]
Clinical Manifestations					
Hematochezia	Yes	*	Less Common		No
Mucus in Rectum	Yes	*	Less Common		No
Small Bowel Involvement	No		Yes		No
Upper GI tract involvement	No		Yes		No
Abdominal Cramping	Yes	*	Yes	*	Yes
Abdominal Pain	Yes	*	Yes	*	Yes
Increased bloating	Yes	*	Yes	*	Yes
Excessive Flatulence	Yes	*	Yes	*	Yes
Diarrhea and Constipation	Yes	*	Yes	*	Yes
Possible Skin, Bone and Joint Manifestations	Yes	*	Yes	*	Yes
Biochemical Findings					
Genetic Components	Yes	*	Yes		Feasible, needs further investigation[16]
ANCA-Positive	More Common		Less Common		
ASCA-Positive	Less Common		More Common		
Histopathology					
Acute and Chronic Inflammation	Proximally diffuse	*	Focal		
Mucosal Involvement	Transmucosal	*	Transmural	*	Some studies have showed increased numbers of activated immunocompetent cells in the intestinal mucosa on quantitative immunohistology, implicating the mucosal immune system in pathogenesis.[15]
Granulomas and Serositis	Very Rare	*	Common		
Cryptitis	Yes	*	Yes		
Fissures or Skip Lesions	Very Rare	*	Common		

Table 2: Quality Assessment of Reviewed Articles

Study	Design	Downgrade Criteria					Upgrade Criteria	Quality
		Limitations	Indirectness	Inconsistency	Imprecision	Publication bias		
Portincasa et al[9]	RCT	Not Serious	Serious[a]	Not Serious	Serious[a]	Unlikely	None	Moderate
Singla et al[10]	RCT	Not Serious	Serious[c]	Not Serious	Serious[b]	Unlikely	None	Moderate

[a] The Portincasa et al study has a small cohort size (121 participants).
[b] The Singla et al study size (45 participants).

FIGURE 1 PORTINCASA

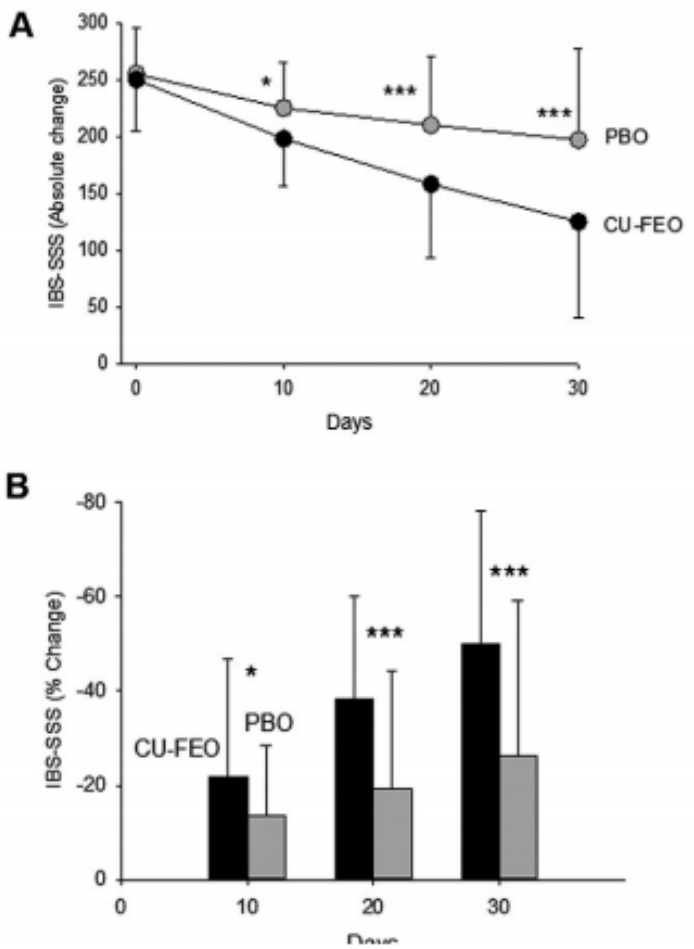

Fig. 2. Absolute (A) and relative (B) time-dependent changes from baseline of IBS-SSS in CU-FEO and Placebo (PBO) treatment groups. Data are mean±SD. Asteriks (*) indicate significant differences between groups at each time point (***P < 0.001; *P < 0.05).