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REVIEW ARTICLE

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Major approaches and clinical studies of the relationship of inflammatory bowel diseases with nutrients, gut microbiota, and exosomes/microRNAs: a systematic review

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Abstract

Introduction: Inflammatory bowel diseases (IBDs) are multifactorial diseases characterized by chronic inflammation of the gastrointestinal tract. Nutrients, gut microbiota, exosomes, and microRNAs play crucial roles in the pathophysiology of IBD. **Objective:** It was to carry out a systematic review of the main approaches and clinical studies on the relationship between inflammatory bowel diseases and nutrients, intestinal microbiota, and exosomes/microRNAs. **Methods:** The PRISMA Platform systematic review rules were followed. The search was carried out from August to September 2023 in the Web of Science, Scopus, PubMed, Science Direct, Scielo, and Google Scholar databases. The quality of the studies was based on the GRADE instrument and the risk of bias was analyzed according to the Cochrane instrument. **Results and Conclusion:** A total of 177 articles were found, and 58 articles were evaluated in full, and 30 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 06 studies with a high risk of bias and 25 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=67.7%>50%. It was concluded that inflammatory bowel diseases are associated with various gastrointestinal symptoms and, therefore, affect patients' quality of life. Although intestinal bacteria and the host's immune response are considered important factors in its pathogenesis, a sufficient explanation of their role in its pathophysiological mechanism has not been presented. Exosomes and microRNAs, together with nutrients and gut microbiota, participate in the molecular interactions of inflammatory bowel diseases. Recent studies have confirmed the important role of miRNAs in targeting certain molecules in signaling pathways that regulate intestinal barrier homeostasis, inflammatory reactions, and autophagy of the intestinal epithelium. Several studies have identified specific miRNAs associated with inflammatory bowel diseases in colon tissues. The correlation between the gut microbiota and cytokines suggests that exosomes and microRNAs can modulate intestinal immunity by influencing the gut microbiota.

Keywords: Inflammatory bowel diseases. Nutrients. Gut microbiota. Exosomes/microRNAs.

Introduction

Inflammatory bowel diseases (IBDs) are multifactorial diseases characterized by chronic inflammation of the gastrointestinal tract, being denoted by Crohn's disease (CD) and ulcerative colitis (UC). CD and UC mainly affect young people, causing bloody diarrhea, abdominal pain, malabsorption, fatigue, and impaired quality of life. Long-lasting inflammation also increases the risk of colorectal cancer in patients with IBDs, which has a mortality rate of 10-15% **[1,2]**.

In this context, microRNAs (miRNAs or miR-) play important roles in the pathophysiology of IBD **[1]**. miRNAs are endogenous, single-stranded, evolutionarily conserved noncoding RNAs that bind to the 3' untranslated region (UTR), 5'UTR, or partially translated region of a target mRNA, inhibiting translation of the mRNA and blocking its expression. MiRNAs are important regulators of cellular function and

homeostasis, and their abnormal activity has been demonstrated in several diseases, including IBD. Thus, new treatment options could be developed to alter imbalances in miRNA expression. MiRNAs affect the intestinal barrier and inflammatory reactions through various pathological mechanisms **[3]**.

In this aspect, metabolism encompasses the interactions between the diet, the microbiome, and cellular enzymatic processes that generate the chemical pathways necessary to maintain life and regulate the balance of the intestinal microbiota, especially in the treatment of IBD. Endogenous metabolites and dietary nutrients can directly influence epigenetic enzymes **[3-6]**. Epigenetic modifications to DNA and histone proteins alter cell fate by controlling chromatin accessibility and downstream gene expression patterns **[7-10]**.

In addition to the connection between metabolism and epigenetic pathways, nutrients can impact cellular state by modulating signaling pathway activity. A clear example is through the mechanistic target of rapamycin (mTOR) signaling pathway and in particular mTOR complex 1 (mTORC1), which regulates cell growth only when nutrients and growth factors are present **[3,10]**. It is also noteworthy that nutrients impact the cellular state through AMP-activated protein kinase (AMPK), which at low levels of cellular ATP phosphorylates substrates to restore the cell's energy balance **[3,4]**.

All these epigenetic and nutritional mechanisms are of paramount importance, as around 70.0 to 80.0% of patients lose weight during 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 **[11,12]**. The Western diet is characterized by excessive consumption of refined sugars, salt, and saturated fat and low consumption of dietary fiber, as well as low overall dietary variability. New features of human nutrition in modern society include artificial sweeteners, gluten, and genetically modified foods **[9]**.

Thus, micro and macronutrient deficiencies and an overabundance of calories and macronutrients trigger inflammatory processes and susceptibility to infections **[13]**. Several micronutrients are especially important for immunonutrition, including vitamins such as vitamins A, C, D, and E, folic acid, beta-carotene, and trace elements such as zinc, selenium, manganese, and iron. Deficiencies of zinc and vitamins A, C, and D can reduce the functions of natural killer cells **[14-17]**.

Therefore, the present study aimed to carry out a systematic review of the main approaches and clinical studies on the relationship between inflammatory bowel diseases and nutrients, intestinal microbiota, and exosomes/microRNAs.

Methods

Study Design

The present study followed the international systematic review model, following the rules of PRISMA (preferred reporting items for systematic reviews and meta-analysis). Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 09/12/2023. The methodological quality standards of AMSTAR-2 (Assessing the methodological quality of systematic reviews) were also followed. Available at: https://amstar.ca/. Accessed on: 09/12/2023.

Data Sources and Research Strategy

The literary search process was carried out from August to September 2023 and was developed based on Web of Science, Scopus, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various eras to the present. The descriptors (MeSH Terms) were used: "Inflammatory bowel diseases. Nutrients. Intestinal microbiota. Exosomes/microRNAs" (in English: Inflammatory bowel diseases. Nutrients. Gut microbiota. Exosomes/microRNAs), and using the Boolean "and" between the terms MeSH and "or" between historical discoveries.

Study Quality and Risk of Bias

Quality was classified as high, moderate, low, or very low in terms of risk of bias, clarity of comparisons, precision, and consistency of analyses. The most evident emphasis was on systematic review articles or meta-analyses of randomized clinical trials, followed by randomized clinical trials. The low quality of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using the Cohen test (d).

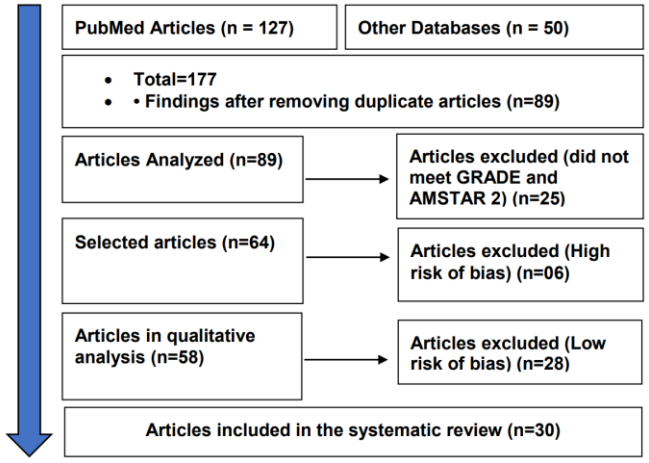
Results and Discussion

Summary of Findings

A total of 177 articles were found that were subjected to eligibility analysis, with 30 final studies being selected to compose the results of this systematic review. The studies listed were of medium to high quality (Figure 1), considering the level of scientific evidence of studies such as meta-analysis, consensus, randomized clinical, prospective, and observational. The biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies showed homogeneity in their results, with X^2=67.7%>50%. Considering the Cochrane tool for risk

of bias, the overall assessment resulted in 06 studies with a high risk of bias and 25 studies that did not meet GRADE and AMSTAR-2.

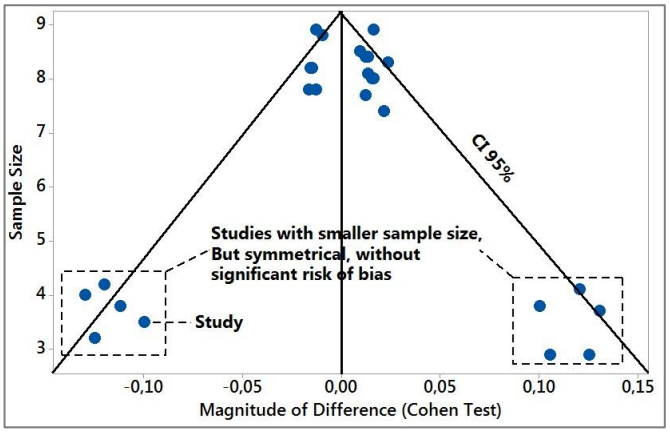
Figure 1. Flowchart showing the article selection process.



Source: Own authorship.

Figure 2 presents the results of the risk of bias of the studies using the Funnel Plot, showing the calculation of the Effect Size (Magnitude of the difference) using the Cohen Test (d). Precision (sample size) was determined indirectly by the inverse of the standard error (1/Standard Error). This graph had a symmetrical behavior, not suggesting a significant risk of bias, both between studies with a small sample size (lower precision) that are shown at the bottom of the graph and in studies with a large sample size that are presented at the top.

Figure 2. The symmetric funnel plot suggests no risk of bias among the small sample size studies that are shown at the bottom of the plot. High confidence and high recommendation studies are shown above the graph (n=30 studies).



Source: Own authorship.

Major Clinical Findings

Ruptured intestinal membranes are one of the most significant factors in the pathogenesis of IBD. TNF-α is known to be an important pro-inflammatory cytokine in the pathogenesis of IBD **[18]**. It is known that miR-191a and miR-212 damage intestinal barriers and others strengthen the intestinal barrier. c-Jun and myosin light chain kinase (MLCK) are the targets of miR-200b **[19]**. Silencing protein tyrosine kinase 6 (PTK6) expression with miR-93 in intestinal epithelium increases resistance to TNF-α-induced injury **[20]**.

Furthermore, it is known that miRNAs contribute to the immunological reactions that lead to IBD. Nucleotide-binding oligomerization domain-containing protein 2 (NOD2) is one of the genes associated with CD **[21]**. Some studies have found abnormal elevation of miRNA levels in the mucosal tissues of UC patients compared to healthy controls. The authors found that miR-16, miR-21, miR-23a, miR-24, miR-29a, miR-126, miR-195, and let-7f were upregulated in patients with active UC compared to healthy controls **[22]**. Comparing the colon mucosa of patients with UC and healthy controls, authors showed that miR-7, miR-26a, miR-29a, miR-29b, miR-31, miR-126, miR-127-3p, miR-135b, and miR -324- 3p were increased in the inflamed mucosa of patients with UC **[23]**.

Furthermore, increased levels of miR-21, miR-155, miR-923, let-7a, let-7c, let-7d, and let-7g were found in colon biopsy samples from patients with active UC compared to healthy controls **[24]**. Frozen distal colectomy biopsy samples from patients with UC have been found to have significant increases in the levels of miR-31, miR-146a, miR-206, and miR-424 **[25]**, as well as increases in the levels of miR-20 b, miR-26b, miR-98, miR-99a and miR-203 in colon biopsy samples from patients with active UC compared to healthy controls **[26]**. These findings and others are summarized in Table 1.

Table 1. Main considerations of microRNAs in IBD.

microRNAs - Weaken the intestinal barrier		
miR-874	Aquaporin 3	Decreases the expression of aquaporin 3
miR-675	Cadherin E, ZO-1	Destabilizes the mRNA of cadherin E and ZO-1
miR-122a	EGFR	Enhances the expression of zonulin and increases epithelial permeability
miR-191a, -212	ZO-1	Reduce the expression of ZO-1
miR-21	PTEN/PI3K/Akt pathway	Increases the paracellular permeability of the intestinal epithelium

microRNAs - Strengthen the intestinal barrier		
miR-93 (downregulation)	PTK6	Reduces the expression of PTK6 and) attenuates epithelial injury
miR-200b	c-Jun, MLCK	Decreases epithelial damage induced by TNF-α
microRNAs - Inflammatory decrease		
miR-10a	IL-12/23p40	Downregulates the expression of IL-12/23p40 and Th1/Th17 cell responses
miR-141	CXCL12β	Inhibits CXCL12β-mediated leukocyte migration
miR-320	NOD2	Decreases the expression of NOD2

In this sense, a study carried out by Tong et al. (2021) **[27]** explored the therapeutic effects of exosomes and microRNAs (mEVs) from cow's milk on IBD. The microRNAs and protein content in mEVs were analyzed by RNA sequencing and proteomics, respectively, followed by functional annotation. The abundant proteins and microRNAs in mEVs were involved in the regulation of immunological and inflammatory pathways and oral administration of mEVs prevented colon shortening, reduced disruption of the intestinal epithelium, and inhibited inflammatory cell infiltration and tissue fibrosis. mEVs attenuated the inflammatory response through inhibition of the TLR4-NF-κB signaling pathway and activation of the NLRP3 inflammasome. Furthermore, mEVs were able to correct the cytokine production disorder and restore the balance between type 17 T helper cells (Th17) and interleukin-10+Foxp3+ regulatory T cells (Treg) in the inflamed colon. The disturbed gut microbiota in UC was also partially recovered after treatment with mEVs.

In this context of dietary manipulation of microRNAs, therapies with prebiotics and probiotics can selectively manipulate the intestinal microbiota **[3,4]**. In this sense, prebiotics represent non-digestible carbohydrates that promote the growth of beneficial bacteria in the intestine, increasing the production of short-chain fatty acids and modulating the production of cytokines in the intestinal mucosa **[5]**. Probiotics contain live bacteria that appear to have positive health effects on the human intestine, modulating mucosal permeability and strengthening the maintenance of the immune system by removing pathogens from the surface of the intestinal mucosa **[1]**.

In this sense, the intestinal microbiota is fundamental for the activation of the immune system, with emphasis on *Lactobacillus acidophilus, Lactobacillus bulgaricus*, and *Lactobacillus casei*, increasing IgA for the removal of antigens through a non-inflammatory pathway and increasing T and B lymphocytes, as well as the *Faecalibacterium prausnitzii* is one of the most prevalent intestinal bacterial species in healthy adults, being beneficial and producing butyrate **[7]**. Lactobacilli and Bifidobacteria inhibit the growth of exogenous and/or harmful bacteria, stimulate immune functions, aid in the digestion and/or absorption of food ingredients and minerals, and contribute to the synthesis of vitamins **[1,3,6]**.

In this regard, short-chain fatty acids such as butyrate, propionate, and acetate serve as an energy source for intestinal epithelial cells and induce protective regulatory immune responses **[15]**. The gut's adaptive immune system is also rapidly activated following exposure to commensal bacteria, with an increase in the expression of major histocompatibility complex class II molecules and an increase in T cells **[3]**. T cells can generate subpopulations whose immune response is pro-inflammatory or anti-inflammatory. Th1 and Th17 cells – T helper cells are pro-inflammatory, while Treg cells (CD4+ CD25+ phenotype) and Th2 cells are anti-inflammatory **[10]**.

In this sense, the Gram-negative bacterium *Bacteroides fragilis* induces the differentiation of CD4+ T cells into Treg cells, leading to the production of anti-inflammatory cytokines, such as interleukin-10 (IL-10) and transforming growth factor beta (TGFβ), nullifying the Th17 pro-inflammatory response. The differentiation of Treg cells depends on the recognition by CD4+ T cells of the polysaccharide presented by CDs **[10]**.

Many studies have evaluated the ability of diet to modulate the intestinal microbiota and microRNAs to influence epithelial barrier function. Low-fiber diets have been associated with IBD with a postulated mechanism of reduced production of short-chain 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. In this sense, short-chain fatty acids also promote immunological tolerance by promoting the development of regulatory T cells **[28-30]**.

Conclusion

It was concluded that inflammatory bowel diseases are associated with various gastrointestinal symptoms and, therefore, affect patients' quality of life. Although intestinal bacteria and the host's immune response are considered important factors in its pathogenesis, a sufficient explanation of their role in its pathophysiological mechanism has not been presented. Exosomes and microRNAs, together with nutrients and

intestinal microbiota, participate in the molecular interactions of inflammatory bowel diseases. Recent studies have confirmed the important role of miRNAs in targeting certain molecules in signaling pathways that regulate intestinal barrier homeostasis, inflammatory reactions, and autophagy of the intestinal epithelium. Several studies have identified specific miRNAs associated with inflammatory bowel diseases in colon tissues. The correlation between the intestinal microbiota and cytokines suggests that exosomes and microRNAs can modulate intestinal immunity by influencing the intestinal microbiota.

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