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A natural plant fiber for gut inflammatory diseases: A randomized, double-blind, parallel group, reference controlled study

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ABSTRACT

Background: Recent studies indicate that imbalanced gut microbiota and gut inflammation lead to various gut-related disorders. Natural dietary supplementation is a complementary approach to address gut inflammation and gut-related disorders. In this context, Consolax®developed, a patent-filed innovative plant fiber formula with prebiotic, antioxidant, anti-inflammatory, and immunomodulatory properties. This study aimed to assess the efficacy and safety of Consolax® on gut health/inflammation among human subjects with imbalanced gut microbiota, gut inflammation, and inflammatory bowel syndrome.

Methods: We conducted a randomized, double-blind, parallel reference-controlled study among 24 of 29 subjects screened for the Rome IV Diagnostic Criteria for functional inflammatory disease, predominantly irritable bowel syndrome. The subjects were randomized into the test and reference groups (each, n=12). The test group underwent supplementation with Consolax® powder 5 g daily (b.i.d.) and the reference group received the reference product (psyllium husk powder) at the same dose of 5 g daily (b.i.d.). Both supplements were administered orally for 30 days along with standard care. Efficacy and safety outcomes were evaluated at four different time intervals, days 7+2 (visit 1), 14+2 (visit 2), 21+2 (visit 3), and 30+2 (visit 4).

Results: Consolax® supplementation lowered abdominal pain (based on the Visual Analog Scale) within the treatment groups during visits 3 and 4 compared to the baseline. Beneficial

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bacterial levels increased (p<0.0139) among Consolax®-supplemented subjects during visit 4 and pathogenic bacterial levels (p<0.004) decreased within and between the groups. The test group showed increased stool consistency (p<0.0005) and significantly improved (p<0.0005) spontaneous complete bowel movement during visit 4. The study results further underlie the anti-inflammatory properties of the test product which reflected in decreased inflammatory marker levels.

Conclusion: Consolax® is efficacious with excellent tolerability and safety for patients with imbalanced gut microbiota and in addressing overall gut health issues.

Keywords: Consolax, gut microbiota, inflammatory bowel syndrome, constipation, anti-inflammatory

INTRODUCTION

In the last two decades, several pioneering studies have reported direct associations of gut microbiota with the promotion of overall health and in the pathogenesis of different gastrointestinal diseases[1-3]. The human gut microbiota comprises several types of microorganisms including bacteria, viruses, fungi, and protozoa. Among these, bacteria are well-studied and play a vital role in maintaining immunity, metabolic homeostasis, and protection[1-3]. Imbalances in gut bacterial composition accompany the pathogenesis of irritable bowel syndrome (IBS) [4,5]. Irritable bowel syndrome manifests as altered bowel function, abdominal discomfort with pain ranging from diarrhea-predominant to constipation-predominant irritable bowel syndrome or a mixture of both[4,5]. Globally, Irritable bowel syndrome affects 1 in 10 persons in the general population[6. Irritable bowel syndrome with constipation caused by imbalances in gut microbiota has a substantially negative impact on patients' quality of life (QoL) and significantly worsens their health-related QoL[1,6-8].

The diet is believed to be a significant factor that maintains the gut microbiota across a person's lifetime[9,10]. With the ingestion of specific and fiber-rich food, a substantial proportion of patients with imbalanced gut microbiota demonstrated an excellent range of benefits in maintaining gut microbiota balance and gut health[11,12], and in meeting the required dietary fiber intake. The American Dietetic Association recommends dietary fiber intake ranging from 20–35 g/day for healthy adults and 5 g/day for children[13] to maintain health. However, the recommended dietary fiber intake is usually not met. A fiber-rich diet or supplementation is essential to prevent imbalances in gut microbiota, constipation, irritable bowel syndrome and other gut health issues[9-12]. There is increasing clinical evidence that the first-line intervention for imbalances in gut microbiota, constipation, and other gut health issues is a healthy diet with fiber-rich food and the use of probiotics[3,9,10,12]. Moreover, the gut microbiota allows the fermentation of non-digestible substrates like dietary fibers and endogenous intestinal mucus that support the specific growth of microbes that produce short-chain fatty acids and gases[9-12].

In recent years, attention has been drawn toward dietary supplementation in managing gut microbiota imbalance and gut health issues. Hence, there has been a substantial focus on natural ingredients, proprietary formulas effective in promoting gut microbiota balance. Our research team carefully designed and developed a powder-based formulation (Consolax®) which consists of natural plant fibers. This innovative formula consists of all-natural plant-based active ingredients with nutritional values carrying prebiotic, anti-inflammatory, and immunomodulatory properties and helps to maintain healthy gut

function. Based on the research, Consolax® is expected to be efficacious in addressing gut microbiota imbalance and gut health issues such as constipation, IBS, and inflammatory bowel disease (IBD). This study aimed to assess the efficacy and safety of Consolax® powder among human subjects.

The study protocol was reviewed and approved by the Sri Venkateshwara Hospital Ethics Committee, Bengaluru, Karnataka, India (approval no: ECR/298/Inst/KA/2013/RR-16) and has been registered and published with the Clinical Trials Registry–India (CTRI no. CTRI/2020/05/024972).

MATERIALS AND METHODS

Study design and subjects

This randomized, double-blind, parallel reference-controlled study was conducted per the clinical research guidelines established by the Supplements and Cosmetics Act, 1940 of India; Supplements and Cosmetics Rules, 1945 of India; the principles enunciated in the Declaration of Helsinki (Edinburgh, 2000); and the ICH-harmonized tripartite guideline regarding Good Clinical Practice.

Male or female subjects aged 18–65 years with gastrointestinal disorders were included in this study. Subjects who met the inclusion criteria (fulfilled the Rome IV Diagnostic Criteria for functional inflammatory disease) were included. In addition, subjects who had experienced recurrent abdominal pain on average at least 1 day/week for the preceding 3 months and subjects who met two or more criteria related to defecation, change in frequency of stool, and change in the appearance of stool were included. Subjects with a recurrent feeling of bloating or visible distension at least 1 day/week in the preceding 3 months and disordered bowel habits (constipation, diarrhea, or a mix of constipation and diarrhea) were also selected for the study. The subjects agreed not to use any medications, including vitamins, minerals, and yogurts during this study. Subjects with normal blood chemistry results were recruited. One month preceding the study, the subjects confirmed that they were not on antibiotics or other gastrointestinal medications.

Subjects who met the exclusion criteria were omitted from the study. In addition, subjects with a clinically significant medical history and findings or ongoing medical conditions were excluded from the study. Subjects with organic bowel disorders, mechanical bowel obstruction, pseudo-obstruction, unexplained weight loss, or rectal bleeding, as well as subjects with significant abnormal findings on physical examination, vital signs (blood pressure, pulse rate, and respiration rate), hematological examination, and biochemistry analyses at the baseline were excluded. Subjects with a history or presence of significant alcoholism, drug abuse, smoking, consumption of tobacco products, and history of malignancy, or any contraindication to blood sampling were also excluded. Subjects with blood-related products donated in the past 30 days before study supplement administration and pregnant and lactating women were also excluded. All subjects provided written informed consent before enrolment in the study-specified tests.

Twenty-four of the 29 subjects screened were enrolled in the study and were randomized into two groups (12 per group). The remaining 5 subjects were screen failures and did not participate in the trial. All the subjects complied with the study protocol and treatment schedule. One group received 5 g Consolax® powder (a proprietary combination of psyllium husk, inulin, and curcumin powder) manufactured by ZeusHygia LifeSciences Pvt Ltd (Hyderabad, India) twice a day as a dietary supplement. The other group underwent oral supplementation with a similar quantity of the reference product (psyllium husk powder) twice a day for 30 days, to be taken 30 mins before food, along with standard care. The study flow chart is shown in Figure 1.

The subjects were allowed to discontinue study participation at any time. The investigator was also allowed to discontinue study treatment at any time at their discretion for the following circumstances: consent withdrawal or non-

adherence to the study procedures; protocol deviation/violation which in the sponsor's opinion warranted study discontinuation; severe or intolerable adverse events (AEs) necessitating discontinuation at the investigator's discretion; and the occurrence of an allergic reaction/anaphylaxis to the investigational product.

Study protocol

All subjects received explanations about the clinical trial and provided written informed consent, and all patients' questions were answered to their satisfaction. During the screening investigator performed a detailed physical examination. We collected information regarding subjects' medication history, physical examination findings, demographic data, basic hematology results, biochemistry tests, virological tests, and urine tests. Stool samples were also analyzed at the baseline visit for *Entamoeba histolytica* to eliminate cases of amoebiasis. Stool cultures were also performed during the screening and final visits. Subjects' colonoscopy/sigmoidoscopy reports were examined by the principal investigator, and information regarding co-morbid conditions and vital signs was documented. The Visual Analog Scale (VAS) was used to assess abdominal pain.

Subjects reported to the study site for visit 1 (day 0, within 7 days after the screening visit). Subjects were assessed for study eligibility, as per the inclusion and exclusion criteria. Subjects who met the inclusion criteria were randomized to receive the investigational products. Subjects reported to the study site for the screening visit, visits 1 (day 7+2), 2 (day 14+2), 3 (day 21+2), and 4 (day 30+2). Consolax® and the reference supplements were dispensed to the participants once physical examination was performed and vital signs were measured and recorded. The primary efficacy endpoints included gut microbial analysis results (changes in gut microflora from days 0 to 30), VAS score, QoL (assessed via questionnaire), physician global assessment (PGA) of pain, spontaneous complete bowel movement (SCBM), stress levels assessed via questionnaire, and bowel movement with normal fecal consistency assessed via a self-administered questionnaire. Inflammatory marker (erythrocyte sedimentation rate [ESR], interleukin-6 [IL-6], tumor necrosis factor-α [TNF-α], and nuclear factor kappa B [NF-κB]) levels were also analyzed. Secondary efficacy variables included stress improvement, QoL, and the safety of the product throughout supplementation.

Subjects were informed about their subsequent scheduled dates of visit. Follow-up via telephone (at least 15 days from the last visit) was conducted to assess AEs from the time of the last visit. Any AEs were documented along with concomitant medications. Details of the diet were captured, and empty supplement containers were collected from the subjects. Blood and stool samples were collected for assessment. Biomarker levels were assessed using plasma samples with enzyme-linked immunosorbent assay kits. Blood samples were shipped from the clinical site to Radiant Research Pvt Ltd (Bengaluru, India) for further blood analyses.

Statistical analysis

The data generated from individual case report forms were compared between groups from visits 1 to 4. Two-tailed analysis of variance (ANOVA) was used to assess efficacy variables between and within treatment groups for investigational products. Related groups were also subjected to repeated-measures ANOVA. The statistical analyses were performed using SAS® version 9.1.3 (SAS Institute Inc., Cary, NC, USA). Analysis items with $p<0.05$ were considered statistically significant.

RESULTS

Primary outcomes

Gut microbial analysis

The average number of gut microbes present in both groups were evaluated among subjects during visits 1 and 4. The levels of two beneficial bacteria (*Lactobacillus* and *Bifidobacterium*) and 5 pathogenic bacteria (*Escherichia coli*, *Enterococcus faecium*, *Faecalibacterium prausnitzii*, *Clostridium* sp., and *Bacteroides*)

were quantified in all the subjects during both visits. Beneficial bacterial levels significantly increased ($p<0.05$) among Consolax®-treated subjects during visit 4, whereas pathogenic bacterial levels (67%) decreased significantly ($p<0.05$) (Table 1, Figure 2). A statistically significant difference ($p<0.05$) was also observed between supplements regarding both pathogenic and beneficial bacterial levels. No changes in both pathogenic and beneficial bacterial levels were observed in the reference group. Consolax® supplementation yielded a significant improvement (300%) in beneficial bacterial levels compared to the baseline and reference, thus indicating the prebiotic characteristics of Consolax®.

VAS abdominal pain score

Consolax® supplementation yielded a significantly decreased VAS score compared to the reference (Table 2, Figure 3). There were statistically significant changes within the treatment groups from the baseline to visit 3 ($p<0.0020$) and visit 4 ($p<0.0005$). Consolax® supplementation yielded statistically significant improvement (60%) compared to the reference, indicating that subjects experienced relief of abdominal pain during the supplementation period.

Bowel movement with normal fecal consistency and spontaneous complete bowel movement

Bowel movement with normal fecal consistency

Stool consistency ranges from 0 (indicative of stool that comprises separate hard lumps or nuts) to 7 (indicative of watery stool with no solid pieces). The Consolax®-supplemented group showed significantly increased stool/fecal consistency (type 2/3: sausage-shaped, but lumpy) from the baseline (visit 1) to the final visit (visit 4) compared to the reference control group (type 3/4: sausage-like, smooth, and soft) (Table 3, Figure 4a). Consolax® yielded a 43% improvement at the end of supplementation as compared to the baseline. A statistically significant change was also observed from visits 2 to 4 ($p<0.05$). These findings indicate that Consolax® is efficacious in improving fecal consistency, bowel movement, and relieving constipation.

Spontaneous complete bowel movement (SCBM)

SCBM indicates the average frequency of stools (complete evacuation) among the subjects in one week. Consolax®-supplemented subjects had significantly increased SCBM than the reference subjects at visit 4, and SCBM increased statistically from visits 1–4 ($p<0.05$) within the treatment group (Table 3, Figure 4b). Consolax®-supplemented subjects showed 194% improvement in SCBM at the end of supplementation compared to the baseline (Table 2). All subjects (100%) demonstrated increased SCBM per week and normal fecal consistency. These findings indicate that Consolax® showed a good response among constipation-predominant subjects as it increased the stool frequency (complete evacuation) from the baseline to the last visit.

Physician global assessment

The PGA measures patients' betterment on a scale of 1 to 10, indicating betterment in terms of very poor to excellent as evaluated by a physician or health practitioner. Both Consolax® and the reference showed similar trends at the end of the supplementation period and statistical differences ($p<0.05$) from visits 1–4 (Table 4, Figure 5). Within-group Consolax® supplementation yielded a 20% improvement, whereas the reference yielded only a 14% improvement. Consolax® supplementation showed significant results for overall gut health improvement, and the patients' feeling of wellness significantly improved.

Inflammatory biomarkers

Chronic mucosal inflammation is caused by the hyperactivation of effector immune cells, producing high levels of NF-κB and other inflammatory markers such as ESR, TNF-α, and IL-6. It is well known that inflammatory marker levels are highly elevated in chronic inflammatory conditions such as IBS, IBD, chronic constipation, and other gut diseases. TNF-α levels were higher at the baseline (visit 1) and significantly reduced during visit 4 in both

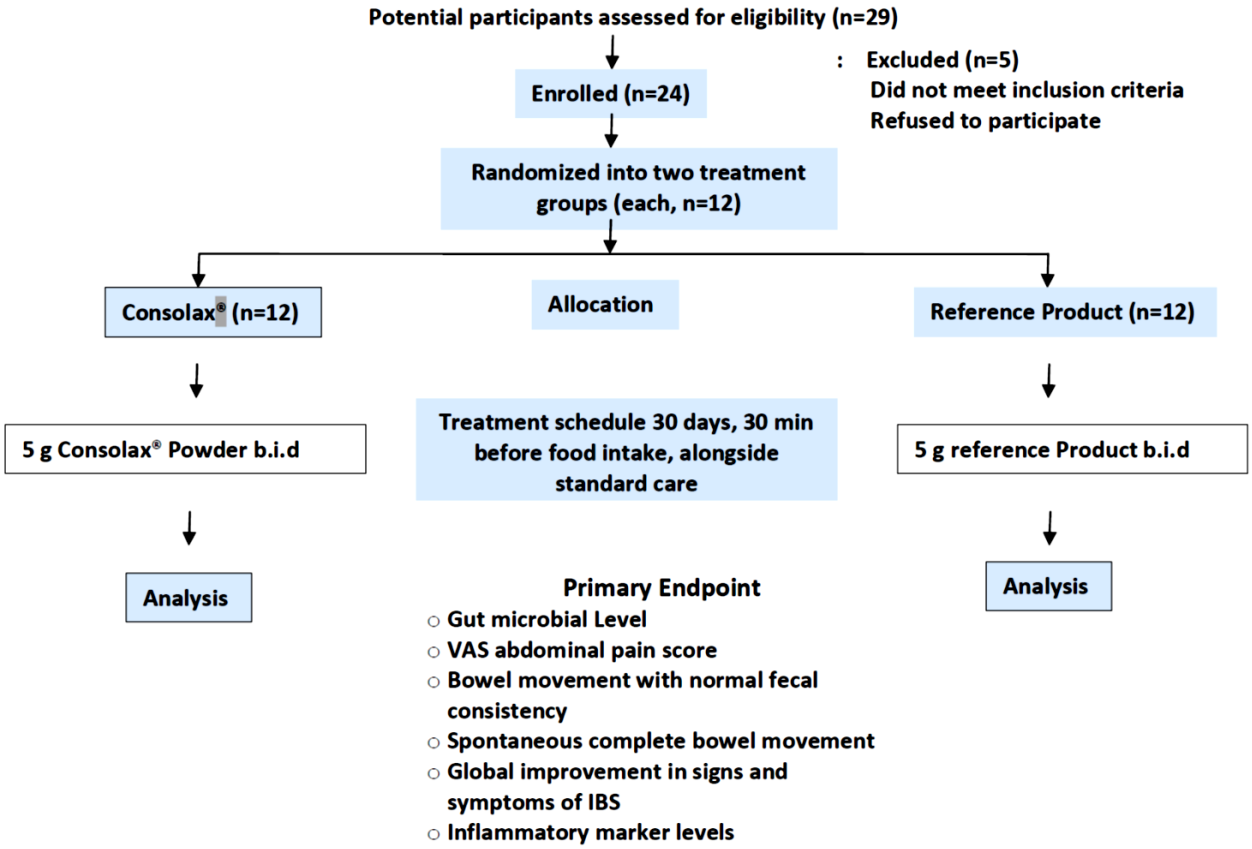

Figure 1: Study Design

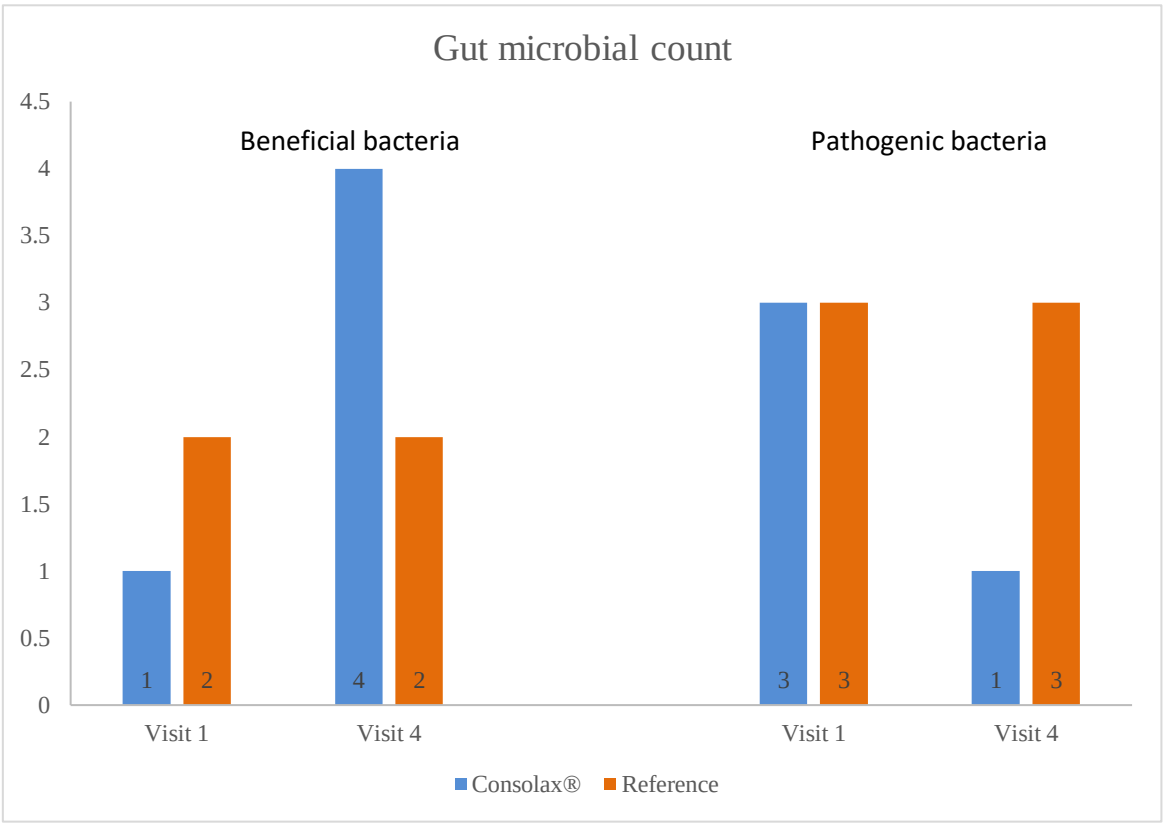

Figure 2: Gut Microbial Count assessed in inflammatory disease condition after the administration of the test product Consolax® and reference control. Images showing mean Gut microbial count in the Consolax® and reference control groups during Visit 1 and Visit 4

n=12. Data represented as mean ± S.D.

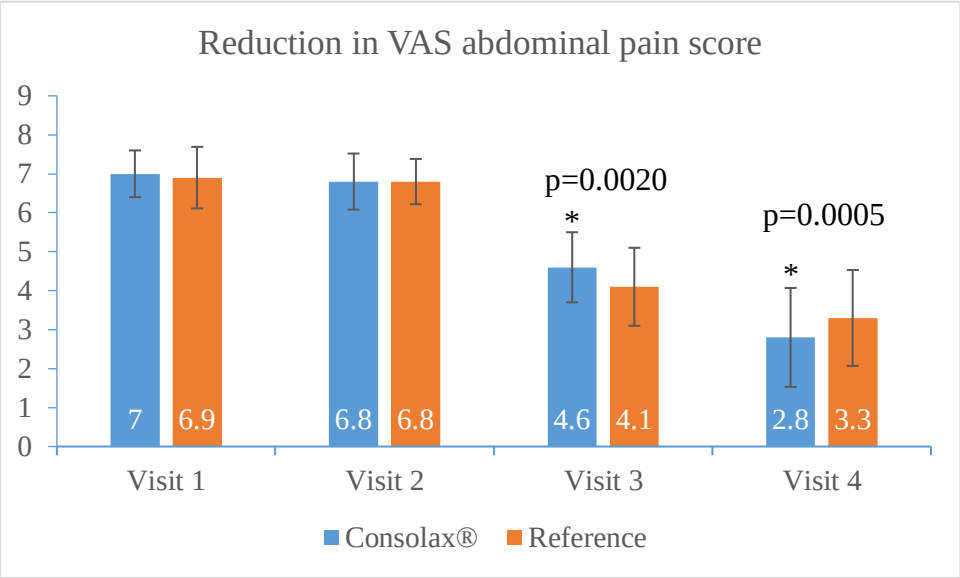

Figure 3: Reduction in VAS abdominal Pain Score in inflammatory disease condition after the administration of the test product, Consolax®, and reference control. Images showing mean Reduction in VAS abdominal Pain Score in the Consolax® and reference control groups from Visit 1 to Visit 4.n=12, statistical significance: p<0.05, data represented as mean ± S.D.

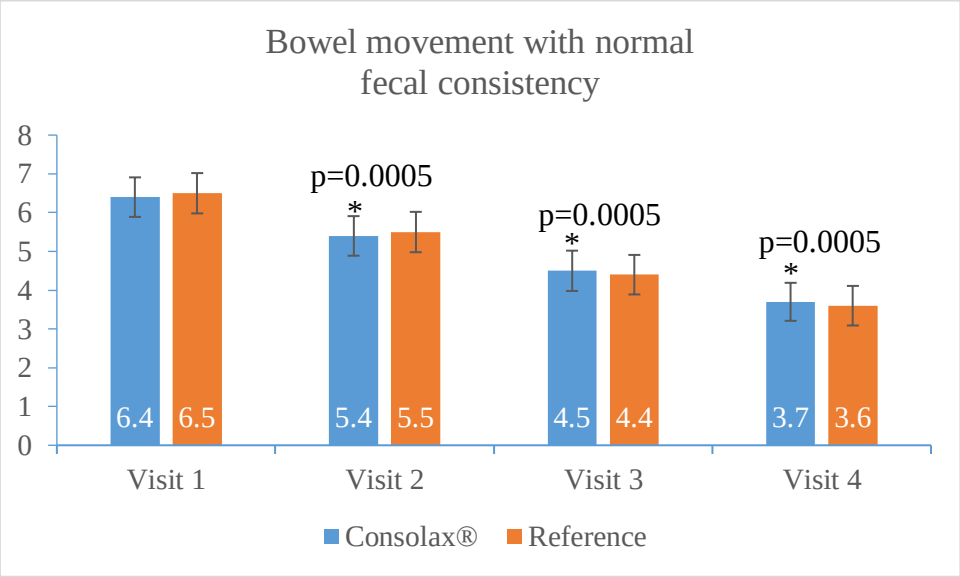

Figure 4a: Bowel Movement with Normal Fecal Consistency in inflammatory disease condition after the administration of the test product, Consolax®, and reference control. Images showing changes in mean Bowel Movement with Normal Fecal Consistency score in the Consolax® and placebo control groups from Visit 1 to Visit 4.n=12, statistical significance: p<0.05, data represented as mean ± S.D.

Table 1. Results of gut microbial analysis

Gut microbe counts				
Supplementation	**Nature of bacteria**	**Visit 1**	**Visit 4**	**p-value**
Consolax®	Beneficial bacteria	1×10^9	**/*4×10^9	0.0005
	Pathogenic bacteria	3×10^9	**/*1×10^6	0.0005
Reference	Beneficial bacteria	2×10^9	2×10^9	
	Pathogenic bacteria	3×10^9	3×10^9	

*p<0.05: significant between visits 1 and 4; **p<0.05: statistically significant between treatment groups

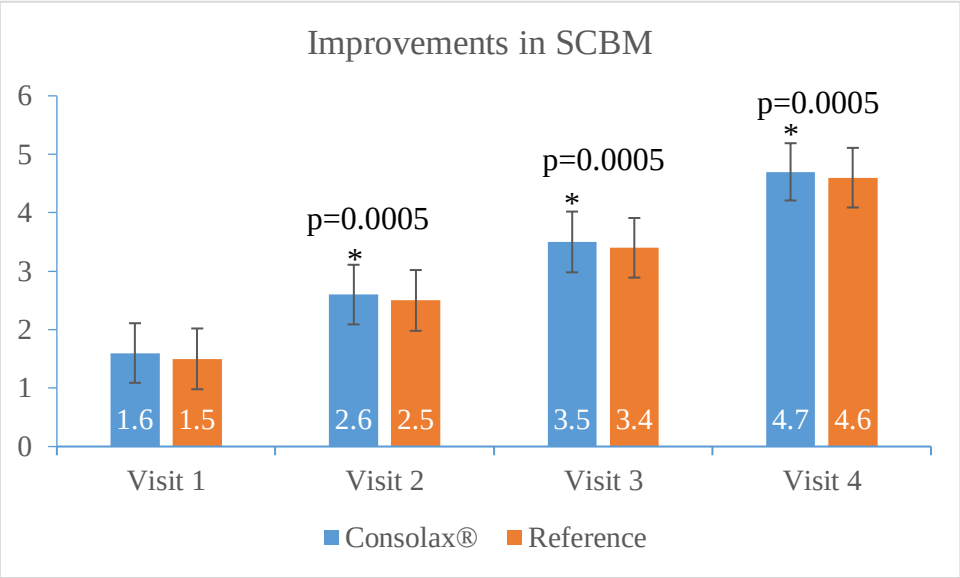

Figure 4b: Improvements in SCBM in inflammatory disease condition after the administration of the test product, Consolax®, and reference control. Images showing changes in mean SCBM score in the Consolax® and reference control groups from Visit 1 to Visit 4. n=12, statistical significance: $p<0.05$, data represented as mean ± S.D.

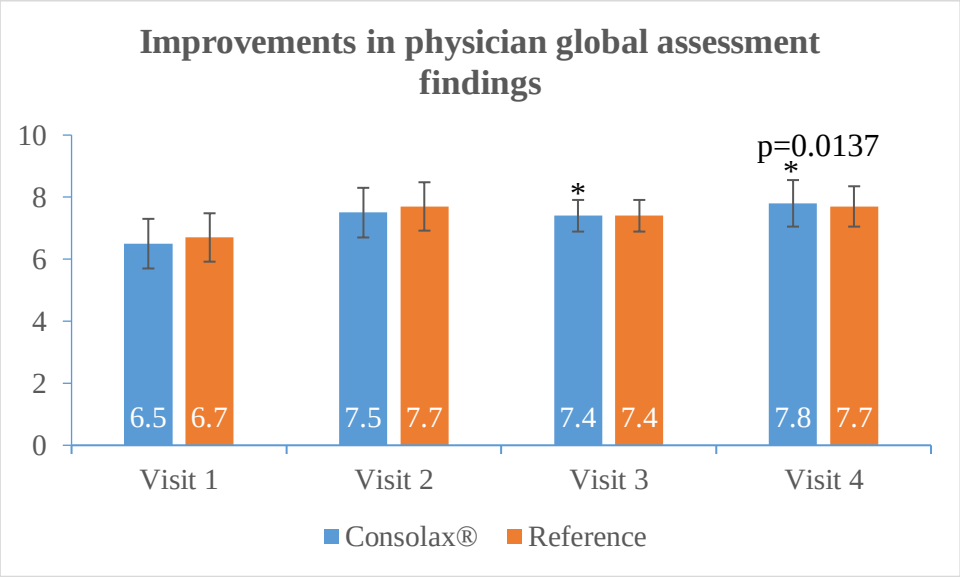

Figure 5: Improvements in Physician's Global Assessment Findings. Improvements in Physician's Global Assessment score in inflammatory disease conditions after the administration of the test product, Consolax®, and reference control. Images showing Improvement in mean score of Physician's Global Assessment in the Consolax® and reference control groups from Visit 1 to Visit 4. n=12, statistical significance: $p<0.05$, data represented as mean ± S.D.

Table 2. Distributions of Visual Analog Scale abdominal pain scores

VAS pain score reduction			
Visit/group	**Consolax®**	**Reference**	**p-value**
Baseline	7.0 ± 0.60	6.9 ± 0.79	
Visit 2	6.8 ± 0.72	6.8 ± 0.58	
Visit 3	4.6 ± 0.90*	4.1 ± 1.00	0.0020
Visit 4	2.8 ± 1.27*	3.3 ± 1.23	0.0005

*$p<0.05$: statistically significant within treatment groups

Table 3. Distributions of bowel movement with normal fecal consistency and spontaneous complete bowel movement (SCBM)

Bowel movement with normal fecal consistency			
Visit/group	**Consolax®**	**Reference**	**p-value**
Baseline	6.4 ± 0.51	6.5 ± 0.52	
Visit 2	5.4 ± 0.51*	5.5 ± 0.52	0.0005
Visit 3	4.5 ± 0.52*	4.4 ± 0.51	0.0005
Visit 4	3.7 ± 0.49*	3.6 ± 0.51	0.0005
Improvements in SCBM			
Baseline	1.6 ± 0.51	1.5 ± 0.52	
Visit 2	2.6 ± 0.51*	2.5 ± 0.52	0.0005
Visit 3	3.5 ± 0.52*	3.4 ± 0.51	0.0005
Visit 4	4.7 ± 0.49*	4.6 ± 0.51	0.0005

*p<0.05: statistically significant within treatment groups

Table 4. Distributions of physician global assessment scores

Improvements in physician global assessment scores			
Visit/group	**Consolax®**	**Reference**	**p-value**
Baseline	6.5 ± 0.80	6.7 ± 0.78	
Visit 2	7.5 ± 0.80*	7.7 ± 0.78	0.0005
Visit 3	7.4 ± 0.51*	7.4 ± 0.51	0.0078
Visit 4	7.8 ± 0.75*	7.7 ± 0.65	0.0137

*p<0.05: statistically significant within treatment groups

Table 5. Distributions of inflammatory biomarker levels

Inflammatory biomarkers			
Visit/group	**Consolax®**	**Reference**	**p-value**
ESR (mm/hr)			
Baseline	12.7 ± 5.52	12.9 ± 4.85	
Visit 4	12.7 ± 5.52**	13.8 ± 4.79	NE
TNF-α (pg/ml)			
Baseline	20.876 ± 1.233	19.435 ± 1.269	
Visit 4	17.391 ± 1.041*/**	16.755 ± 0.945	0.0005
IL-6 (pg/ml)			
Baseline	14.533 ± 1.525	14.036 ± 3.226	
Visit 4	11.510 ± 1.552*	11.132 ± 1.446	0.0005
NF-κB (ng/ml)			
Baseline	10.025 ± 0.455	10.033 ± 0.565	
Visit 4	8.230 ± 0.525*	8.037 ± 0.357	0.0005

*p<0.05: statistically significant within treatment groups; **p<0.01: statistically significant between treatment groups

Table 6. Improvements in stress levels

Improvements in stress levels			
Visit/group	**Consolax®**	**Reference**	**p-value**
Baseline	76.75 ± 8.996	73.33 ± 9.018	
Visit 2	59.00 ± 2.449*	61.00 ± 2.449	<0.0001
Visit 3	42.25 ± 2.137*	52.17 ± 2.167	<0.0001
Visit 4	37.50 ± 2.541*	46.92 ± 2.644	<0.0001

the Consolax® and reference groups (Table 5). TNF-α levels declined considerably ($p<0.0005$) within the groups as compared to the baseline (Table 5). Considering a 90% confidence interval, the TNF-α level showed a significant difference between supplement groups ($p<0.0478$). IL-6 levels were elevated at visit 1, and a statistically significant difference ($p<0.0005$) was observed within the treatment groups at visit 4 (Table 5). However, there was no significant difference between the groups. NF-κB level was elevated at visit 1 in both groups but reduced during visit 4. There was a statistically significant reduction in NF-κB level within the groups ($p<0.0005$) (Table 5). These findings indicate that Consolax® supplementation reduces inflammation by regulating inflammatory marker levels.

Secondary outcomes

Stress questionnaire

In theory, stress is a well known factor among persons with chronic constipation. A high score allocated to responses to 23 questions indicates a poor or slow improvement in stress symptoms, and a low score reflects better improvement in stress symptoms. There was a significant difference ($p<0.05$) within and between the treatment groups from the baseline. Consolax® showed 51% stress improvement, whereas the reference showed only 36% improvement at the end of supplementation (Table 6). These findings imply that Consolax® significantly improved stress and emphasizes its effectiveness on stress related to gut health and constipation.

QoL questionnaire

The QoL data combined 34 questions regarding subjects' apprehensions in their day-to-day activities and their QoL due to inflammatory conditions such as IBS, IBD, and chronic constipation. A high value indicated a low QoL, and a low value indicated better QoL. Consolax®-supplemented subjects had a low QoL during visit 1 and a better QoL by visit 4. There was a significant change ($p<0.05$) within the treatment groups from the baseline to the end of supplementation. Within groups, Consolax®-supplemented subjects showed 34% improvement in QoL at the end of supplementation.

Self-assessment questionnaire

All subjects provided feedback at each study visit and their responses were scored on a scale of 1 to 4, with 1 implying "strongly agree", 2 implying "agree", 3 implying "disagree", and 4 implying "strongly disagree" to a set of 7 statements. There was a considerable change in the feedback provided by the study subjects between the treatment groups from the baseline visit for 4 out of 7 questions, more specifically from visit 2 onwards, and reached statistical significance. Within the treatment groups, Consolax®-treated subjects responded more positively when compared to their responses from the baseline to other visits. A greater degree of statistical significance was obtained within the Consolax® group when compared to the respective reference group values. The self-assessment feedback questionnaire clearly showed that the subjects were more satisfied with Consolax® than the reference product.

Safety assessment

No AEs or serious AEs (SAEs) were reported in this study. As there were no abnormal vital signs (temperature, blood pressure, heart rate, and pulse rate) and no AEs/SAEs, the products under study were considered safe for oral consumption. Also, as none of the participants had abnormal vital parameters and hematological and biochemical test results, the test product was deemed to have demonstrated complete safety during this study.

DISCUSSION

The present study evaluated the efficacy and safety of Consolax® among subjects with gut microbiota imbalance and predominately inflammatory gut conditions. We assessed the efficacy of Consolax® by performing gut microbial analysis and determining VAS abdominal pain scores, proportions of SCBM, PGA scores, bowel movement with fecal consistency scores, and inflammatory marker (ESR, IL-6, TNF-α, and NF-κB) levels. Secondary endpoints included stress levels,

QoL, and safety, with parameters pointing toward test product efficacy and safety. The present findings demonstrated that Consolax®, a unique proprietary formula, improves bowel movements and the levels of beneficial bacteria and reduces pathogenic bacterial levels. Consolax® ameliorated abdominal pain related to chronic constipation-predominant IBS and improved stress associated with gut issues/chronic constipation, immunity, and QoL. In this study, beneficial bacterial levels increased (300%) among Consolax®-supplemented subjects ($p<0.0139$) during visit 4, whereas pathogenic bacterial levels decreased (67%) ($p<0.004$). Numerous studies have reported the role of bacteria in gut health. Gut microbiota balance is mainly regulated by specific bacterial substrates present in dietary fiber[14-17]. In this context, supplementation with a proprietary natural ingredient formula (Consolax®) could regulate gut microbiota balance. On the other hand, balanced gut microbiota might regulate the metabolism or fermentation of Consolax®. Correlation analysis of the relationship between fermentation products of Consolax® and microbiota could provide additional insights into their interactions and gut health. In addition, Consolax® possesses prebiotic characteristics and regulates the gut microbiota balance, which appears to beneficially impact gut health and potentially explains the amelioration of gut health issues.

VAS is a one-dimensional measure of pain intensity. Voluminous studies indicate that VAS abdominal pain score typically captures the main physical concerns of inflammatory disease with abdominal pain[18,19]. The VAS abdominal pain score is designed to detect complaints related to bowel symptoms, quantify the impact of gastrointestinal symptoms, and overall health. The VAS abdominal pain score is a more valid and reliable system and appears to be user-friendly for patients and health professionals. It was noteworthy that Consolax® supplementation decreased the VAS score and resulted in an almost 60% improvement as compared to the reference, which indicates a remarkable reduction in gastrointestinal pain with Consolax® supplementation. Consistent with our study results, previous studies reported that decreased VAS scores in treatment groups implied improvements in gut health[18,19].

SCBM refers to a bowel movement associated with a sensation of complete evacuation. A higher proportion of subjects who achieved primary durable overall SCBM experienced improvements in gut health[20-22]. A weekly SCBM responder was defined as a patient who experienced ≥3 SCBMs each week and an increase of ≥1 SCBM (compared with their baseline) in that same week[20-22]. Regarding the effect on SCBM, Consolax® showed an improvement equivalent to 194%. In particular, Consolax®-supplemented subjects showed increased SCBM at visit 4 and also during treatments. All the subjects (100%) showed an increase in the SCBM per week and normal fecal consistency. The Consolax®-supplemented group showed increased stool consistency (sausage-shaped, but lumpy) from the baseline (visit 1) to the final visit (visit 4). Consistent with other findings[20-22], Consolax® showed a good response among constipation-predominant subjects as it improved the rates of complete evacuation, improved fecal consistency, bowel movement, and relieved constipation from the baseline to the final visit.

Inflammatory markers are valuable and essential components of the global management of patients with IBS and IBD[23,24]. Inflammatory markers, such as ESR, TNF-α, IL-6, and NF-κB levels are additive tools for clinical observation. Potential underlying mechanisms include the modulation of IκB kinase activity, driven by inhibiting NF-κB and proinflammatory cytokines that further improve the overall well-being and immunity[23,24]. In the present study, Consolax®-supplemented groups showed decreased inflammatory marker levels at the final visit, predominantly underlining significant anti-inflammatory properties.

Inflammatory conditions disturb the balance between the brain and the gut. This leads to

stress, and anxiety sometimes triggers gut hyperactivity. Consolax® improved stress by about 51% while the reference improved stress by 36% at the end of supplementation.

Consolax® consists of curcumin[25], psyllium husk[26], and inulin or chicory extract[27], which provide several benefits. Particularly, they ameliorate intestinal inflammation, leading to improved bowel movements and relief of constipation. However, the administration of a combination of these products is not backed by any established clinical evidence. Consolax® is a proprietary combination of soluble and insoluble dietary fibers at concentrations optimized to manage gastrointestinal health and constipation. Consolax® contains multiple dietary fibers that improve bowel habits by increasing the stool bulk with the mechanical stimulation of the colonic mucosa. The fermentation of dietary fibers by intestinal microbiota lowers the luminal pH and has several by-products, such as gas and short-chain fatty acids[9,11-13,22]. The gas increases the luminal pressure, while short-chain fatty acids, particularly butyrate, affect gastrointestinal secretion and motility[9,11-13,28]. Inulin, a dietary fiber, is a non-digestible carbohydrate that reaches the colon intact and serves as a substrate for microbiota metabolism. The main characteristic of this fiber is its prebiotic properties, as it selectively stimulates beneficial bifidobacteria[9,11-13,28]. Inulin improves bowel function and contributes to normal laxation in different ways. It leads to softer stools and facilitates excretion. On the other hand, it enhances the propulsion of colonic contents via chemical and mechanical stimulation (increased bowel content) of the peristaltic reflex. Dietary fibers have additional health benefits such as lowering the blood cholesterol level, improving glycemic control, and bodyweight management[3,9,13,22,28]. Curcumin and its fiber powder possess systemic and local anti-inflammatory properties[25]. Consolax® had a positive effect on gut health, alleviated pain, and improved the QoL of subjects with at least moderate symptom severity.

Conclusion

The present findings demonstrated that Consolax® supplementation led to a significantly higher number of responders and significantly improved individual symptoms of subjects complaining of abdominal discomfort and imbalanced gut microbiota. Also, Consolax® was shown to be more effective at regulating bowel movements and improving digestive health, enhancing beneficial bacterial levels and reducing pathogenic bacterial levels, thereby relieving abdominal pain related to chronic constipation-predominant IBD. Moreover, our findings based on biomarker evaluation implied that Consolax® improves stress associated with gut issues and chronic constipation, immunity, and the overall QoL. These findings signify that Consolax® possesses potent anti-inflammatory properties, thereby improving the overall gut health. These clinical evidence underlies that Consolax® is efficacious with excellent tolerability and safety for subjects with gut-related diseases. No AEs and SAEs were reported throughout the study supplementation period. The results of this trial indicate that longer supplementation might yield a better efficacy profile.

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REFERENCES

[1]. 1Fan Y, Pedersen O. Gut microbiota in human metabolic health and disease. *Nat Rev Microbiol* 2021;19:55-71.

[2]. 2Santonicola A, Gagliardi M, Guarino MPL, et al. Eating Disorders and Gastrointestinal Diseases. *Nutrients* 2019;11:3038.

[3]. 3Valdes AM, Walter J, Segal E, Spector TD. Role of the gut microbiota in nutrition and health. *BMJ* 2018;361:k2179.

[4]. 4Andrews CN, Sidani S, Marshall JK. Clinical Management of the Microbiome in Irritable Bowel Syndrome. *J Can Assoc Gastroenterol* 2020;4:36-43.

[5]. 5Lo Presti A, Zorzi F, Del Chierico F, et al. Fecal and Mucosal Microbiota Profiling in Irritable Bowel Syndrome and Inflammatory Bowel Disease. *Front Microbiol* 2019;10:1655.

[6]. 6Sperber AD, Bangdiwala SI, Drossman DA, et al. Worldwide Prevalence and Burden of Functional Gastrointestinal Disorders, Results of Rome Foundation Global Study. *Gastroenterology* 2021;160:99-114.e3.

[7]. 7Chey WD, Kurlander J, Eswaran S. Irritable bowel syndrome: a clinical review. *JAMA* 2015;313:949-958.

[8]. 8El-Salhy M, Hatlebakk JG, Hausken T. Diet in Irritable Bowel Syndrome (IBS): Interaction with Gut Microbiota and Gut Hormones. *Nutrients* 2019;11:1824.

[9]. 9Sakkas H, Bozidis P, Touzios C, et al. Nutritional Status and the Influence of the Vegan Diet on the Gut Microbiota and Human Health. *Medicina (Kaunas)* 2020;56:88.

[10]. 10Zmora N, Suez J, Elinav E. You are what you eat: diet, health and the gut microbiota. *Nat Rev Gastroenterol Hepatol* 2019;16:35-56.

[11]. 11Holscher HD. Dietary fiber and prebiotics and the gastrointestinal microbiota. *Gut Microbes* 2017;8:172-184.

[12]. 12Makki K, Deehan EC, Walter J, Bäckhed F. The Impact of Dietary Fiber on Gut Microbiota in Host Health and Disease. *Cell Host Microbe* 2018;23:705-715.

[13]. 13Slavin JL. Position of the American Dietetic Association: health implications of dietary fiber. *J Am Diet Assoc* 2008;108:1716-1731.

[14]. 14Burns AM, Zitt MA, Rowe CC, et al. Diet quality improves for parents and children when almonds are incorporated into their daily diet: a randomized, crossover study. *Nutr Res* 2016;36:80-89.

[15]. 15Krupa-Kozak U, Drabińska N, Jarocka-Cyrta E. The effect of oligofructose-enriched inulin supplementation on gut microbiota, nutritional status and gastrointestinal symptoms in paediatric coeliac disease patients on a gluten-free diet: study protocol for a pilot randomized controlled trial. *Nutr J* 2017;16:47.

[16]. 16Baer DJ, Stote KS, Henderson T, et al. The metabolizable energy of dietary resistant maltodextrin is variable and alters fecal microbiota composition in adult men. *J Nutr* 2014;144:1023-1029.

[17]. 17Béghin L, Tims S, Roelofs M, et al. Fermented infant formula (with Bifidobacterium breve C50 and Streptococcus thermophilus O65) with prebiotic oligosaccharides is safe and modulates the gut microbiota towards a microbiota closer to that of breastfed infants. *Clin Nutr* 2021;40:778-787.

[18]. 18Bengtsson M, Hammar O, Mandl T, Ohlsson B. Evaluation of gastrointestinal symptoms in different patient groups using the visual analogue scale for irritable bowel syndrome (VAS-IBS). *BMC Gastroenterol* 2011;11:122.

[19]. 19Bengtsson M, Ohlsson B, Ulander K. Development and psychometric testing of the Visual Analogue Scale for Irritable Bowel Syndrome (VAS-IBS). *BMC Gastroenterol* 2007;7:16.

[20]. 20Ding C, Fan W, Gu L, et al. Outcomes and prognostic factors of fecal microbiota transplantation in patients with slow transit constipation: results from a prospective study with long-term follow-up. *Gastroenterol Rep (Oxf)* 2018;6:101-107.

[21]. 21Rao SSC, Xiang X, Yan Y, et al. Randomised clinical trial: linaclotide vs placebo-a study of bi-directional gut and brain axis. *Aliment Pharmacol Ther* 2020;51:1332-1341.

[22]. 22Zhang X, Tian H, Gu L, et al. Long-term follow-up of the effects of fecal microbiota transplantation in combination with soluble dietary fiber as a therapeutic regimen in slow transit constipation. *Sci China Life Sci* 2018;61:779-786.

[23]. 23He X, Cui LH, Wang XH, et al. Modulation of inflammation by toll-like receptor 4/nuclear factor-kappa B in diarrhea-predominant irritable bowel syndrome. *Oncotarget* 2017;8:113957-113965.

[24]. 24Peng C, Ouyang Y, Lu N, Li N. The NF-κB Signaling Pathway, the Microbiota, and Gastrointestinal Tumorigenesis: Recent Advances. *Front Immunol* 2020;11:1387.

[25]. 25Yang Z, Liu W, Zhou X, et al. The effectiveness and safety of curcumin as a complementary therapy in inflammatory bowel disease: A protocol of systematic review and

meta-analysis. *Medicine (Baltimore)* 2020;99:e22916.

[26]. 26Lin CY, Lee AH, Chiu KK, et al. *Saccharomyces cerevisiae* Fermentation Product Did Not Attenuate Clinical Signs, but Psyllium Husk Has Protective Effects in a Murine Dextran Sulfate Sodium-Induced Colitis Model. *Curr Dev Nutr* 2020;4:nzaa159.

[27]. 27Rizvi W, Fayazuddin M, Shariq S, et al. Anti-inflammatory activity of roots of Cichorium intybus due to its inhibitory effect on various cytokines and antioxidant activity. *Anc Sci Life* 2014;34:44-49.

[28]. 28So D, Whelan K, Rossi M, et al. Dietary fiber intervention on gut microbiota composition in healthy adults: a systematic review and meta-analysis. *Am J Clin Nutr* 2018;107:965-983.