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REVIEW ARTICLE

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Major considerations of nutrological aspects, gut microbiota, and regulation (down or up-regulation) of microRNAs/exosomes in inflammatory bowel diseases: a systematic review

Mayelin Abreu Jorrin[1*], Sergio Hernandez Cumbá[2], Justa Carmen Columbié Regüeiferos[2]

[1] Santo André II Clinical Center, Santo André, São Paulo, Brazil.
[2] HCC Saturnino Lora. Santiago de Cuba, CUBA.

*Corresponding Author: Dr. Mayelin Abreu Jorrin.
Santo André II Clinical Center, Santo André, São Paulo, Brazi.
E-mail: mayeadjoa72@yahoo.com.br
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Abstract

Introduction: Inflammatory bowel diseases (IBD) are multifactorial, chronic, continuous, relapsing, and immune-mediated diseases of the gastrointestinal tract. The pathogenesis of IBD is linked to genetically susceptible individuals, dysregulated gut microbiota (dysbiosis), chronic inflammation, and poor dietary patterns. Diet and microRNAs/exosomes play an important role in modulating the intestinal microbiota, and can be applied as a therapeutic tool to improve the course of IBD. **Objective:** It was to carry out a systematic review of the main considerations of nutrological aspects, intestinal microbiota, and the regulation (Down or Up-regulation) and modulation of microRNAs/exosomes in inflammatory bowel diseases. **Methods:** The present study followed the international model of systematic review and meta-analysis (PRISMA). Clinical studies were included, involving randomized controlled, prospective, and retrospective studies, as well as pre-clinical studies, published in previous years as gold standard articles until 2023. **Results and Conclusion:** A total of 154 articles were found. A total of 78 articles were fully evaluated and 55 were included in this systematic review. Considering the Cochrane tool for risk of bias, 22 studies with a high risk of bias and 24 studies that did not meet the GRADE were removed. Most studies showed homogeneity in their results, with X^2 =93.5% >50%. The present study analyzed the main interactions between dietary therapy, intestinal microbiota, microRNAs, exosomes, and inflammatory bowel disease, elucidating the main clinical outcomes of the disease after nutrological treatment. As a corollary, important randomized controlled clinical studies were found in the last ten years that showed the important role of diet modulation in the control and even in the remission of inflammatory bowel disease, revealing important reductions in persistent intestinal symptoms, in the balance of the intestinal microbiota, in the regulatory role of microRNAs, reducing inflammation markers and improving quality of life. Recognition of the need for additional data from clinical trials, the inherent uncertainty of efficacy for all inflammatory bowel disease therapies, and the potential for benefit with dietary interventions will help guide progress toward a better understanding of the usefulness of dietary therapy for individuals with inflammatory bowel disease.

Keywords: Inflammatory bowel disease. Nutrological treatment. Gut microbiota. microRNAs. Exosomes.

Introduction

Inflammatory bowel diseases (IBD) are multifactorial, chronic, continuous, relapsing, and immune-mediated diseases of the gastrointestinal tract. IBD have increased in incidence worldwide **[1]**. The main proven risk factor for both IBD is a positive family history in 10-25% of patients. Crohn's disease (CD) can affect individuals from 15 to 40 years old and from 50 to 80 years old, it has a higher percentage in women and has increased around 15 times in recent decades **[1,2]**. As for Ulcerative Colitis (UC), the disease can start at any age **[3]**.

The pathogenesis of IBD is that genetically susceptible individuals develop intolerance to dysregulated gut microbiota (dysbiosis) and chronic inflammation develops as a result of poor dietary triggers **[4-6]**. Thus, diet plays an important role in the

modulation of the gut microbiota and can be applied as a therapeutic tool to improve the course of the disease **[7]**. Current research in the field of IBDs is largely focused on establishing the role of causal variants in gene expression **[8-11]**.

In this scenario, the evolution and clinical manifestation of IBD are related to the interaction between genetic factors, with emphasis on mutations in the NOD2 gene (or CARD15) and also three other main mutations (R 702W, G908 R, and 1007 frameshift) have been described and linked to disease phenotype, intestinal microbiota and mucosal immunoregulation **[12-17]**. In this context, metabolism encompasses the interactions between diet, the microbiome, and cellular enzymatic processes that generate the chemical pathways necessary to sustain life. Endogenous metabolites and dietary nutrients can directly influence epigenetic enzymes. Epigenetic modifications to DNA and histone proteins alter cell fate by controlling chromatin accessibility and downstream gene expression patterns **[18]**.

In addition to the connection between metabolism and epigenetic pathways, nutrients can impact the cellular state by modulating signaling pathway activity. One example is through the mechanistic targeting of the rapamycin (mTOR) signaling pathway and, in particular, the mTOR complex 1 (mTORC1), which regulates cell growth only when nutrients and growth factors are present. Depletion of specific nutrients including arginine, leucine, and S-adenosyl methionine prevents growth factor-induced mTORC1 activation by blocking Rag GTPase-mediated recruitment of mTORC1 to the lysosome where it can be activated by Rheb GTPase **[18]**.

Another way that nutrients are sensed to impact cellular status is through AMPactivated protein kinase (AMPK), which at low levels of cellular ATP phosphorylates substrates to restore the cell's energy balance and in the process regulates cell growth and autophagy. Furthermore, transcription factors can be directly regulated by metabolites such as tryptophan kynurenine **[18]**. Furthermore, dietary manipulations and metabolites can affect tissue stem cells and direct cell fate decisions, as highlighted in the small intestine by intestinal stem cells (ISC). In this case, the enzyme 3-hydroxy-3-methylglutaryl-CoA synthase (Hmgcs2) is highly expressed. Also, sources of ketogenic or high-glucose diets regulate the balance of self-renewal by ISC **[18]**.

Thus, all these epigenetic and nutrological mechanisms are of paramount importance, as approximately 70.0 to 80.0% of patients lose weight with IBD, leading to some degree of nutritional impairment, and around 23.0% of patients outpatients and 85.0% of those hospitalized with a predominance of malnutrition **[19,20]**. In this regard, diet also plays a decisive role in modulating the composition of the microbiome **[13]** and influences the inflammatory response **[17]**. Thus, a balanced diet low in fat and fiber may be important in preventing dysbiosis and preserving the immune system **[21]**.

Furthermore, the adaptive immune system of the intestine is also rapidly activated after exposure to commensal bacteria, with an increase in the expression of class II molecules of the major histocompatibility complex and an increase in T cells **[1]**. T cells can generate subpopulations whose immune response is either pro-inflammatory or anti-inflammatory. Th1 and Th17 cells – helper T cells are pro-inflammatory, while Treg cells (CD4+ CD25+ phenotype) and Th2 are anti-inflammatory **[8]**.

In this sense, the Gram-negative bacterium *Bacteroides fragilis* induces the differentiation of CD4+ T cells into Treg cells, leading to the production of antiinflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor beta (TGFβ), nullifying the Th17 pro-inflammatory response **[8]**. The differentiation of Treg cells depends on the recognition by T CD4+ cells of the polysaccharide presented by DC. In turn, segmented filamentous bacteria, after contact with antigen-presenting cells, have been shown to induce pro-inflammatory cells, such as Th17 cells **[8]**.

Still in this regard, microRNAs (miRNAs) have been associated with several physiological processes, such as cell development and proliferation, apoptosis, and cancer. In addition, they play an important role in inflammatory processes, acting in the regulation of pro- and anti-inflammatory pathways. Differences in miRNA profiles may represent a useful tool in the diagnosis of IBD and as a prognostic marker. Several studies have shown the role of miRNAs in the modulation of the intestinal microbiota and induction of dysbiosis. The microbiota, in turn, can regulate the expression of miRNAs and, consequently, alter intestinal homeostasis **[22]**.

Given this information, the present study aimed to carry out a systematic review of the main considerations of nutritional aspects, gut microbiota, and the regulation (Down or Up-regulation) and modulation of microRNAs/exosomes in inflammatory bowel diseases.

Methods

Study Design

The present study followed the international model of systematic review and metaanalysis, following the

rules of PRISMA **[23]**. Table 1 shows the main variables of the present study that were addressed according to the PICOS classification (P=Patients; I=Intervention; C= Control; O=Outcomes; S=Study Design).

Table 1. PICOS chart (Patients; Intervention; Control; Outcomes and Study Design).

Patients	Patients with inflammatory bowel disease
Intervention	Nutrological Treatment/Probiotics
Control	pharmacological treatment
Outcomes	Increased modulation of microRNAs and inflammatory reduction
Study Design	Randomized Controlled Studies; Prospective; Retrospectives (observational/epidemiological), and pre-clinical studies

Study Eligibility Criteria

Inclusion criteria were clinical studies, involving randomized controlled studies, prospective and retrospective (observational/epidemiological), and preclinical studies published in previous years as gold standard articles until 2023 on the main clinical outcomes of nutrological treatment and aspects of modulation of microRNAs in the intestinal microbiota, and vice versa, in inflammatory bowel diseases. The main characteristics of the studies that were analyzed in this study included patients in all age groups and patients with inflammatory bowel disease, with or without the use of drugs. Exclusion criteria for the present study were case report studies, editorials, letters to the editor, review studies, and meta-analysis.

Risk of Bias

The quality of scientific evidence in the studies addressed was classified as high, moderate, low, or very low, according to the risk of bias in the body of evidence, clarity of comparisons, precision, and consistency in treatment effects, according to the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) **[24]**. High-quality evidence was assigned to well-designed randomized controlled trials with consistent results. Evidence quality was downgraded to moderate if 1 of the 4 evidence quality criteria are not met and lower if 2 or more are not met. A low quality of evidence was assigned to studies with inconclusive results. The Cochrane Instrument was adopted to assess the risk of bias in the included studies **[25]**.

Data Sources and Research Strategy

The search strategies for this systematic review and meta-analysis were based on the keywords (MeSH Terms) *"Inflammatory bowel disease. Nutrilogical treatment. Gut microbiota. microRNAs. exosomes"*. The survey was conducted from March to April 2023 and developed using Scopus, Web of Science, PubMed/Medline, Embase, Science Direct, Ovid, Lilacs, Cochrane Library, and EBSCO databases, including the National Institutes of Health database. RePORTER Grant and Clinical Trial Records. In addition, a combination of keywords with the Booleans "OR", AND and the operator "NOT" were used to target scientific articles of interest. The title and abstracts were screened under all conditions. Table 2 presents an example of the search structure in PubMed. Similar search strategies were used in the other databases.

Table 2. For example in the search structure in PubMed, the same search strategy was used in the other databases.

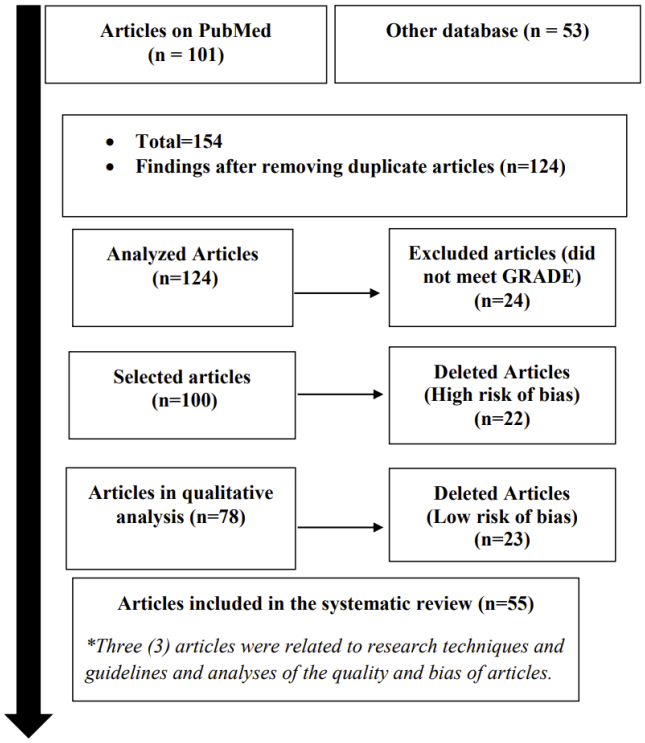
PubMed	Inflammatory bowel disease **OR** Nutrition **OR** Nutrological treatment **OR** Gut microbiota **OR** microRNAs
	AND
PubMed	Randomized controlled trial **OR** Prospective study **OR** Retrospective study **OR** Observational/Epidemiological studies **OR** Experimental studies (animals or *in vitro* studies)
	NOT
PubMed	**OR** Case reports **OR** Editorials **OR** Letters to the editor **OR** Review study **OR** Metaanalysis

Results

Summary of Findings

A total of 154 articles were found. Initially, duplication of articles was excluded. After this process, the abstracts were evaluated and a new exclusion was performed, removing the articles that did not include the theme of this article, resulting in 124 articles. A total of 78 articles were evaluated in full and 55 articles were included and developed in this systematic review study (Figure 1). Three (3) articles were related to research techniques and guidelines and analyses of the quality and bias of articles. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 22 studies with a high risk of bias and 24 studies that did not meet GRADE. According to the GRADE instrument, most studies showed homogeneity in their results, with X2=93.5%>50%.

Figure 1. Flowchart showing the article selection process.



Source: Own authorship

Major Outcomes and Clinical Relevance

According to the objective of the present study, this research showed the important role of diet modulation in the control and even in the remission of IBD. In this sense, they showed important reductions in persistent intestinal symptoms, improvement of the intestinal microbiota and in the modulation of microRNAs, reduction of inflammation markers, and improvement in quality of life, through randomized controlled clinical studies and other clinical and pre-clinical studies in recent years. ten years that showed the important role of diet modulation in the control of IBD **[26-42]**.

One of the most significant challenges in IBD research is understanding how alterations in the symbiotic relationship between the host's genetic makeup and gut microbiota, under the impact of specific environmental factors, lead to chronic gut inflammation. Genomic-wide association studies, followed by functional studies, have identified a role for numerous autophagy genes in IBD, especially Crohn's disease. Studies using *in vitro* and *in vivo* models, in addition to human clinical studies, have revealed that autophagy is critical for maintaining intestinal homeostasis, regulating intestinal ecology, adequate intestinal immune responses, and antimicrobial protection **[43]**.

Still, a study elaborated by the authors Tong et al. 2021 created a protocol for the isolation of extracellular milk vesicles (mEVs) and found that mEVs contained large amounts of immunoactive proteins and modulated intestinal immunity and microbiota in healthy mice. After that, the therapeutic effects of mEVs in inflammatory bowel disease were explored. MicroRNAs and protein content in mEVs were analyzed by RNA sequencing and proteomics, respectively, followed by functional annotation. Ulcerative colitis was induced by feeding mice sodium dextran sulfate. Intestinal immune cell populations were phenotyped by flow cytometry, and the intestinal microbiota was analyzed by 16S rRNA sequencing. It was observed that abundant proteins and microRNAs in mEVs were involved in the regulation of immune and inflammatory pathways and that oral administration of mEVs prevented colonic shortening, reduced intestinal epithelium breakdown, inhibited inflammatory cell infiltration and tissue fibrosis in a mouse model of ulcerative colitis. Mechanically, mEVs attenuated the inflammatory response via inhibition of the TLR4-NFκB signaling pathway and activation of the NLRP3 inflammasome. Furthermore, the mEVs were able to correct the cytokine production disturbance and restore the balance between type 17 helper T cells (Th17) and interleukin-10+Foxp3+ regulatory T cells (Treg) in the inflamed colon. The disturbed intestinal microbiota in ulcerative colitis was also partially recovered after treatment with mEVs. The correlation between gut microbiota and cytokines suggests that mEVs can modulate gut immunity by influencing gut microbiota **[44]**.

In this sense, tumor necrosis factor (TNF) neutralizing antibodies have been widely used to treat IBD in clinical practice. Key biomarker analysis revealed that fecal calprotectin, C-reactive protein, serum or mucosal concentrations of anti-TNF monoclonal antibodies (mAbs) and antibodies to anti-TNF mAbs are commonly used as current biomarkers in the assessment of anti-TNF. However, transcripts of mucosal cytokines, microRNAs, proteomics, and profiling of fecal and intestinal mucosal microbiota and histological characteristics of the mucosa are reported as new candidates for biomarkers with high clinical utility in the assessment of anti-TNF therapeutic efficacy in patients with IBD **[45]**.

In this scenario, it is noteworthy that microRNAs (miRNAs) are small non-coding RNAs and are involved in the production of pro-inflammatory cytokines and the inflammation process, as seen in IBD. Thus, circulating and fecal miRNAs were considered new candidates for biomarkers that predict therapeutic response in patients with IBD **[46]**. The authors Batra et al. validated that the expression of seven miRNAs showed remarkable changes after treatment in responders but not in non-responders in a small cohort of pediatric IBD with

various treatments including anti-TNF mAbs **[47]**. However, other researchers evaluated the association of miRNA polymorphisms with response to anti-TNF treatment **[48]** and did not detect any correlation between the studied miRNA polymorphisms (miR146 rs2910164, miR-196a rs11614913, miR-221 rs113054794, and miR -224 rs188519172) and patient response to anti-TNF mAbs in 107 patients with Crohn's disease.

Furthermore, discoveries of genes that may regulate gut microbiota homeostasis and IBD pathogenesis have the potential to provide new therapeutic targets for the treatment of IBD. The results suggested that the level of microRNA (miR)-602 expression is negatively related to the development of IBDs and that overexpression of miR-602 in mice can prevent inflammation and intestinal barrier damage in mice induced by dextran sulfate. It was also found that the microbiota is important for the prevention of miR-602-mediated IBD, as the inhibitory effect of miR-602 was lost when the microbiota was depleted with the use of antibiotics. Furthermore, cohabitation or adoptive transfer of miR-602 microbiota could attenuate the pathogenesis of IBD. Furthermore, it has been shown that miR-602 can target tumor necrosis factor receptor-associated factor 6 (TRAF6) in intestinal epithelial cells **[49]**.

In this regard, microRNAs can interact with the intestinal microbiota reciprocally and profoundly affect the health status of the host, leading to several disorders when unbalanced. Host miRNA may be playing a relevant role in the pathophysiology of IBD, shaping the gut microbiota. The gut microbiome, on the other hand, can regulate the expression of host miRNAs, resulting in gut epithelial dysfunction, altered autophagy, and immune hyperactivation **[50]**.

The mechanisms underlying inflammatory bowel diseases are thought to include genetic predisposition, environmental factors, and altered immune response to the gut microbiome. Epigenetic modulation occurs through chromatin modifications, including phosphorylation, acetylation, methylation, sumoylation, and ubiquitination. Colonic tissue methylation levels have been found to correlate well with blood samples in inflammatory bowel disease. Furthermore, the level of methylation of specific genes was different between Crohn's disease and ulcerative colitis. It has been shown that enzymes that affect histone modification, such as histone deacetylases and histone acetyltransferases, not only act on histones but also affect the acetylation of many proteins, such as p53 and STAT3. A nonselective histone deacetylase inhibitor, Vorinostat (SAHA), which is currently being used in various cancer treatments, has already been shown to have anti-inflammatory activities in mouse models. MicroRNAs play significant roles in T cell maturation, differentiation, activation, and senility. The long-expression profiles of RNA and non-coding microRNA can neatly separate patients with inflammatory bowel disease from healthy controls and are touted as biomarkers of IBD **[51]**.

In this sense, research on inflammatory bowel disease (IBD) has produced increasing evidence for the modulation of microRNAs during pathogenesis. However, their distinct regulatory roles in the intestinal epithelial barrier remain elusive because several external and cellular factors contribute to intestinal permeability. miRNAs can compromise two components of the intestinal epithelium that together form the initial physical barrier, the mucus layer, and the intercellular epithelial junctions. MicroRNAs can impact goblet cell secretion and mucin structure, along with the proper function of several junctional proteins involved in paracellular transport, cell adhesion, and communication **[52]**.

Added to this, the presence of miRNA in the stool could be a potential target for differences in the gut microbiota between these patients. One study analyzed differences in miRNA levels in fecal samples from 117 patients diagnosed with IBD. There was a significant difference in fecal miRNAs between healthy subjects and those with inactive IBD. Further analyses showed that some miRNAs can indicate the severity of IBD activity and prognosis. Sequencing analysis of the 16S RNA V4 region in the fecal microbiota in these IBD patients revealed significant differences in phylogenetic architecture between individuals with active or inactive IBD and between IBD patients and healthy individuals. Finally, *in vitro*, studies have shown that these differentially expressed miRNAs have different effects on the proliferative activity of intestinal microorganisms Fusobacterium nucleatum, Escherichia coli, and segmental filamentous bacteria **[53]**.

Regarding pharmacological treatments, corticosteroids are suitable only for the therapy of active disease, and the effects of immunosuppressive agents are mainly limited to the maintenance of remission. Biologics have become widely available and provide therapeutic benefits for patients with IBD. However, only a portion of patients benefit from them. Thus, there is an urgent need to develop new substances in IBD therapy. Thus, exosomes are nanosized lipid vesicles. They are secreted by all living cells and then distributed in various human body fluids. Components, such as microRNAs and functional proteins, secreted by exosomes in different cells have

been reported to be involved in the pathogenesis of IBD. Therefore, exosomes have the potential to become attractive particles in the treatment of IBD as a cell-free therapeutic approach, as well as biomarkers for diagnosis and monitoring of disease status **[54]**. In this context, we reinforce the regulatory role of miRNAs in the stability and maintenance of the gut immune microbiome axis and we detail the challenges and recent advances in the use of miRNAs as putative therapeutic agents for the treatment of IBD **[55]**.

Therefore, it was shown that microRNA-223 (miR-223) is increased both in patients with IBD and animal models of colitis. Although most studies have described miR-223 as having anti-inflammatory effects, several reports have advanced with a pro-inflammatory view **[56]**. Also, it is noteworthy that probiotics compete with pathogenic microorganisms for adhesion sites in the intestine, to antagonize them or to regulate the host immune response, resulting in preventive and therapeutic effects. MicroRNAs can regulate gene expression post-transcriptionally. There is current evidence suggesting that the beneficial properties of probiotics can be explained based on the key role of miRNAs **[57]**.

Regarding the role of miRNAs in the immune response, one study investigated the contribution of miRNAs in the pathogenesis of CD. A total of 53 participants, including 23 CD patients and 30 healthy controls (HCs) were included in this study. miRNAs, including miR-21, miR-29a, miR-29b, miR-31, miR-146a, miR-155, miR-181a and miR-181c were evaluated using TaqMan MicroRNA assays. Among the eight miRNAs, the amounts of miR146a and miR-21 significantly decreased in CD patients compared to CH subjects. Furthermore, we showed that there was a negative correlation between miR-146a and the Harvey-Bradshaw index (HBI), as well as a positive correlation between miR-21 and miR29b with HBI. Underexpression of miR-146a and miR-21, which are critical for the regulatory function of regulatory T cells (Tregs), is associated with Crohn's disease **[58]**.

In this context, many studies have evaluated the ability of diet to modulate the gut microbiota and microRNAs to influence epithelial barrier function **[46]**. Low-fiber diets have been associated with IBD with a postulated mechanism of reduced production of shortchain fatty acids by commensal bacteria whose preferred energy source is fiber. Butyrate, a short-chain fatty acid, is essential for colon health and the main source of energy for colonocytes **[40,41]**.

In this sense, short-chain fatty acids also promote immune tolerance by promoting the development of regulatory T cells. Food additives are commonly consumed by IBD patients and specific dietary emulsifiers (carboxymethylcellulose and polysorbate 80), which have been shown to induce low-grade inflammation and metabolic syndrome in mice; and promote colitis in genetically predisposed IL-10 knockout mice. Emulsifiers can alter the host microbiota, resulting in increased inflammatory potential with an increase in the number of mucolytic bacteria and erosion of the protective mucosal layer **[40]**.

Conclusion

The present study analyzed the main interactions between dietary therapy, intestinal microbiota, microRNAs, exosomes, and inflammatory bowel disease, elucidating the main clinical outcomes of the disease after nutrological treatment. As a corollary, important randomized controlled clinical studies were found in the last ten years that showed the important role of diet modulation in the control and even in the remission of inflammatory bowel disease, revealing important reductions in persistent intestinal symptoms, in the balance of the intestinal microbiota, in the regulatory role of microRNAs, reducing inflammation markers and improving quality of life. Recognition of the need for additional data from clinical trials, the inherent uncertainty of efficacy for all inflammatory bowel disease therapies, and the potential for benefit with dietary interventions will help guide progress toward a better understanding of the usefulness of dietary therapy for individuals with inflammatory bowel disease.

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Ethical Approval

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Informed consent

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Data sharing statement

No additional data are available.

Conflict of interest

The authors declare no conflict of interest.

Similarity check

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