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REVIEW ARTICLE

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Nutrological, microbiological and extracellular vesicle evidence in the modulation and control of inflammatory bowel disease symptoms: a systematic review

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Abstract

Introduction: Inflammatory bowel diseases (IBD) have an increasing incidence and prevalence, such as Crohn's disease (CD) and ulcerative colitis (UC). Gut dysbiosis is affected by host genetics, nutrition, antibiotics, and inflammation, and is associated with the development of IBD, which can be attributed to impaired miRNA expression functions. Micro and macronutrient deficiencies and overabundance of calories and macronutrients trigger inflammatory processes and susceptibility to infections. **Objective:** To present the nutrological, microbiological, and extracellular vesicle (exosome-microRNAs) evidence in the modulation and control of symptoms of inflammatory bowel diseases. **Methods:** The systematic review rules of the PRISMA Platform were followed. The literary search process was carried out from March to May 2025 in the Web of Science, Scopus, Embase, 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 189 articles were found. A total of 27 articles were fully evaluated and 21 were included and developed in the present systematic review study. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 21 studies with a high risk of bias and 29 studies that did not meet GRADE and AMSTAR-2. Most studies showed homogeneity in their results, with X^2=85.7%>50%. It was concluded that 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 several pathological mechanisms. The use of miRNAs as biomarkers and therapeutic targets may help monitor

IBD treatment and support the development of new, more individualized therapies that minimize common side effects. Extracellular vesicles may attenuate the inflammatory response by inhibiting the TLR4-NF-κB signaling pathway and activating the NLRP3 inflammasome. Dietary manipulation of microRNAs through prebiotics and probiotics may selectively manipulate the gut microbiota, with the bacterium *Faecalibacterium prausnitzii* being prevalent in healthy adults, being beneficial and producing short-chain fatty acids, such as butyrate, which serves as an energy source for intestinal epithelial cells and induces protective regulatory immune responses.

Keywords: Inflammatory bowel diseases. Modulation. Nutrology. Gut microbiota. Vesicles.

Introduction

Inflammatory bowel diseases (IBD) are showing increasing incidence and prevalence, such as Crohn's disease (CD) and ulcerative colitis (UC) **[1]**. The etiology and pathogenesis of IBD remain unclear and may be related to genetic susceptibility, gut microbiota, environmental factors, and immune dysfunction. In addition to therapeutic drugs such as aminosalicylic acid, corticosteroids, immunomodulators, and biological agents, the therapeutic effects of microRNAs and exosomes stand out **[2]**.

Among the genetic factors implicated in the etiology of IBD, variants in genes related to autophagy have been identified. Three distinct forms of autophagy have been described, including microautophagy, chaperone-mediated autophagy, and macroautophagy. Autophagy plays a key role in maintaining intestinal homeostasis, regulating the interaction between the gut microbiota and innate and adaptive immunity, and in host defense against intestinal pathogens. Autophagy dysfunction is associated with several human pathologies, including IBD **[3]**.

Furthermore, intestinal dysbiosis is affected by host genetics, nutrition, antibiotics, and inflammation, and is associated with the development of IBD. Furthermore, intestinal epithelial dysfunction, altered autophagy, and immune hyperactivation are frequently detected in individuals with severe IBD, which can be attributed to impaired miRNA expression functions **[4]**. In addition, the potential of microRNA-focused strategies in the diagnosis and treatment of IBD stands out, offering a scientific basis for the advancement of precision medicine in the management of IBD **[5]**.

All these epigenetic and nutrological mechanisms are of paramount importance, since approximately 70.0 to 80.0% of patients lose weight during IBD, leading to some degree of nutritional impairment, and approximately 23.0% of outpatients and 85.0% of hospitalized patients with predominant malnutrition **[6-10]**. Thus, micro and macronutrient deficiencies and an overabundance of calories and macronutrients trigger inflammatory processes and susceptibility to infections **[11-14]**.

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 **[15-18]**.

Therefore, the present study described a systematic review in order to present the nutrological, microbiological, and extracellular vesicles (exosomes-microRNAs) evidence in the modulation and control of the symptoms of inflammatory bowel diseases.

Methods

Study Design

This study followed the international systematic review model, following the PRISMA (preferred reporting items for systematic reviews and meta-analysis) rules. Available at: http://www.prisma-statement.org/?AspxAutoDetectCookieSupport=1. Accessed on: 04/04/2025. The AMSTAR-2 (Assessing the methodological quality of systematic reviews) methodological quality standards were also followed. Available at: https://amstar.ca/. Accessed on: 04/04/2025.

Data Sources and Research Strategy

The literature search process was carried out from March to May 2025 and developed based on Web of Science, Scopus, Embase, PubMed, Lilacs, Ebsco, Scielo, and Google Scholar, covering scientific articles from various periods to the present day. The following descriptors (DeCS/MeSH Terms) were used "Inflammatory bowel diseases. Modulation. Nutrology. Gut microbiota. Vesicles", and using the Boolean "and" between the MeSH terms and "or" between the historical findings.

Study Quality and Risk of Bias

The quality was classified as high, moderate, low, or very low regarding the 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

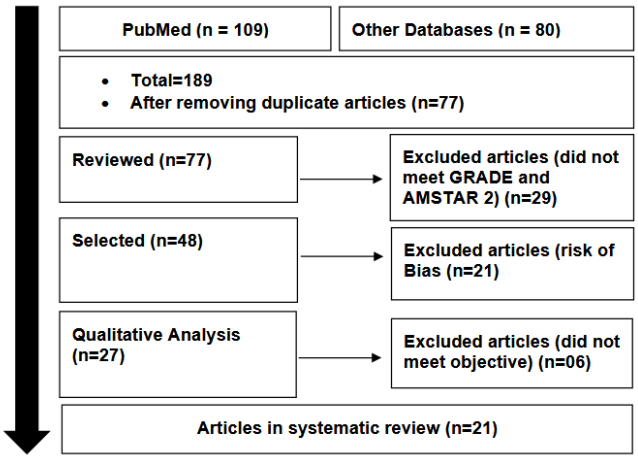
of evidence was attributed to case reports, editorials, and brief communications, according to the GRADE instrument. The risk of bias was analyzed according to the Cochrane instrument by analyzing the Funnel Plot graph (Sample size versus Effect size), using Cohen's test (d).

Results and Discussion

Summary of Findings

A total of 189 articles were found that were submitted to eligibility analysis, and 21 final studies were 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. Biases did not compromise the scientific basis of the studies. According to the GRADE instrument, most studies presented homogeneity in their results, with X^2=85.7%>50%. Considering the Cochrane tool for risk of bias, the overall assessment resulted in 21 studies with a high risk of bias and 29 studies that did not meet GRADE and AMSTAR-2.

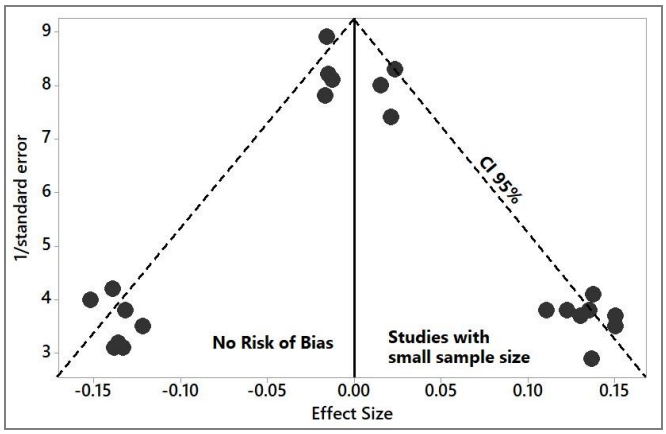
Figure 1. Selection of the articles.



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 Cohen's 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 among studies with small sample sizes (lower precision) that are shown at the base of the graph and in studies with large sample sizes that are presented at the top.

Figure 2. The symmetrical funnel plot does not suggest a risk of bias among the studies with small sample sizes that are shown at the bottom of the graph (n=14 studies). High confidence and high recommendation studies are shown above the graph (n=07 studies). Total =21 studies.



Source: Own authorship.

Major Findings and Development

In the context of immunometabolic activities, microRNAs (miRNAs) play an important role as modulators of IBD, such as miR-31, miR-155, and miR-21. These miRNAs can modulate gene expression at the post-transcriptional level, being important biomarkers and also therapeutic interventions. Although miRNA-based therapies have significant potential, off-target effects, immune activation, and inefficiencies in administration methods may occur. Furthermore, the interaction between miRNAs and the gut microbiota may influence disease mechanisms and responses to treatment **[19]**.

Studies have shown that miRNA dysregulation has been implicated in the development of IBD, as specific miRNAs are differentially expressed in patients with IBD compared to healthy individuals. Regulation of their expression may modulate the inflammatory response, the composition of the gut microbiota, and the function of the intestinal barrier. MiRNAs can regulate the immune and inflammatory response through multiple mechanisms, from regulating Th1/Th17 and ferroptosis to modulating NLRP3 (NOD-like receptor family, pyrin domain 3) and controlling the NF-κB (nuclear factor kappa-light chain-enhancer of activated B cells) pathway **[20,21]**.

In this sense, Tong et al. (2021) **[22]** explored the therapeutic effects of extracellular vesicles (mEVs) in IBD. The microRNAs and protein content in mEVs were analyzed by RNA sequencing and proteomics, and the gut microbiota was analyzed by 16S rRNA sequencing. It was demonstrated that the abundant proteins and microRNAs in mEVs were involved in the regulation of immune and inflammatory pathways and that oral administration of mEVs prevented colon shortening, reduced intestinal epithelial disruption, and

inhibited inflammatory cell infiltration and tissue fibrosis. mEVs attenuated the inflammatory response by inhibiting the TLR4-NF-κB signaling pathway and activating the NLRP3 inflammasome. Furthermore, mEVs were able to correct the disturbance of cytokine production and restore the balance between T helper type 17 (Th17) cells and interleukin-10+Foxp3+ regulatory T (Treg) cells in the inflamed colon. The disturbed gut microbiota was also partially recovered after mEV treatment.

The authors Lv et al. (2024) **[23]** investigated the relationship between fecal gut microbiome (FIM) and gut tissue miRNAs at different stages of pediatric Crohn's disease (CD). Metagenomic analyses and miRNA sequencing were conducted to examine the gut MIF and miRNA profiles of CD patients before and after clinical induction therapy and controls. A total of 27 newly diagnosed and therapy-naïve pediatric patients with active CD and 11 IBD controls were recruited. The MIF and miRNA profiles were significantly altered between CD patients and controls. Seven key bacteria were identified at the species level, including *Defluviitalea raffinosedens, Thermotalea metallivorans, Roseburia intestinalis, Dorea sp. AGR2135, Escherichia coli, Shigella sonnei*, and *Salmonella enterica*, the exact proportions of which were further validated by quantitative qPCR analysis. A total of 8 key miRNAs were also identified, including hsa-miR-215-5p, hsa-miR-194-5p, hsa-miR-12135, hsa-miR-509-3-5p, hsa-miR-212-5p, hsa-miR-4448, hsa-miR-501-3p and hsa-miR-503-5p. Functional enrichment analysis of differential miRNAs indicated the cyclin protein, cyclin-dependent protein, and cell cycle pathway were significantly altered. Both the gut microbiome structure and miRNA profiles were significantly altered in the different stages of CD.

It is also observed that IBD is characterized by chronic inflammation and damage to colonocytes, with genetic, epigenetic, and environmental factors as the etiology. It was observed that microRNA-223 (miR-223) is increased in patients with IBD **[24]**. In addition, the authors Li et al. (2024) **[25]** analyzed the mechanism of action of honeysuckle MIR2911, the main component of traditional Chinese medicine preparations for UC. The results demonstrated that MIR2911 can be absorbed through the diet and secreted into the host's small extracellular vesicles, directly acting on intestinal bacteria, reducing the abundance of *Escherichia shigella* and improving UC symptoms.

MiR-191a and miR-212 are known to damage the intestinal barrier, while others strengthen the intestinal barrier. C-Jun and myosin light chain kinase (MLCK) are targets of miR-200b **[26]**. Silencing of protein tyrosine kinase 6 (PTK6) expression with miR-93 in the intestinal epithelium increases resistance to TNF-α-induced injury **[27]**.

MiRNAs have also been shown to 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 **[28]**. Some studies have found abnormal elevation of miRNA levels in the mucosal tissues of UC patients compared with 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 with healthy controls **[29]**. 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 **[30]**.

In this context of dietary manipulation of microRNAs, prebiotic and probiotic therapies can selectively manipulate the gut microbiota **[6,7]**. 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. Probiotics contain live bacteria that appear to have positive effects on the health of the human intestine, modulating the permeability of the mucosa and strengthening the maintenance of the immune system by removing pathogens from the surface of the intestinal mucosa **[6]**.

The gut microbiota is essential for the activation of the immune system, with emphasis on *Lactobacillus acidofilus, Lactobacillus bulgaricus* and *Lactobacillus casei*, increasing IgA for the removal of antigens by a non-inflammatory pathway and increasing T and B lymphocytes, as well as *Faecalibacterium prausnitzii*, one of the most prevalent intestinal bacterial species in healthy adults, being beneficial and a producer of butyrate **[15,16]**. 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 **[6,8]**.

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 **[15,16]**. The adaptive immune system of the intestine is also rapidly activated after exposure to commensal bacteria, with an increase in the expression of major histocompatibility complex class II molecules and an increase in T cells **[13]**. T cells can generate subpopulations whose immune response is pro-inflammatory or antiinflammatory. Th1 and Th17 cells

– T helper cells are pro-inflammatory, while Treg cells (CD4+ CD25+ phenotype) and Th2 cells are anti-inflammatory **[10,13]**.

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), overriding the pro-inflammatory Th17 response. Treg cell differentiation depends on the recognition by CD4+ T cells of the polysaccharide presented by CD **[10,13]**.

Finally, many studies have evaluated the ability of diet to modulate the gut microbiota and microRNAs to influence epithelial barrier function. 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 energy source for colonocytes. In this sense, short-chain fatty acids also promote immune tolerance by promoting the development of regulatory T cells **[31-33]**.

Conclusion

It was concluded that 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 several pathological mechanisms. The use of miRNAs as biomarkers and therapeutic targets may help monitor the treatment of IBD and support the development of new, more individualized therapies that minimize common side effects. Extracellular vesicles may attenuate the inflammatory response through inhibition of the TLR4-NF-κB signaling pathway and activation of the NLRP3 inflammasome. Dietary manipulation of microRNAs through prebiotics and probiotics can selectively manipulate the gut microbiota, with the bacterium *Faecalibacterium prausnitzii* being prevalent in healthy adults, being beneficial and producing short-chain fatty acids, such as butyrate, which serves as an energy source for intestinal epithelial cells and induces protective regulatory immune responses.

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The authors declare no conflict of interest.

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Application of Artificial Intelligence (AI)

Not applicable.

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