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Impact of probiotics on inflammatory bowel disease - a systematic review

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Abstract

Introduction: Inflammatory bowel disease (IBD) is a chronic nonspecific inflammatory disease of the gastrointestinal tract that includes ulcerative colitis (UC) and Crohn's disease (CD). Both disease entities have many features in common, such as a basis of chronic inflammation, similar clinical symptoms as well as periods of remission and relapse. The difference between them lies in the lesions location. Treatment of IBD is primarily based on reducing inflammation and maintaining as long a remission time as possible. Increasing evidence is being attributed to the therapeutic potential of probiotics in IBD.

Purpose: This review aims to present the preventive and therapeutic effects of probiotic use in IBS through an analysis of recent studies.

Methods: A review of recent literature was conducted to investigate the impact of probiotic use on the treatment of IBD.

Results: In studies, probiotics help induce and maintain remission in patients with mild to moderate ulcerative colitis, especially when used in combination therapy. In contrast, the usage of probiotics in Crohn's disease does not provide due benefit: it does not induce or prolong remission.

Conclusions: In conclusion, the effect of probiotics on IBD is inconclusive. Some probiotics, particularly the VSL#3 probiotic blend, have shown decent effects on induction and remission in patients with mild to moderate UC. However, no therapeutic effect has been demonstrated in patients with Crohn's Disease. Therefore studies under more restrictive and standardized conditions are required.

Keywords: probiotics, inflammatory bowel disease, Crohn’s disease, ulcerative colitis

Introduction: Inflammatory bowel disease is a nonspecific, chronic inflammation of the gastrointestinal tract that includes two main types: ulcerative colitis and Crohn's disease. The problem is estimated to affect more than 2 million people in Europe and another 1.5 million in North America. In Western populations, this corresponds to a total incidence of 450 patients per 100,000. [1] These conditions are typically characterized by abdominal discomfort, frequent diarrhea, and in some cases, the presence of blood. [2] Ulcerative Colitis is confined to the colon, with inflammation primarily affecting the inner mucosal layer. The inflammation is continuous, spreading uniformly along the colon. In contrast, involvement of any part of the gastrointestinal tract, from the mouth to the anus, describes Crohn's Disease. The inflammation in CD is transmural, meaning it involves all layers of the intestinal wall. [30] Notably, areas of inflammation in CD are often interspersed with healthy sections of the intestine. [3] Patients with both UC and CD may experience extra-intestinal manifestations that affect the skin, eyes, and bones. These can include conditions such as erythema nodosum, aphthous stomatitis, uveitis, arthritis, and ankylosing spondylitis. [4] Treatment of IBD focuses on reducing inflammation and maintaining as long a remission time as possible. Therapy consists of glucocorticosteroids, immunomodulator therapy (mainly methotrexate (MTX), thiopurines (TPs), Janus kinase (JAK) inhibitors, calcineurin inhibitors), 5-aminosalicylates and biological agents (Anti-TNF Therapy, Anti-IL-12/23 Therapy, Anti-integrin Therapy). [31][32]

Methods: To write this review, PubMed and Google Scholar databases were searched for information, and publications on the effects of probiotics on the prevention and treatment of inflammatory bowel disease. Keywords used in the search included: "probiotics," "inflammatory bowel disease," "Crohn's disease," and "ulcerative colitis." English-language articles available in full-text format were carefully reviewed and included in the review based on their relevance. Published articles from 2017-2023 in English were included in the review, including review articles on clinical trials. Articles in a language other than English were excluded.

ETIOLOGY OF IBD

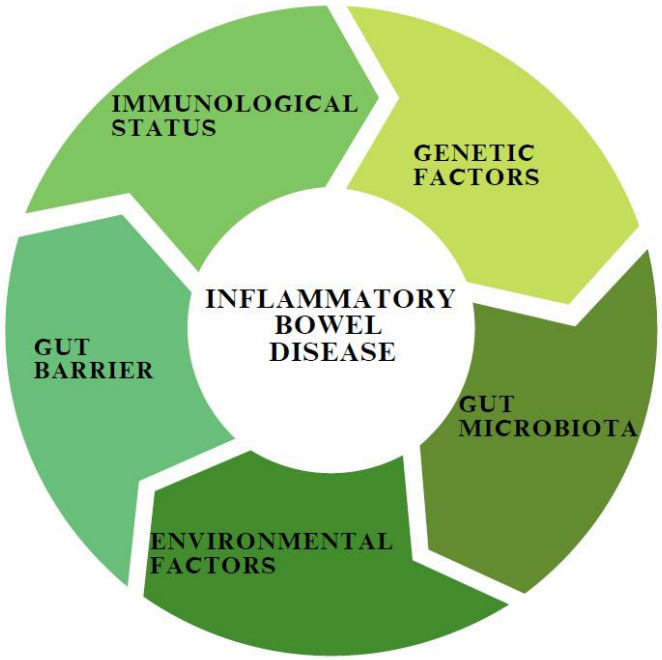

Figure 1. Etiology of IBD

The etiology of IBD is multi-determinant and involves a complex interaction of genetic predisposition, immune response, and environmental influences. [5] However, the exact cause of this disease is unknown. [1]

1. **Genetic Factors**: Genetic predisposition is a significant factor in developing IBD. Genome-wide association studies have identified several loci directly connected with this condition. Some of them are characteristic only to CD or UC and some are associated with both IBD subtypes. It's been observed that first-degree relatives of affected individuals have a five times or more greater relative IBD risk. Over 240 genetic risk loci are associated with IBD, with a significant portion (30%) of these loci being common to both Crohn's disease and ulcerative colitis. [5] However, these genetic factors alone are not sufficient to cause the disease and must interact with other stimuli to lead to the IBD.
2. **Immunological Status**: IBD is an autoimmune disease. [11] The immune system plays a pivotal role in IBD with helper lymphocytes (Th1, Th2, Th17) and regulatory T cells being of particular importance. [1] Th1 cells, associated with CD, and Th2 cells, associated with UC, produce different cytokines in response to microorganism recognition by microbe-associated molecular patterns (MAMPs). Th17 cells, which

reside on the gut's mucosa, are crucial for both diseases and produce a range of cytokines including IL-17, TNF-alpha, IL-22, and INF-gamma. In the course of IBD, the gut microbiota is disturbed, leading to an imbalance between Th17 and Treg cells.

3. **Environmental Factors**: Environmental factors such as diet, lifestyle, and air pollution can influence the onset and progression of IBD. Diet high in trans-unsaturated fats and low in fruits, vegetables, and fish, low-fiber diet, and low vitamin D levels have been associated with a higher risk of IBD. [5][8] Certain medications, such as NSAIDs along with oral contraceptive pills, have also been linked to an escalation of IBD symptoms. [3]
4. **Gut Barrier**: Intestinal Epithelial Cells (IECs) create a boundary between the internal and external environments of the intestine, serving as the primary physical defense against foreign pathogens. IECs include intestinal epithelial cells, goblet cells, microfold cells, neuroendocrine cells, and Paneth cells. [14] The paracellular pathway is strictly controlled, permitting only specific solutes and fluids to pass, thereby forming a selectively permeable barrier. Junctional complexes are primarily composed of tight junctions (TJs), adhesion junctions (AJs) and bridging granules that connect the intracellular skeleton, seal the cellular gap, and provide structural support. TJs, primarily made up of transmembrane proteins like occludin, claudins, and Zonula occludens Protein 1 (ZO-1), are the main factors limiting cellular bypass. These proteins, linked to the cytoskeleton, regulate the selective passage of macromolecules through the TJs and are direct targets and effectors of various signaling pathways that influence the assembly, maintenance and barrier function of the TJs complex. The mucus layer, closely associated with IEC, separates the intestinal epithelium from the intestinal lumen and forms the intestine's chemical barrier. Mucus is produced by the polymerization of mucin (MUC), which is secreted by goblet cells. The outer layer consists of various modifications of carbohydrates and MUC-2, which interacts with the colon flora. The mucus in this barrier offers nutrients and attachment sites for microorganisms and is linked to the production of antimicrobial agents like α-defensins, β-defensins, protein hydrolases, glycolytic enzymes, antimicrobial peptides (APMs), immunoglobulins (Ig) and macrophages. This barrier contains microbial pathogen-associated molecular barriers and patterns (PAMPs),including peptidoglycan, flagellin, lipopolysaccharides (LPS), muraminic acid, double-stranded viral RNA and bacterial DNA, in addition to microbiota-derived enterotoxins. [10] Clinical symptoms of Inflammatory Bowel Disease arise from intestinal inflammation

and the resulting dysfunction, which includes impaired absorption and compromised intestinal barrier function.

5. **Gut Microbiota:** The human gut harbors a diverse and complex community of microorganisms, including bacteria, fungi and archaeons. [12] It's projected that the quantity of microbes in the large intestine's contents can reach from 10^{11} to 10^{12} Colony Forming Units (CFU) per gram. [9] These microorganisms play crucial role in food digestion, maintaining the internal environment and regulating human immune function.[28] In the human gut, the main bacteria are those belonging to 4 species: Firmicutes, Bacteroidetes, Actinobacteria, and Proteobacteria. Approximately 90% of bacteria found in the large intestine belong to the types Bacteroidetes and Actinobacteri. [9][13] The gut microbiota helps inhibit the invasion of pathogenic microorganisms and participates in human metabolic activities. The interaction between these commensal bacteria and the immune system contributes to the maturation of human immunity and shapes the gut microbiota structure to a relatively stable status. However, an imbalance in this interaction can lead to various disorders, including Inflammatory Bowel Disease, systemic autoimmune diseases, cardiometabolic diseases, and cancer.

GUT MICROBIOTA DYSBIOSIS

Dysbiosis is defined as changes in the structure and composition of the gut microbiota that induce the occurrence and development of IBD. [13][9][16] Dysbiosis affects barrier integrity and the host immune system, leading to chronic inflammation. [15] IBD patients typically show a reduction in the diversity of the intestinal microflora (decrease of Firmicutes), a decrease in short-chain fatty-acids (SCFA) - producing bacteria (decrease Faecalibacterium prausnitzzi and Clostridium cluster IV, XIVa, XVII), an increase in mucolytic bacteria (Ruminococcus torques, Ruminococcus gnavas), an increase in sulfate-reducing bacteria (Desulfovibrio) and an increase in pathogenic bacteria (invasive and adhesion E.coli). [8][15][28][31] These changes in the intestinal microflora indicate effects such as a reduction in the energy source of epithelial cell growth, altered differentiation of regulatory T cells, mucus degradation, increased epithelial cell damage and altered mucosal permeability. Both inflammatory and non-inflammatory tissues in IBD patients show reduced flora diversity compared to healthy individuals. Bacteria, such as Cloacibacterium and Tissierellaceae, are more prevalent in inflammatory tissues in IBD patients. [9] The presence of opportunistic pathogens, such as Enterobacteriaceae and Clostridium difficile, may exacerbate IBD

symptoms and induce a more significant dysbiosis of the gut microbiota. The number of beneficial bacterial species is significantly reduced in patients with IBD and their lower abundance may be associated with IBD activity. Studies have shown that the amount of Faecalibacterium duncaniae, a bacterium known for its anti-inflammatory properties, is reduced in patients with IBD, particularly in Crohn's disease patients with ileal involvement, compared to healthy controls. Interestingly, a steady increase in F. duncaniae after relapse in patients with ulcerative colitis is associated with disease remission. Patients with Crohn's disease have higher E. coli counts compared to both healthy controls and patients with IBS. [17]

DECREASE ↓	INCREASE ↑
Firmicutes	Ruminococcus torques,
Faecalibacterium prausnitzzi	Ruminococcus gnavas
Faecalibacterium duncaniae	Desulfovibrio
Clostridium cluster IV, XIVa, XVII	invasive and adhesion E.coli
	Cloacibacterium
	Tissierellaceae

Table 1. Dysbiosis in inflammatory bowel disease

PROBIOTICS

The World Health Organization has defined probiotics as "live microorganisms that, when administered in adequate amounts, exert beneficial effects on the health of the host."[7] [8] To be considered as a probiotic, a microorganism must meet several criteria. It must not cause disease in the host, it should originate from the same species, it must be able to endure the journey through the gastrointestinal tract and importantly it must maintain its liveliness over extended storage periods. [8] Research has been conducted on various probiotic bacterial strains, including Bifidobacterium strains (B. infantis, B. longum, B. breve), Lactobacillus strains (L. acidophilus, L. casei, L. plantarum, L. bulgaricus), Escherichia coli Nissle 1917, and Streptococcus thermophilus, for their potential use in treating Inflammatory Bowel Disease. These beneficial bacteria, which are not harmful, are believed to increase the population of good microbes in the gut, providing anti-inflammatory and immunosuppressive

properties. [21] Evidence suggests that they can enhance the gut's protective lining, reduce the production of inflammation-causing proteins and receptors, inhibit TNF-α (a substance that causes inflammation) and stimulate the production of protective proteins like IL-10. [7]

Antimicrobial Activity	Strengthening the intestinal epithelial barrier	Immunoregulation
Decrease intestinal pH	Increase mucin-2 expression	Increase production of IL-10, TGF-β
Production of bacteriocins, defensins, lactic acid, hydroperoxides	Increase mucus production	Inhibit TNF-α
Increase autophagy	Enhancement of tissue repair processes	Increase production of Immunoglobulin A (IgA)
	Promoting the formation of tight connections	
	Production of short-chain fatty acid (SCFA)	

Table 2. The tasks of probiotics

PROBIOTICS AND IBD

Langhorst's comprehensive review suggests that people with inflammatory bowel disease are interested in alternative treatments because of concerns about the side effects or ineffectiveness of conventional drugs. Patients are showing interest in probiotics. There has been a 50% increase in the use of probiotics by IBD patients. This is most likely related to the belief that probiotics are safe and beneficial as an additional treatment for IBD during exacerbations and periods of remission. Despite numerous publications on the use of probiotics in IBD, definitive conclusions are lacking due to the high variability of interventions, the lack of standardized study methods, and the too-small study group. [18]

PROBIOTICS AND COLITIS ULCEROSA

The highest concentration of microorganisms in the human body is in the colon, which could benefit from treatment aimed at normalizing any imbalance in the composition of the microbiome, particularly in patients with ulcerative colitis. A variety of probiotic strains have been investigated that may provide significant benefits to patients with UC. In particular, the non-pathogenic E. coli strain Nissle 1917 was proven to have a similar efficacy and safety profile to salicylate treatment for maintenance therapy in patients with mild to moderate UC.

Zocco showed that the use of Lactobacillus rhamnosus GG alone or in combination with mesalazine prolonged the duration of clinical remission in UC patients at one-year follow-up, compared to patients treated with mesalazine alone. [18][29]

Preliminary studies have shown that non-pathogenic S. boulardii yeast was effectively used to induce and maintain remission in patients with mild to moderate UC.

One of the most widely studied probiotics is the VSL#3 complex, which consists of Streptococcus thermophilus, Bifidobacterium breve, Bifidobacterium longum, Bifidobacterium infantis, Lactobacillus acidophilus, Lactobacillus plantarum, Lactobacillus paracasei and Lactobacillus delbrueckii subsp. bulgaricus. [20][26] Studies in mouse models have shown that this probiotic mixture inhibits the expression of NF-B and TNF-α through the TLR4-NF-B signaling pathway, decreasing the expression of pro-inflammatory cytokines and toll-like receptors (TLRs) and increasing the levels of regulatory cytokines. The use of VSL#3 in patients with mild to moderate UC is effective in inducing and maintaining remission in monotherapy and polytherapy. Tursi reported that combination therapy (standard with VSL#3) is more effective in inducing remission than standard therapy alone. [19][29] A meta-analysis and systematic review conducted by Derwa in 2017 showed that VSL#3 is as effective in inducing remission and preventing exacerbations in patients with UC as 5-ASA. VSL#3 is significant in 5-ASA intolerance. [27] Miele's study revealed that the addition of VSL#3 to conventional treatment was effective in inducing and maintaining remission in children recently diagnosed with ulcerative colitis, compared to children receiving a placebo for one year. Another meta-analysis with rigorous statistical techniques showed that the efficacy of VSL#3 and E. coli Nissle 1917 in treating exacerbations and maintaining remission in patients with UC is limited. [18] In another study comparing the therapeutic response to VSL#3 with placebo, a meta-analysis involving a total of 319 UC patients was conducted. UC symptoms decreased in approximately 44.6% of those treated with VSL#3, compared to a 25.1% reduction in the placebo group. [8] Also conducted a meta-analysis evaluating the effect of probiotics, prebiotics, and synbiotics compared to placebo in people with UC. No effect on remission maintenance was seen in the studies in the standard treatment and placebo groups. Zhang conducted a meta-analysis on the effect of prebiotics, probiotics, and synbiotics. It was noted that prebiotics, probiotics and synbiotics showed efficacy in achieving as well as maintaining remission and their use reduced the disease activity rate only in UC. [24]

All of the above suggest the need for further studies to definitively determine whether these probiotics are beneficial in the treatment of UC.

Studies have shown that VSL#3 and E. coli Nissle 1917 are most beneficial in the treatment and prevention of UC. [23] Specific probiotics (VSL#3, E. coli Nissle 1917) can be used to induce remission in patients with mild to moderate ulcerative colitis. [6][25][31] In patients with UC, probiotics reduce inflammatory markers and decrease rectal bleeding. [30] The use of probiotics is not recommended in severe cases of UC. Probiotics may be particularly beneficial as an alternative therapy for patients intolerant to 5-ASA. [18][5]

PROBIOTICS AND CROHN'S DISEASE

The use of probiotics in the treatment of patients with CD is not recommended, as no significant benefit has been discovered from the use of probiotics to induce or maintain remission compared to standard therapy. [18][22][25]

In a randomized trial, patients with CD who achieved remission after steroids or salicylates did not reduce the relapse rate after 52 weeks when Saccharomyces boulardii was used. [19] [22] Lactobacillus johnsonii and Escherichia coli Nissle 1917 also did not affect the relapse rate after 52 weeks. VSL#3 did not reduce the endoscopic recurrence rate after 90 days. However, the use of VSL#3 for 1 year resulted in lower mucosal inflammatory cytokine levels and a lower recurrence rate. There were two studies (14 patients with CD in total) that showed an improvement in the Crohn's Disease Activity Index (CDAI) score when different preparations were used, Lactobacillus rhamnosus GG in the first study and a combination of Lactobacillus and Bifidobacterium in the second. [20] Guslandi conducted a study in which he randomly assigned patients to groups: group 1 received S. boulardii plus mesalazine and group 2 received mesalazine alone for six months. There were fewer clinical relapses in group 1 receiving the combination of substances compared to group 2 receiving mesalazine alone. [19] Studies have shown that the combination of the probiotics VSL#3, Lactobacillus and Saccharomyces boulardii leads to improvements in patients with CD. [22]

The effect of L. rhamnosus GG in the treatment of children with CD has been studied. No benefit was obtained over the use of a placebo and it has even been suggested that its use may increase relapse rates in children. VSL#3 is also ineffective in the treatment of children with CD. The use of VSL#3 in addition to 5-ASA therapy does not benefit patients with CD.

Also, it has not been confirmed that probiotic yeast strains (Saccharomyces boulardii) reduce the frequency of exacerbations in adult CD patients. [18]

Conclusions: Inflammatory bowel diseases, including Crohn's disease and ulcerative colitis, have very similar clinical manifestations, but differ in the location and depth of lesions. These

characteristics affect the effect of probiotics. Conclusions based on the described studies are inconclusive and have important limitations, including small study groups, too much clinical heterogeneity, and short follow-up time. Probiotics may have positive effects on the intestinal epithelial barrier, microbiota, and anti-inflammatory response. However, it cannot be assumed that probiotics are harmless and free of side effects. Studies have shown that some probiotics have a beneficial effect on induction and maintenance of remission in patients with UC and may be an alternative for patients intolerant to 5-ASA. The effect of probiotics on Crohn's disease is still unclear. The best-known probiotic is the probiotic mixture VLS#3, which has the greatest benefit from supplementation, but not all studies support this. The use of multicomponent probiotics has greater therapeutic effects than the use of single-component probiotics. In conclusion, the evaluation of the effect of probiotics on IBD requires further research. These studies should be well-designed, and conducted under stricter conditions and the research procedures should be standardized to optimize the use of probiotics.

Author's contribution:

Conceptualization, JF, AK, ŁC ; methodology, JF, MP; software, MP, ŁC; check, JF, AK, MP; formal analysis, MP, ŁC; investigation, JF, ŁC; resources, JF, AK, MP, data curation, JF, AK, ŁC; writing - rough preparation, JF, AK, MP; writing - review and editing, JF, AK, MP, ŁC; supervision, ŁC;.

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