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A review of the use of probiotics in the treatment of inflammatory bowel disease

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ABSTRACT

Ulcerative colitis (UC) is a chronic inflammatory disease that affects the colon and rectum. There is a constant need for improvements to be made in the current medical therapy since UC is extremely burdensome and kills many individuals. There are significant proportion of patients who experience adverse effects with current therapies. Consequently, new alternatives for the treatment of UC are constantly being sought. Probiotics are living microorganisms that are meant to improve one's health whether taken orally or topically. Gut microbiota balance, gut barrier function, and host immune responses all benefit from probiotic microorganisms. Probiotic supplementation is therefore becoming an increasingly popular treatment approach for treating UC and reducing chronic inflammation while also enhancing patients' quality of life. In order to assess the clinical effectiveness of probiotics, we examined the databases of PubMed, Web of Science, Embase, Science Direct, and Google Scholar. Probiotics are equally beneficial as conventional medication therapy in treating UC, according to several studies. Here, we've outlined the key findings of research that employed probiotics either alone or in conjunction with traditional UC treatment on individuals with UC.

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Abbreviations

UC, Ulcerative colitis; E. coli, Escherichia coli; MPO, Myeloperoxidase; Cox-2, Cyclooxygenase-2; TNBS, 2,4,6-trinitrobenzenesulfonic acid; DSS, Dextran sulfate sodium; IL-6, Interlukine-6; IL- 1ß, Interlukine-1ß; TNF-α, Tumor Necrosis Factor-Alfa; BB, Bifidobacterium; IEC, Intestinal epithelial cells; NF-kB, Nuclear factor kappa B; CRP, C reactive protein; IBD, Inflammatory bowel disease; CLA, Conjugated linoleic acid; CD4, Cluster of differentiation 4; VDR, Vitamin D receptor

Introduction

Ulcerative colitis and Crohn's disease are two types of inflammatory bowel diseases that impact individuals (1). Traditionally, this condition is referred to as Zuhair in medical texts. The etiology of chronic inflammatory ulcerative colitis is unknown, marked by recurring episodes. Both genders across all age groups (often 15 to 39 years) are affected. Genetic factors, environment, and the microbiome contribute to ulcerative colitis, which can involve the mouth and rectum, leading to varying symptoms (2). Disruption of intestinal homeostasis arises from continuous immune system activity and improper neutrophil control (3). Common symptoms of Crohn's disease include stomach pain, diarrhea, loose stools, joint pain, fatigue, frequent bowel movements, nausea, abdominal cramps, weakness, lack of appetite, rectal bleeding, skin rash, fecal incontinence, fever, and weight loss (Figure 1) (4, 5). Conversely, colitis is primarily characterized by recurring stomach discomfort, bloody stools, diarrhea, and fever (6, 7). In the moderate stage, symptoms comprise bloody stools, anemia, stomach discomfort, a short fever, and recurring diarrhea. Minor symptoms include occasional rectal bleeding with mucus, mild cramping pain, and minor diarrhea (less than 4 times daily). Severe stage indicators involve weight loss, extreme anemia, severe diarrhea, and a high fever surpassing 40 degrees (8). Consideration should be given to inflammatory infectious agents such as Salmonella, Shigella, Yersinia, Campylobacter, Aeromonas, Escherichia coli, and amoebae. Other factors for rectal hemorrhage encompass anal fissures, hemorrhoids, diverticula, and polyps (9). Precise identification of the affected body part enables the most effective treatment. Distinguishing between ulcerative colitis and Crohn's disease aids in selecting surgical interventions and treatment plans.

When differentiation is challenging, it is termed intermediate colitis. Colonoscopy is a diagnostic tool, supported by barium enema and upper extremity imaging if needed, while biopsy remains the definitive diagnostic method (10).

The inflammatory pathway in colitis triggers increased synthesis of Myeloperoxidase, inducible nitric oxide synthase, and cyclooxygenase. This pathway leads to decreased anti-inflammatory proteins and cytokines, while producing proinflammatory proteins like interleukin-6, interleukin-1β, and Tumor Necrosis Factor-Alpha. Consequently, oxidative stress, inflammation, and antioxidant depletion occur, intensifying cell inflammation and immune cell invasion, particularly neutrophils. This damages cell lining and disrupts the intestinal barrier (11).

For colitis treatment, immunosuppressive and anti-inflammatory medications are used. Aminosalicylates, such as sulfasalazine (12), pentasa (13), asacol (14), balsalazide (15), and budesonide (16), along with azathioprine, mercaptopurine (17), methotrexate (18), cyclosporine A (19), infliximab, sertolizumab, and adalimumab (20), are employed. Additionally, therapeutic approaches like biologic therapies (21), small molecule inhibitors (22), and stromal cell therapy (23) are considered. Unfortunately, these medications come with severe adverse effects including hepatitis, pancreatitis, diabetes, hypertension, hyperlipidemia, osteoporosis, and hemolytic anemia (12). Regrettably, limited efficacy and substantial side effects pose significant challenges to successful therapy. Probiotics, living bacteria, play a crucial role in gut protection and offer diverse beneficial properties. Probiotic use impacts various body areas including the skin, oral cavity, gastrointestinal system, respiratory tract, urinary tract, and reproductive tract. Clinical trials show positive health effects of probiotic use in children, adults, the elderly, and immunocompromised patients (20).

Figure 1. symptoms of Crohn's disease.

Efficacy of probiotics in animal models of colitis

Probiotics, beneficial microorganisms, exhibit promising effects in colitis animal models. They influence gut microbiota composition, bolster intestinal barrier function, and regulate the immune response. Studies indicate that probiotics like Lactobacillus and Bifidobacterium strains can mitigate colitis symptoms by reducing inflammation, oxidative stress, and tissue damage. Their potential in restoring gut homeostasis makes them an intriguing avenue for colitis management (24).

Javed and colleagues (25) demonstrated Bifidobacterium infantis' positive impact on reducing TNBS-induced colitis. Rats supplemented with Bifidobacterium infantis showed symptom reduction and less mucosal architecture damage, implying a protective role on goblet and epithelial cells. In a murine TNBS colitis model, oral Bifidobacterium bifidum supplementation lowered colonic edema, gross lesions, histological scores, and prevented weight loss (26, 27). Another study reported increased IL-10 and decreased IL-1β levels in colonic sections due to Bifidobacterium bifidum supplementation, confirming anti-inflammatory effects (27). These findings support Bifidobacterium strains' regulatory properties in reducing inflammation and colitis symptoms. However, not all probiotic strains are effective.

In a TNBS-induced colitis model by Kenned et al. (28), Lactobacillus plantarum sp. 299 didn't exhibit beneficial effects on intestinal permeability, body weight changes, colonic microscopic findings, and blood albumin levels in rats. This contrasts with other reports, attributed to TNBS dose (30 mg), colitis severity, and distinct bacterial strains modulating the environment differently. Conversely, Bifidobacterium strains have shown favorable effects in mouse models of Dextran sulfate sodium colitis.

Probiotics in Colitis, Clinical Studies

Bifidobacterium animalis subsp. lactis BB12 and Bifidobacterium longum subsp. Infantis BB_02 demonstrated alleviation of disease susceptibility and symptoms (29, 30). Bifidobacterium animalis subspecies lactis BB12 provided protection against reduced colon breadth, improved colon histology, decreased apoptosis of intestinal epithelial cells, and lowered TNF_α levels (29).

Bifidobacterium longum subspecies Infantis BB_02 reduced clinical symptoms, preserved colonic structures, and decreased edema compared to non-probiotic groups (30). In a T_bet/Rag2/ulcerative colitis mouse model, Bifidobacterium lactis mitigated early-stage colitis and inflammation, suggesting a role in lowering colitis-inducing bacteria (31).

Diverse outcomes emerge in patient-related studies. Saccharomyces boulardii administration helped maintain remission and alleviate intestinal obstruction in Crohn's disease (32). For ulcerative colitis, strains like Escherichia coli Nissle1917, Bifidobacterium breve, Bifidobacterium bifidum, and Lactobacillus acidophilus appear promising in maintaining remission (33, 34). Lactobacillus fermentum administration in UC patients reduced Nuclear factor kappa B regulation, IL_6, and TNF_α levels (35). Bifidobacterium infantis35,624 lowered C-reactive protein and TNF_α levels in gastrointestinal and non-gut inflammatory diseases (36), while Bifidobacterium breve strain Yakult showed varied results in UC maintenance (37, 38).

Differences in probiotic effects could arise from bacterial activity and interactions with other strains in the host organism. A study involving Lactobacillus acidophilus strain LA-5 and Bifidobacterium animalis subsp. lactis BB12 in ulcerative colitis patients indicated remissions in 25% of treated patients versus 8% in the placebo group (39). Treatment with Bifidobacterium longum 536 reduced disease activity and achieved clinical remission in mild to moderate ulcerative colitis (40). Combination therapy of probiotics and anti-inflammatory drugs showed greater efficacy, exemplified by a probiotic mix of Lactobacillus salivarius, Lactobacillus acidophilus, and Bifidobacterium bifidum strains (41, 42, 43), with VSL#3 being a popular blend showing proven efficacy (41, 42, 43).

Probiotic bacteria and IBD-related cancers

Inflammatory Bowel Disease (IBD) is associated with chronic inflammation and an increased risk of malignancies, including colon cancer, small bowel cancer, lymphoproliferative intestinal diseases, and cholangiocarcinoma (44, 45, 46). Probiotic strains' potential in preventing tumor formation in IBD patients is under scrutiny. Bifidobacterium lactis presence reduced NF_κB activity in proinflammatory stimulator cell lines (47).

Mouse models revealed reduced NF-κB activity and improved clinical presentation with Bifidobacterium lactis. In colorectal cancer models, VSL#3 or conjugated linoleic acid supplementation led to shorter recovery times and milder disease (48). Lactobacillus acidophilus and Lactobacillus fermentum showed antioxidant, anti-proliferative, and pro-apoptotic activities in colon cancer mouse models, particularly when combined (49).

Preliminary evidence suggests probiotics may hinder cancer progression. VSL#3 supplementation improved colon histology and increased angiostatin and vitamin D receptor levels with potential antitumor effects in a colorectal cancer model (50). However, probiotic effects were inconclusive in another study (51). In humans, postoperative supplementation with Lactobacillus acidophilus, L. plantarum, Bifidobacterium lactis, and Saccharomyces boulardii reduced postoperative pneumonia, site infection, and anastomotic leakage after colorectal surgery (52).

Conclusions

In summary, Inflammatory Bowel Disease (IBD) remains a complex disorder with multifaceted causes and mechanisms not fully elucidated. It's influenced by genetic, environmental, immunological, and microbiotic factors. Probiotics offer a promising avenue for therapy, potentially impacting various aspects of IBD pathology. However, their mode of action and full characteristics require further exploration. It's important to acknowledge that many studies are conducted on animal models, which might not precisely mirror human IBD due to diverse contributing factors. Gut differences between species further complicate translation. Probiotics' effectiveness should be assessed across diverse models. Recent attention has shifted to bacterial components and metabolites known as "postbiotics," which could offer safer alternatives. While live probiotics have advantages, they also carry risks, like bacteremia. Postbiotics present a compelling option, though more research is needed. Combining live probiotics and postbiotics might yield optimal outcomes, capitalizing on their synergistic effects. The future of gut bacteria-based therapies may lie in this combined approach, potentially revolutionizing IBD management.

Declaration

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Conflicts of interest/Competing interests

The authors declare no conflict of interest.

Authors' contributions

HEGG and SB designed the study concept, collected and interpreted the data and drafted the manuscript.

Ethics approval

Not applicable.

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