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Role of exercise in preventing and restoring gut dysbiosis in patients with inflammatory bowel diseases: A review

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Abstract

Inflammatory bowel diseases (IBD) include a spectrum of chronic inflammatory disorders of the gastrointestinal tract whose pathogenesis is yet to be elucidated. The intestinal microbiome has been studied as a causal component, with certain microbiotic alterations having been observed in subtypes of IBD. Physical exercise is a modulator of the intestinal microbiome, causing shifts in its composition that are partially corrective of those observed in IBD; furthermore, physical exercise may be beneficial in patients with certain IBD subtypes. This review studies the effects of physical exercise on the human gut microbiome while investigating pathophysiologic mechanisms that could explain physical activity's clinical effects on patients with IBD.

Key Words: Inflammatory bowel disease; Ulcerative colitis; Crohn's disease; Pouchitis; Microbiome; Exercise

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Core Tip: Inflammatory bowel diseases (IBD) are a spectrum of diseases that are characterized by their complex pathogenesis. The intestinal microbiome is thought to be a part of their pathogenesis, with certain alterations having been associated with

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IBD subtypes. Physical exercise is a modulator of the intestinal microbiome that has, furthermore, been associated with positive clinical outcomes in certain patients with IBD. Herein we discuss certain types of physical exercise, their effect on the intestinal microbiome, and its clinical effects on patients with IBD, as well as investigating underlying pathophysiologic mechanisms that could mediate the observed associations.

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INTRODUCTION

Inflammatory bowel disease (IBD) comprises a spectrum of chronic inflammatory diseases that primarily but not exclusively affect the gastrointestinal tract, including ulcerative colitis (UC), Crohn's disease (CD), and other related conditions[1]. Their pathogenesis is classically thought to include interactions between genetic, immune-mediated, and environmental factors[2]. Studies on the molecular epidemiology of IBD have shown that the gut microbiome composition is a biomarker of prognostic importance for CD and UC[3]. Other molecular phenotypes include *NOD2*, *MHC*, and *MST1* genotypes, which are correlated to disease location and activity, microRNA miR-215 levels, and DNA methylation, which are correlated to disease activity, *FOXP3* haplotype, which is of prognostic importance, and oncostatin M and IL-1 β levels, which predict response to anti-tumor necrosis factor therapy[3,4]; furthermore, serum C-reactive protein levels correlate to disease activity but are generally nonspecific[4]. Increased serum miR-595 and miR-1246 levels are associated with active IBD[4]. Serum interleukin (IL)-2 and IL-6l and positivity for anti-bacterial flagellin, anti-outer membrane porin C, anti-A4-Fla2, and anti-Fla-X antibodies predict recurrence of disease[4]. The heterogeneity of IBD phenotypes underlines the need for new markers that can subclassify, diagnose, inform prognosis, and guide IBD treatment; but owing to the low sensitivity or specificity of known molecular markers, current knowledge is far from adequate to support their use in everyday clinical practice, a limitation that includes the microbiome as biomarker[3,4].

Early studies on animal models have shown that immune cells could not cause inflammation in the absence of intestinal bacteria, therefore suggesting a putative role for the intestinal microbiome in the induction and/or maintenance of local inflammation and disease[5]. This was further supported by the observation that intestinal inflammation in IBD was greatest in parts of the bowel richer in bacteria[2]. Further studies have demonstrated that certain patterns of microbiotic alterations, including increases or reductions in the plethora of bacterial, fungal, and viral species, were likely linked to the risk for IBD[2].

Physical exercise is a possible modulator of intestinal microbiome composition, altering the functional activity of the gut ecosystem. Exercise is associated with increased biodiversity and a beneficial metabolic function, while exhaustive exercise training might be associated with dysbiosis of the gut microbiota, promoting negative metabolic effects and inflammation[6,7]. Thus, physical activity/exercise has been studied as a significant modifier of the intestinal microbiome in animal[8,9] and human[6,7,10] studies. Specifically, more active individuals' microbiomes tend to harbor a higher abundance in *Akkermansia muciniphila*, a health-promoting species, as well as decreased Bacteroidetes bacteria and increased bacterial diversity[11,12]. Specific types of physical exercise have not only been associated with microbiotic signatures, but also with a reduction in endotoxemia and serum inflammatory markers [11,13,14]. These alterations persist as statistically significant, even when normalizing for age, weight, body composition, and nutritional habits as confounding factors[15]. Nevertheless, it should be noted that researchers have also reported a lack of correlation between a certain type of exercise and changes in the microbiome[16,17]; moreover, some contradictions as to the observed patterns of microbiotic alterations associated with exercise are evident[18]. This ambiguity is, however, expected to be partly clarified when common definitions and detailed description of exercise charac-

teristics [*i.e.* frequency, intensity, type (mode), time (duration), and volume/dose (duration x intensity)] and methods of fecal sampling are utilized among the same study groups.

Given the established pathobiological role for the microbiome in IBD and taking into account the more recent data assessing patterns of microbiotic alterations associated with exercise, this review aims to summarize and clarify the important findings linking dysbiosis in IBD to physical activity, with a focus on preventative medicine and therapeutics.

METHODOLOGY

Our literature search utilized the PubMed literature database. Search keywords included “inflammatory bowel disease”, “IBD”, “ulcerative colitis”, “Crohn’s disease”, “indeterminate colitis”, “microbiome”, “microbiota”, “physical activity”, “exercise”, as well as combinations of the aforementioned with the AND/OR operators. Articles were first filtered by title, followed by abstract screening, and the remaining were finally selected based on their full text.

EXERCISE AND ITS INFLUENCE ON THE MICROBIOME

In healthy mice, *Allobaculum* and *Clostridiales* are more abundant in exercised mice than in controls[19]. In diabetic mice, total intestinal bacteria and Enterobacteriaceae are lower in the exercise groups than in diabetic controls[9]. In high-fat diet obese mice, exercise increases Bacteroidetes as well as increases the Bacteroidetes/Firmicutes ratio in the cecum and colon[20]. In an early obesity and non-alcoholic fatty liver disease model, where male rats fed a control or a high-fat diet, a combined aerobic and resistance exercise training resulted in increased *Parabacteroides*, *Bacteroides*, and *Flavobacterium* genera, while *Blautia*, *Dysgonomonas*, and *Porphyromonas* exhibited an opposite pattern[8] (Table 1).

Several factors that modify the human gut microbiome have been identified; those include country of residence, specific genotypes (such as those affecting the ABO antigens), delivery by caesarian section, diet, cigarette smoking, breastfeeding, gastroenteritis, increased hygiene, use of antibiotics, obesity, immune response, as well as physical exercise[2,13,21,22]. Human studies have shown that sedentary individuals have a predominance of *Bacteroides* and *Parabacteroides* in their gut microbiome, while participants with a higher level of activity, as gauged by accelerometers, have a predominance of *Coprococcus*, *Blautia*, and *Eubacterium*[23]. Women with an active lifestyle have a higher proportion of *Faecalibacterium prausnitzii*, *Roseburia hominis*, and *Akkermansia muciniphila* bacteria in their gut than sedentary women[24]. Aerobic brisk walking increases *Bacteroides* species in healthy elderly women[25]. Endurance training has been observed to reduce *Streptococcus*, *Proteobacteria*, *Porphyromonadaceae*, *Odoribacter*, *Desulfovibrionaceae*, and *Enterobacteriaceae* and to increase *Verrucomicrobiaceae*, *Bifidobacteriaceae*, *Dorea*, *Anaerofilum*, and *Akkermansia* bacteria in overweight women[26]. In obese children, a strength and endurance combined training program led to an increase in *Blautia*, *Dialister*, and *Roseburia* species, accompanied by a reduction in inflammasome activation[14]. In elderly men, endurance exercise has been observed to reduce *Clostridium difficile* and increase intestinal populations[27]. Male elite rugby players have been found to have a more diverse microbiome than body mass index (BMI)-matched controls, with the athletes having higher proportions of *Akkermansiaceae* and *Akkermansia* than high-BMI controls and lower proportions of *Lactobacillaceae*, *Bacteroides*, and *Lactobacillus* than low-BMI controls[10]. In swimmers, a reduction in training volume is accompanied by a significant reduction in *Coprococcus* and *Faecalibacterium* populations[28]. In marathon runners, *Lentisphaerae* and *Acidobacteria* increase in intestinal population after running[29]. Ultra-endurance exercise has been observed to increase butyrate-producing bacteria, such as *Subdoligranulum* and *Roseburia hominis*, which are thought to reduce intestinal inflammation by producing butyrate[30]. In martial arts athletes, *Parabacteroides*, *Phascolarctobacterium*, *Bilophila*, and *Oscillibacter* are higher in higher-level athletes than in lower-level ones, with *Allisonella*, *Citrobacter*, and *Megasphaera* found at lower levels[31]. Other researchers have reported no change in gut bacterial diversity or composition after short-term high-intensity interval training in lean and overweight men[16]. Exercise has also been found to induce microbial transformations in the context of damaging intestinal conditions, such as a high-fat diet and toxic substances[32] (Table 1). These changes

Table 1 Effect of exercise on the gut microbiome

Ref.	Study subject	Sample type	Exercise protocol	Exercise vs controls	Notes
Lambert <i>et al</i> [9]	Mouse, type 2 diabetic, (C57BL/KsJ-leprdb/leprdb)	Cecal matter	Treadmill, 5 d/wk, 66 min/d, 2.87 m/min	<ul style="list-style-type: none"> ↑ <i>Clostridium leptum</i> ↑ <i>Lactobacillus</i> ↓ Total bacteria ↓ <i>Bacteroides</i> ↓ <i>Bifidobacterium</i> ↓ <i>Methanobrevibacter</i> ↓ <i>Prevotella</i> 	↑ <i>Bifidobacterium</i> with exercise in non-diabetic mice
Campbell <i>et al</i> [19]	Mouse C57BL/6NTac, male	Fecal matter from the distal colon	Free running wheel	<ul style="list-style-type: none"> ↑ <i>Allobaculum</i> ↑ Clostridiales ↑ <i>Faecalibacterium prausnitzii</i> 	Normal-diet, not observed in a high-fat diet, except for <i>Faecalibacterium prausnitzii</i>
Denou <i>et al</i> [20]	Mouse, C57 BL/6, high-fat diet, obese	Feces from anal area, then full intestinal sampling	Treadmill, 6 wk total, 3 d/wk, 1 h/d, 17 m/min at 5% grade for 2 min + 2 min rest, increase by 1 m/min every week	<ul style="list-style-type: none"> ↑ Bacteroidetes/Firmicutes ratio in the cecum ↑ Bacteroidetes/Firmicutes ratio in the rectum 	-
Carbajo-Pescador <i>et al</i> [8]	Juvenile male Wistar rats on early obesity and non-alcoholic fatty liver disease onset	Fecal matter	Treadmill, 11 wk total, 60 min/d combined aerobic and resistance training (10-min running; eight 2-min progressive incline run from 10°-25° at 20-25 cm/s /1 min rest; 30 min aerobic exercise)	<ul style="list-style-type: none"> ↑ <i>Parabacteroides</i> ↑ <i>Bacteroides</i> ↑ <i>Flavobacterium</i> genera ↓ <i>Blautia</i> ↓ <i>Dysgonomonas</i> ↓ <i>Porphyromonas</i> 	-
Clarke <i>et al</i> [10]	Human, rugby player, male	Fecal matter, self-collected	Rugby training, capacity determined by EPIC-Norfolk questionnaire	<ul style="list-style-type: none"> ↑ <i>Akkermansia</i> (than high-BMI controls) ↓ <i>Bacteroides</i> (than low-BMI controls) ↓ <i>Lactobacillus</i> (than low-BMI controls) 	-
Bressa <i>et al</i> [24]	Human, female, premenopausal, BMI 20-25 kg/m ²	Fecal matter, self-collected	No forced exercise, physical activity level gauged by accelerometers	<ul style="list-style-type: none"> ↑ <i>Akkermansia muciniphila</i> ↑ <i>Faecalibacterium prausnitzii</i> ↑ <i>Roseburia hominis</i> 	-
Munukka <i>et al</i> [26]	Human, female, sedentary, BMI > 27.5 kg/m ²	Fecal matter, self-collected	Ergometer, Weeks 1-2: at 60 rpm, low intensity, 3 d/wk, 40 min/d	<ul style="list-style-type: none"> ↑ <i>Akkermansia</i> ↑ <i>Anaerofilum</i> ↑ Bifidobacteriaceae ↑ <i>Dorea</i> 	-
			Weeks 3-4: 3 d/wk, 50 min/d, every other session 3 10-min intervals of moderate-intensity cycling, the rest low intensity	<ul style="list-style-type: none"> ↑ Verrucomicrobiaceae ↓ Desulfovibrionaceae ↓ Enterobacteriaceae ↓ <i>Odoribacter</i> ↓ Porphyromonadaceae ↓ Proteobacteria 	
			Weeks 5-6: 3 d/wk, 60 min/d, four 10-min moderate intensity intervals, the rest low intensity	<ul style="list-style-type: none"> ↓ <i>Streptococcus</i> 	
Taniguchi <i>et al</i>	Human, male, age > 60	Fecal matter,	Cycling, Weeks 1-2: 3 d/wk, 30	<ul style="list-style-type: none"> ↓ <i>Clostridium difficile</i> 	-

<i>al</i> [27]	yr, healthy	self-collected	min/ d, 60% of VO ₂ peak (week 1), 70% of VO ₂ peak (week 2) Weeks 3-5: 3 d/wk, 45 min/ d, 70% of VO ₂ max (week 3), 75% of VO ₂ max (weeks 4-5)	↑ Oscillospora	
Zhao <i>et al</i> [29]	Human, marathon runners	Fecal matter, self-collected	The 2016 Chongqing half marathon, before and after the race	↑ Acidobacteria ↑ Lentisphaerae	Post- <i>vs</i> pre-running
Castellanos <i>et al</i> [23]	Human	Fecal matter, self-collected	No forced exercise, physical activity level gauged by accelerometers	↑ Blautia ↑ Coprococcus ↑ Eubacterium ↓ Bacteroides ↓ Parabacteroides	-
Keohane <i>et al</i> [30]	Human, male, athlete	Fecal matter, self-collected	Rowing race, 33 d 22 h, 151.8 km per day	↑ Roseburia hominis ↑ Subdoligranulum	Post-ultra-endurance exercise
Liang <i>et al</i> [31]	Human, martial arts athlete	Fecal matter, self-collected	Martial arts, athletes, divided into higher- and lower-level based on General Administration of Sport of China criteria	↑ Bilophila ↑ Oscillibacter ↑ Parabacteroides ↑ Phascolarctobacterium ↓ Allisonella ↓ Citrobacter ↓ Megasphaera	Higher- <i>vs</i> lower-level athletes
Morita <i>et al</i> [25]	Human, female, age > 65 yr, sedentary	Fecal matter, self-collected	Trunk strengthening training, 12 wk, 1 h/wk: 5-10 min of warm-up + 45 min of targeted resistance training of trunk muscles + 5 - 10 cool-down and at-home exercise daily	↑ Bacteroides	After 12 wk of aerobic training
Hampton-Marcell <i>et al</i> [28]	Human, age 18-24 yr, swimmers	Cotton swab sample	Self-reporting of daily swimming distance and duration during daily practice	↑ Coprococcus ↑ Faecalibacterium	Before <i>vs</i> after reduction of training volume
Quiroga <i>et al</i> [14]	Human, age 7-12 yr, obese	Fecal matter, self-collected	Strength and endurance training 12 wk, 2 d/wk: Warm-up on an ergometer for 7 min, low-medium load, 60 rpm Third minute onwards, a sprint of 30s at 3'30", 4'30", 5'30", and 6'30" Strength exercises for five muscle groups, initially 3 sets of 12 repetitions at 30% 1RM, up to 3 sets of 8 repetitions at 70% 1RM Cool-down at an elliptical cardiovascular device, 7 min, 50 rpm, 4 min low-medium load + 3 min high load	↑ Blautia ↑ Dialister ↑ Roseburia	After a 12-wk strength and endurance training program
Rettedal <i>et al</i> [16]	Human, male, age 20-45 yr	Fecal matter, self-collected	9 sessions of high-intensity interval training on non-consecutive days over 3 wk: 60 s cycling at VO ₂ peak 75 s rest 8 intervals initially, up to 12 intervals by the end of the protocol	No significant changes in composition	Before and after high-intensity interval training

BMI: Body mass index.

could in part be attributed to increased gut motility during exercise, which promotes shedding of loosely bound bacteria and the growth of health-promoting species[33].

ROLE OF THE MICROBIOME IN IBD

Patients with CD have a diminished diversity of the fecal intestinal microbiome, with Lachnospiraceae, Bacteroidetes, and the species *Clostridium leptum* being decreased, with Proteobacteria, Actinobacteria, and the genus *Prevotella* being increased[13]. Patients with inflammatory bowel disease also have increased *Fusobacterium*, *Pasturellaceae*, *Ruminococcus gnavus*, *Veillonellaceae*, *Candida albicans*, *Candida tropicalis*, *Clavispora lusitaniae*, *Cyberlindnera jadinii*, *Kluyveromyces marxianus*, and *Caudivirales* in their gut microbiota, as well as decreased *Bacteroides*, *Bifidobacterium*, *Clostridium XIVa*, *Clostridium IV*, *Faecalibacterium prausnitzii*, *Roseburia*, *Sutarella*, and *Saccharomyces cerevisiae* [2]. Therefore, it can be argued that intestinal dysbiosis may be a component of IBD pathogenesis[34].

The involvement of the microbiome in the pathogenesis of IBD is further supported by the effectiveness of antibiotic therapy in the treatment of certain IBD phenotypes, such as perianal CD and pouchitis, and in the prevention of postoperative relapse in patients with CD[2].

Fecal microbiota transplantation involves the transfer of feces from a donor to the GI tract of a recipient, as an attempt to enrich the recipient's gut microbiota and correct any dysbiosis. Fecal microbiota transplantation is currently systematically used in the treatment of *Clostridium difficile* colitis[35]. Some researchers have also investigated its implementation in IBD therapeutics, with some promising findings having been reported, although no concrete conclusions can yet be drawn about its efficacy and safety, plausibly owing to the dissimilarities between the associated studies[35].

ANIMAL CLINICAL DATA

Gut microbiota transplant from exercise-trained mice leads to a reduction in inflammatory markers in the distal colons of sedentary mice, combined with an attenuated colitis histology score[36]. In mouse models of colitis, voluntary treadmill exercise has been found to reduce inflammation while forced exercise exacerbates tissue damage and leads to increased mortality[37]. The same researchers then attributed part of this effect to an increase in *Tenericutes* bacteria in the large intestine in the forced-exercise group, since the family *Mollicutes*, a member of the phylum *Tenericutes*, has been linked to UC in humans[38]. In another study, exercise was shown to ameliorate the symptoms of chemically induced colitis and to alter significantly gut microbiota, with decreased populations of *Bacteroides vulgatus* and increased numbers of *Akkermansia muciniphila*[39]. In mice born without a normal mucus layer in their intestines due to a genetic knockout of mucin-2, exercise neither significantly alters the gut microbiome nor reduces the severity of chronic colitis, in contrast to wild-type mice where both effects have been observed[40].

HUMAN CLINICAL DATA

Based on current literature, it is not clear whether dysbiosis is a cause or a result of IBD[13]; however, some conclusions could be drawn from certain scientific findings: Disease activity is mostly focused on bowel segments where the fecal stream is slower and bacterial populations are higher[2]. Mutations in genes affecting the functions of intestinal Paneth cells (*e.g.*, *NOD2*), which defend the small intestine against bacteria, are risk factors for IBD[2]; moreover, exposure to antibiotics in early life is linked to IBD later in life[13]. Antibiotics are, however, effective in certain conditions involving IBD, such as in inflammation of the ileoanal pouch after colectomy indicated by IBD-related complications[41]. Surgical fecal diversion is beneficial in the treatment of CD, as bowel segments excluded from the fecal stream tend to show remission[2]; furthermore, probiotics and fecal transfer are a therapeutic option for inducing and maintaining IBD remission[13]. These findings suggest that there exists a causal component to the microbiotic patterns associated with IBD, despite the inconsistencies between observed microbiotic changes as reported by different studies[13].

Regarding the probable protective effect of exercise in IBD, it is thought to stem from anti-inflammatory actions[6]. These include the secretion of myokines by skeletal muscles, such as myostatin, irisin, IL-15, brain-derived neurotrophic factor, myonectin, decorin, and secreted protein acidic and rich in cysteine, mediators with autocrine, paracrine, and endocrine anti-inflammatory actions[42]; moreover, in obese humans, exercise has been found to alter the gut microbiome and reduce endotoxemia, as

measured by the levels of the endogenous protein lipopolysaccharide binding protein [11], thus suggesting another probable anti-inflammatory effect for physical activity. Exercise training has also been found to reduce the levels of NLR Family Pyrin Domain Containing 3 and caspase 1, proteins that participate in the inflammasome activation pathway, in obese children[14].

Several mechanisms have been proposed by which exercise may influence gut microbiota. These include crosstalk between muscles and the gut microbiota through the 5' adenosine monophosphate-activated protein kinase and fasting-induced adipose factor pathways as well a reduction of fecal bile acids, an increase in production of short-chain fatty acids, an increase in gut luminal immunoglobulin A, a reduction in luminal transit time, and the activation of the stress hypothalamic-pituitary-adrenal axis, effects found to be produced by exercise[43-46].

The functions of a healthy microbiome include metabolic functions, such as the production of anti-inflammatory short-chain fatty acids, vitamin K, and biotin, protective effects, such as induction of secretions that attack pathogenic bacteria, triggering of mucosal proliferation through the Toll-like receptor pathway, inhibition of adhesion of pathogenic bacteria, and trafficking of neutrophils, as well as trophic functions, *i.e.* protecting the intestinal mucosa from immune-mediated damage[46-48]. Part of the pathogenesis of IBD is thought to include a loss of these effects, probably caused by a damaging shift to the microbial composition in the gut[1]. These include reductions in Bacteroidetes, *Clostridium leptum*, *Prevotella*, *Bifidobacterium*, and *Roseburia* as well as increases in Proteobacteria, as mentioned above. All of these alterations are restored by exercise interventions in animal and human studies (Table 1), suggesting a plausible mechanism for the beneficial effect of exercise in IBD.

Current exercise guidelines from the American Heart Association for adults aged 18 years to 65 years of age recommend moderate-intensity aerobic exercise for at least 30 min, 5 d a week or vigorous-intensity exercise physical activity for 20 min, 3 d a week [49]. No specific guidelines exist for patients with IBD, however, evidence suggests that mild-to-moderate exercise harbors multiple benefits for patients with at least mild IBD, and excessive exercise could pose hazards for patients' health[41]; therefore, physicians should be cautious when prescribing exercise for patients with IBD, being on the lookout for exercise addiction[41].

Clinical data studying the association of IBD with exercise suggest that sedentary occupations confer a higher risk for IBD than more physically demanding occupations, as found in a retrospective study of German employees[50]; moreover, both CD and UC have been associated with low physical activity during childhood[51]. Exercise has been reported to decrease the risk of relapse in patients with IBD in remission[52]. Mild-to-moderate exercise is beneficial in patients with at least mild IBD[41]. A recent study reported that prolonged moderate-intensity walking did not appear to increase blood cytokine levels in patients with IBD more than it did in healthy controls, and fecal calprotectin levels were found to be comparable between patients who walked and patients who did not walk, suggesting that exercise does not cause exacerbation of IBD[53].

CONCLUSION

The findings of the present review imply that there exists a promising field of research regarding exercise-induced changes of the microbiome in IBD. What needs to be elucidated is whether the microbiome is a passive "bystander" in the systemic effects induced by physical activity, *i.e.* observing and reacting to activity-related systemic metabolic and endocrine signals by altering its composition, or whether it is a necessary physiological intermediate in the restoration of immune tolerance and normal gastrointestinal function in the context of IBD. Further research should also focus on disease determinants, such as age, sex, type, localization, histology, refractory phenotype, disease activity, molecular markers, and performance status, which could affect the disease's response to certain types of physical exercise. Besides, considering that there is not only one optimal microbiota composition for the IBD patients, more studies are also needed to reveal how microorganisms interact with each other and with their host to identify different healthy microbiota schemes and an optimal, potentially personalized, dose of exercise for these patients. Lastly, an interesting field might exist for the microbiome as an index predictive or indicative of exercise-induced amelioration of IBD clinical symptoms, as part of current research on the molecular epidemiology of IBD.

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