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Review

Alternative therapeutic applications used in the treatment of ulcerative colitis: probiotics, prebiotics, synbiotics and fecal microbiota transplantation

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Abstract. *Background:* Recently, some new generation therapeutic applications that can be used as an alternative to routine pharmacological agents in the treatment of ulcerative colitis (UC) have emerged. These applications are using of probiotics, prebiotics, synbiotics, and fecal microbiota transplantation. *Objective:* In this review, these therapeutic applications, which have the potential to be used as an alternative to pharmacological agents in the treatment of UC will be investigated. *Results:* Probiotic supplements are aimed increasing the number of beneficial bacteria in the intestinal microbiota composition, prebiotic supplements support the development of probiotics, and synbiotic supplements combine the positive metabolic effects of both prebiotic and probiotic supplements. Fecal microbiota transplantation (FMT) is used to correct dysbiosis in UC. In studies in the literature, we observed that all these applications generally mediate the improvement of the clinical remission levels of patients with UC, strengthening of the intestinal barrier mechanism, changing of the metabolic parameters of the inflammation picture positively, and the attainment of a healthier composition of the intestinal microflora. *Conclusions:* Alternative therapeutic applications used in the treatment of UC have been shown to have positive metabolic results on the clinical course of the disease. However, because there is no scientific consensus on the form, duration and content of such applications, further comprehensive studies should be conducted on the subject. Thus, the potential of using probiotic, prebiotic, synbiotic supplements and FMT as an alternative therapeutic application in the treatment of UC will be revealed more clearly.

Key words: Ulcerative colitis, probiotic, prebiotic, synbiotic, fecal microbiota transplantation

Introduction

Ulcerative colitis is one of the inflammatory bowel diseases (IBD) that can occur at any part of the gastrointestinal (GI) tract from the rectum to the colon and continues with relapses / attacks. The mucosal structure and integrity of the area affected by UC change negatively, and because of this effect, widespread involvements take place in the GI tract. Among the most prominent symptoms of UC are diarrhea, severe abdominal pain, and bloody stools. In addition, tissue erosions occur in areas with UC frequently, which paves the way for the development of serious conditions such as ulcerations. These ulcerations and tissue erosions that occur due to UC in the colon significantly increase the risk of developing colon cancer, one of the most common cancer types (1). In the treatment of UC, pharmacological agents such as anti-inflammatories and antibiotics are used to achieve remission. The primary purpose in using these agents is to prevent the symptoms of UC or, if this is not possible, to reduce the incidence of symptoms. In addition, steroids may be administered during the pharmacological treatment process (2).

The International Agency for Research on Cancer (IARC), which is a subsidiary of the World Health Organization (WHO) and collects statistics on cancer cases globally, published a report called "Global Cancer Observatory" in 2020. In this report, it was stated that deaths due to colorectal cancers ranked third among all cancer-related deaths globally (3). Within this context, the treatment of UC, accepted as one of the main etiological factors in the development of colon cancer, does not only cause a decrease in the prevalence and incidence of UC alone, but also creates a cumulative positive effect by preventing possible colon cancer cases (4).

Analysis of studies involving different analysis methods and scientific hypotheses conducted to understand the pathogenesis of UC demonstrated the presence of three important etiological factors. Of these etiological factors, the first one is the intestinal barrier mechanism, the second one is the dysbiosis that occurs in the intestinal microbiota composition and in which the number of pathogenic microorganisms generally increases, and the third one is the inflammation process that occurs after the immune response system activation triggered by dysbiosis (5). In the literature, there are several studies indicating that the intestinal barrier mechanism plays a decisive role in the formation of UC. There is a dynamic signal cascade process between the various layers in the structure of this mechanism, responsible for the homeostasis of the intestinal system, and the protein-structured compounds involved in the formation of these layers. In this barrier mechanism, damage may occur due to exposure to some internal and external stimuli (6). To eliminate this situation, various components of the immune system infiltrate into the damaged area. After the infiltration process, a relative increase in intestinal permeability occurs in order to restore homeostasis in the damaged tissue or area. However, in this process, some pathogenic microorganisms, which have been previously blocked by the intestinal barrier mechanism, can also reach the cell by taking advantage of the increased intestinal permeability. Thus, pathogenic bacteria multiply in the regions into which they have infiltrated and the toxic compounds (endotoxins) existing in the structure of these bacteria significantly increase the risk of endotoxemia. After the interaction between endotoxins and monocyte/macrophage cells, some metabolic signaling cascades mediated by Toll-like receptors (TLRs) are stimulated, and thus the inflammation process in which various proinflammatory cytokines are produced begins (7).

Inflammation, which occurs as a result of the process triggered by immune system elements and is one of the most important etiological factors of UC, is a metabolic response created by the host organism to limit the negative effects of infections developed by some microbial stimuli or tissue damage caused by various external factors. The role of inflammation and proinflammatory cytokines in the pathogenesis of UC has been demonstrated in several studies. However, how exactly this inflammation process occurs and how the metabolic roadmap including inflammatory cytokines works have not been clearly clarified yet. In the pioneering studies carried out in recent years, various data on the mechanistic relationships between inflammation, intestinal microbiota, and intestinal barrier mechanism have been presented (8, 9). In their study in which they investigated the relationship between UC and the inflammation process, Hu et al. (2021) found that damage to the intestinal barrier mechanism negatively affected the intestinal permeability level, and therefore, various antigens were localized in the mucus. They stated that non-physiological immune system responses emerged in the developing process, and inflammation was observed due to all these metabolic activities (10). In another study, the relationship between the development of UC and the intestinal barrier mechanism was investigated and the textural erosion of the mucus layer in the colon was shown to be one of the first markers that occurred in the development of UC (11).

Besides the intestinal barrier mechanism and the inflammation process, another etiological factor involved in the development of UC is the intestinal microbiota. After the deterioration of the intestinal microbiota composition, the release of proinflammatory cytokines, which are the key components of the inflammation, increases. In addition, after pathogenic bacteria dominate the microbiota composition, the amount of endotoxins in the intestines increases significantly, which damages the textural integrity of the intestinal barrier mechanism (12). The gut microbiota in humans is a dynamic ecosystem, which often hosts fungi, viruses and bacteria. The most important element

of this ecosystem is bacteria, and there are about 1000 bacterial species in the intestinal microbiota. There is a mutualistic, dynamic and symbiotic relationship between the bacteria in the intestinal microbiota and the host in which they carry out their metabolic activities. The host provides habitat and nutrients for these bacteria to survive, while commensal bacteria in the gut microbiota contribute to some metabolic processes that positively affect the host's health. Among these contributions are the fermentation of complex polysaccharides that reach the intestinal system by being partially digested, short-chain fatty acids (SCFA) produced as a result of fermentation of various prebiotics, synthesis of some vitamins as a result of metabolic activities of bacteria, and preservation of the structural integrity of the mucosa, which prevents pathogenic bacteria from localizing in the intestinal epithelium (13). In addition, some symbiotic bacteria species affect various signal cascades involved in the secretion of proinflammatory or anti-inflammatory cytokines through the different metabolites they produce, and thus they play an important role in the maintenance of the host's immune system homeostasis. This dynamic process between the intestinal microbiota composition and the formation of UC and some applications that may affect this process are summarized in Figure 1 (14).

In studies in which the relationship between intestinal microbiota and UC was investigated, it was determined that there might be a relationship between various bacterial species in the microbiota composition and the symptoms of UC, and that there was a decrease in both the diversity and total amount of bacteria in the intestinal microbiota composition in the UC (15). In germ-free (GF) mice, in which the intestinal microbiota composition is considered sterile, it was determined that either there was no UC development or there was minimal inflammation in the colon. However, it was observed that the UC developed after the isolates of fecal samples taken from UC-induced mice were administered to GF mice through FMT. Therefore, intestinal microbiota is stated to play a role in the initiation of the inflammation process in the colon and to be effective in the emergence of UC (16).

In various studies conducted with patients with UC, it was determined that the number of "Firmicutes" and "Bacteroidetes" bacterial phyla, which enabled the emergence of SCFA by digesting prebiotics and, thus contributed positively to the intestinal barrier mechanism, and exhibited anti-inflammatory capacity, decreased. On the other hand, in some studies

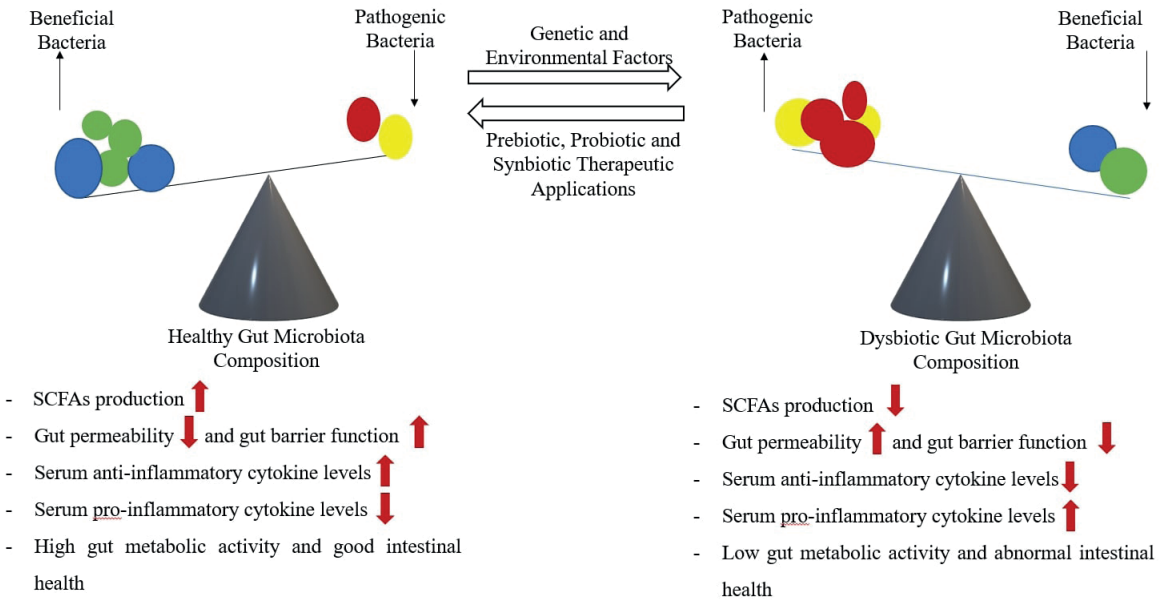

Figure 1. The characteristic features of healthy and dysbiotic gut microbiota composition and the effect of therapeutic applications on these features.

in the literature, it was determined that the number of bacteria belonging to the "Proteobacteria" phylum, which contributed to the increase in proinflammatory cytokine levels and was thought to be effective in the development of UC, also increased (17). In their meta-analysis, Dordevic et al. (2021) reported that after the administration of bacteria belonging to the "*Lactobacillus*" and "*Bifidobacterium*" genera as a probiotic supplement to patients with UC, dysbiosis in these patients tended to improve, and thus, significant remissions were detected in the disease in addition to a decrease in UC symptoms (18). On the other hand, Zakerska-Banaszak et al. (2021) conducted a study in which they compared patients with UC and healthy individuals in order to determine the relationship between the intestinal microbiota composition and the pathogenesis of UC. In the same study, they found that the number of bacteria belonging to the "Bacteroidetes" and "Verrucomicrobia" phyla, which are known to play an important role in the production of anti-inflammatory cytokines, was significantly lower in individuals with UC. On the other hand, they also demonstrated that bacterial branches such as "Proteobacteria", "Actinobacteria" and "Saccharibacteria (TM7)", responsible for the production of proinflammatory cytokines, were more common in individuals with UC than they were in healthy individuals (19).

In the current literature, the number of studies in which alternative therapeutic applications are tried instead of the pharmacological agents routinely used in the clinic for the treatment of UC has significantly increased. Especially in the last ten years, various studies in which mechanistic relationships between these therapeutic applications and the formation of UC are demonstrated have been published (20). In line with these findings, researchers have tested the effects of these therapeutic applications on the remission of UC. What is meant by these applications is the administration of probiotic or prebiotic supplements, or of the synbiotic supplement in which probiotic or prebiotic supplements are administered together. In addition to the aforementioned supplements, FMT, aimed at bringing the intestinal microbiota composition to a healthy composition by administering the isolates obtained from fecal samples taken from healthy people to patients with UC, is another method. Although pharmacological agents used in the treatment of ulcerative colitis provide short-term improvements in the quality of life and the course of the disease, they may also lead to serious side effects in their long-term use. Therefore, new generation therapeutic applications should be performed in order to minimize the side effects likely to occur in the medical treatment of ulcerative colitis. In this review, probiotic, prebiotic, synbiotic and FMTs, which have the potential to be used as an alternative to pharmacological agents in the treatment of UC and whose effects on UC are intensively investigated, will be examined.

Probiotics:

One of the alternative treatment methods applied to individuals with UC, other than pharmacological agents, is probiotic bacteria supplement, which is called beneficial microorganisms, and does not cause any negative side effects after their consumption (21). Probiotics are defined as "live microorganisms that have positive effects on the health of the host when they are consumed in sufficient quantities" (22). Short-chain fatty acids such as butyrate emerge after the metabolism of probiotics, and accordingly, the colonic pH level decreases. This low pH value, not suitable for the development and survival of pathogenic bacteria, plays a role in increasing the number of beneficial bacteria in the intestinal microbiota. On the other hand, beneficial bacteria, whose number increases after probiotic bacteria supplementation, gain an advantage over pathogenic bacteria in terms of accessing nutrients and thus become dominant in the intestinal microbiota composition. In addition, butyrate is used as a substrate by epithelial cells in the colon. Due to the increase in the functional capacity of epithelial cells, mucin secretion increases, which prevents the attachment of pathogens to cells, and thus the structure of tight junction proteins (TJP) in epithelial cells is strengthened. In addition, butyrate exhibits anti-inflammatory properties by providing down-regulation of signaling pathways such as nuclear factor kappa-B (NF-kB), which plays an important role in the production of proinflammatory cytokines (23).

Since probiotics have all these positive metabolic effects listed above, they have been used by scientists in various studies to test the hypothesis that dysbiosis seen in the microbiota composition may play a role in the development of UC. Probiotics used in studies can be not only in the form of a single strain, but also in the form of products containing different probiotic bacteria. The single probiotic strains in question are generally selected from the microorganisms belonging to the "*Lactobacillus*" and "*Bifidobacterium*" genera. Commercial products in mixed form, as in the example of VSL3#, contain probiotic bacteria such as *"Lactobacillus acidhophilus", "Lactobacillus bulgaricus", "Lactobacillus casei", "Lactobacillus plantarum", "Bifidobacterium infantus", "Bifidobacterium breve", "Bifidobacterium longum"* and *"Streptococcus thermophiles"*. The most important point to be considered in the application of probiotic bacteria for therapeutic purposes in UC is that the strain or product to be used must have positive effects on the intestinal barrier mechanism, inflammation, and especially on the intestinal microbiota (24).

In their meta-analysis, Dang et al. (2020) demonstrated that administration of VSL3# resulted in a significant increase in both clinical remission (OR = 2.40, 95% CI = 1.49 – 3.88; p<0.001) and clinical response values (OR = 3.09, 95% CI = 1.53 – 6.25; p<0.001). Another noteworthy output obtained in their study is that, compared to the placebo group, the VSL3# application realized all these positive metabolic changes without causing any serious side effects (OR = 0.90, 95% CI = 0.33 – 2.49; p=0.87) (25). On the other hand, in their updated systematic review, Kaur et al. (2020) analyzed studies in which a single probiotic strain or commercial products containing a mixture of probiotic strains were included. In the present study, probiotic use was compared not only with the placebo group, but also with the mesalazine (5-aminosalicylic acid (5-ASA)) group, which is a pharmacological agent commonly used to treat UC. The comparison of the probiotic group with the placebo group revealed that there was a significant improvement in clinical remission (RR = 1.73, 95% CI = 1.19 – 2.54; p=0.005) but that there was no difference between the probiotic group and the group receiving mesalazine in terms of clinical remission values (RR = 0.92, 95% CI = 0.73 – 1.16; p=0.46). On the other hand, the clinical remission values of the new group to whom probiotics were administered in addition to mesalazine were higher (RR = 1.22, 95% CI = 1.01 – 1.47; p=0.04) than were those of the group receiving only mesalazine. Thus, probiotics could be used in the treatment of UC when they are administered alone as a therapeutic agent or when they are used as an alternative treatment method to strengthen existing medical therapy (26).

In their randomized controlled study conducted with UC patients, Chen et al. (2020) administered mesalazine + probiotic combination to the intervention group, and only mesalazine to the placebo group. The comparison of the intervention group and the placebo group at the end of the study demonstrated that there was a significant decrease in the disease activity index (DAI) scores (p=0.043) and a significant increase in clinical remission level (p=0.034) in the intervention group. In addition, after the administration of the probiotic mixture, an improvement was observed in the total bacterial amount and diversity of the intestinal microbiota composition; however, such an effect was not observed in the placebo group. Especially in the intervention group, the number of bacteria in the *"Ruminococcus", "Blautia", "Eubacterium"* species belonging to the genus "*Clostridium cluster XIV"* containing butyrate-producing bacteria increased (p<0.05). Finally, in the same study, it was determined that there was a negative correlation between bacteria belonging to the genus *"Weisella"* and the DAI score used to assess the severity of UC, and that this bacterial genus increased in the intestinal microbiota composition of the intervention group (p<0.05) (27). On the other hand, in their study in which they reviewed randomized controlled trials conducted with patients with UC, Iheozor – Ejiofor et al. (2020) found that probiotic administration as an alternative treatment method in UC neither significantly reduced clinical relapse compared to placebo administration (RR = 0.87, 95% CI = 0.63 – 1.18; p = 0.36) nor improved clinical remission at a sufficient level (RR = 1.16, 95% CI = 0.98 – 1.37; p=0.08) (28).

In studies in the literature in which probiotics were administered to patients with UC, it was found that clinical remission was generally improved and that the dysbiosis in the intestinal microbiota composition due to UC improved. However, there are also

studies in which probiotic administration does not cause a positive change in both various symptoms of UC, clinical remission and intestinal microbiota composition compared to placebo applications. Although it is known that probiotics causes much fewer side effects than do pharmacological agents used in the treatment of UC, a larger number of comprehensive studies should be conducted for probiotic administration to be widely accepted in the scientific world as an alternative treatment method because the positive effects of probiotics on various metabolic disorders, as in the case of UC, may vary depending on the specific characteristics of some strains. As a result, more and well-planned randomized controlled studies (RCTs) should be conducted to clarify the effects or mechanisms of action of probiotic administration on UC clearly. Therefore, the functional capacity of probiotics on the development and clinical course of UC will be determined and their potential to be used as an alternative therapeutic agent will be determined more accurately.

Prebiotics

Another nutraceutical component that plays a role together with probiotics in shaping the intestinal microbiota composition, which is thought to play a role in the development of UC, is prebiotics. Prebiotics are defined as "non-digestible nutritional components that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of microorganisms in the colon" (29). Prebiotics positively contribute to the intestinal microflora by acting as a necessary substrate for the maintenance and development of beneficial bacteria in the intestinal microbiota composition of the host. The main metabolic function of prebiotics in the intestinal system is to form SCFAs by fermenting them with probiotics because SCFA types such as acetate, propionate and butyrate are used as energy raw materials in colonocytes and are involved in maintaining the structural integrity of the intestinal barrier mechanism. In addition, prebiotics, generally fermented by beneficial bacteria genus such as "*Lactobacillus*" and "*Bifidobacterium*" existing in the intestinal microbiota play a role in preventing various negative metabolic conditions that will be created by pathogens by helping beneficial microorganisms to become dominant components in the intestinal microbiota composition (30).

In studies in which the relationship between UC and prebiotics was investigated, prebiotic sources such as inulin, fructooligosaccharides (FOS) and galactooligosaccharides (GOS) were generally used (31). In their study conducted with UC-induced mice, Kang et al. (2022) determined that butyl-fructooligosaccharide (B-FOS) administration significantly increased the number of bacteria belonging to the *"Bifidobacterium*" genus and the butyrate concentration in the cecum in the intervention group compared to the control group. They also found that as a result of B-FOS application, the mRNA expression level of the occludin component, involved in the intestinal barrier mechanism, increased, and that mRNA expression levels of tumor necrosis factor-alpha (TNF-α), interferon-gamma (IFN-γ) and interleukin-8 (IL-8) components, important cytokines of inflammation, decreased (p<0.05) (32). In another study, Liu et al. (2020) administered inulin to UC-induced mice as a prebiotic source. At the end of their study, they found that DAI scores and serum levels of proinflammatory cytokines IL-1α, IL-6 and TNF-αdecreased in the group with UC in which inulin was administered compared to the control group with UC (p<0.05). On the other hand, body weight and colon length, and serum level of IL-10, an anti-inflammatory cytokine, increased (p<0.05) (33). In their in vivo study, Wang et al. (2019) administered prebiotic chitosan (Chitosan-CS) to UC-induced mice. While an increase was observed in the colon lengths and body weights of the mice, there was a decrease in the DAI scores. It was also reported that the expression of TNF-α, one of the key proinflammatory cytokines, decreased and that the expression levels of TJP components such as occludin, claudin-1 and zonula occludens-1 (ZO-1) changed to strengthen the intestinal barrier mechanism. Another interesting finding obtained in Wang et al.'s study was that the number of "*Lactobacillus*" and "*Blautia*" bacteria decreased in the control group with UC, but that when prebiotic CS was administered to the same group, the number of "*Lactobacillus*" bacteria, one of the important components of bifidobacteria, increased again in the intestinal microbiota (34). In their recently published study, Wu et

al. (2019) administered another prebiotic, phloretin (Phloretin – PH), to UC-induced mice. Then, feces samples obtained from the group receiving PH supplement were administered to another group of UC-induced mice via FMT. In both cases, it was found that the NF-kB signaling pathway was inhibited. Thus, it was observed that inflammation in the colon was reduced, that the intestinal barrier mechanism was strengthened, and that immune system functions were improved (35).

In their open-label study, Wilson et al. (2021) administered GOS as a prebiotic source to patients with UC and investigated the changes in the clinical symptoms of the disease and the intestinal microbiota composition. At the end of their study, they determined that prebiotic administration significantly increased the number of "*Bifidobacterium*" (p=0.046) and "*Christensenellaceae*" (p=0.043) bacteria, but did not lead to a significant improvement in clinical scores reflecting the severity of the disease or in inflammation (36). On the other hand, in their meta-analysis, Zhang et al. (2021) investigated the clinical effects of alternative therapeutic applications such as probiotics, prebiotics and synbiotics on IBD. They found that the administration of prebiotics used for the treatment of ulcerative colitis did not lead to a significant improvement in DAI scores (SDM = 3.45, 95% CI = -0.76 – 7.66; p = 0.108) (37).

In the current literature, it has been determined that the relationship between UC pathogenesis and prebiotics has been investigated much less than the relationship between UC pathogenesis and probiotics.

Most of these studies in which the efficacy of prebiotics as therapeutic agents was investigated were not of a randomized controlled design, and the duration, dosage, and source of prebiotics used showed a wide range of distribution. Although in the general majority of studies on the subject, it was stated that prebiotic administration had positive clinical effects on UC, it is thought that it is still early to recommend the use of prebiotics in UC due to the aforementioned reasons. Therefore, methodologically more detailed and randomized controlled studies should be performed to reveal the potential of prebiotics to be used as an alternative therapeutic agent in UC clearly.

Synbiotics

Numerous studies in the current literature indicate that the use of probiotic bacteria therapy in the treatment of UC is effective and safe. It has also been observed that in some studies, prebiotics consumed by individuals with UC cause a decrease in the symptoms of the disease and inflammation. In the light of all these scientific outputs, it is expected that the synbiotic administration of probiotics and prebiotics that increase their metabolic activity level in UC will increase the efficacy rate of the treatment (38). The main purpose of administrating synbiotics is to reveal a synergistic and stronger effect by using the two components together, rather than the results to be obtained separately through probiotic and prebiotic supplementation. The most important point here is that the prebiotic in the synbiotic administration can only be fermented by the probiotic strain or product, and cannot be fermented by pathogenic bacteria. Thus, the number of beneficial bacteria in the intestinal microbiota composition increases, and the development of dysbiosis is prevented by preventing pathogens from becoming dominant (39).

In their recent study, Wong et al. (2022) investigated the effects of probiotic, prebiotic and synbiotic administrations on various cytokines and intestinal microbiota composition on mice with acute UC. They demonstrated that the administration of synbiotics decreased the level of IL-6, a pro-inflammatory cytokine, increased the level of IL-10, an anti-inflammatory cytokine, increased the expression of occludin, one of the important elements of the intestinal barrier mechanism, and down-regulated the STAT3 signaling pathway, known to play a role in the development of UC more than did probiotic and prebiotic applications. It was observed that all these effects were also reflected in the DAI scores measured after the administrations, and that the group administered synbiotic had the lowest score. In addition, one of the most important findings obtained in the same study is how the aforementioned practices affected the "Firmicutes" and "Bacteroidetes" phyla, the "*Clostridium cluster IV*" species and the Firmicutes:Bacteroidetes (F/B) ratio in the intestinal microbiota composition because there is a direct correlation between F/B ratio and anti-inflammatory

cytokines in UC, and between F/B ratio and clinical remission with the level of "*Clostridium cluster IV*" type. It was demonstrated that probiotic, prebiotic and synbiotic applications all increased the level of both "Firmicutes" and "Bacteroidetes" phyla, and "*Clostridium cluster IV*" in the intestinal microbiota composition and the F/B ratio compared to the positive control group (p<0.05) (40).

In their in vivo study, Son et al. (2018) administered a probiotic strain (LGG) and D-tagatose, used as a source of prebiotics as a synbiotic to experimentally UC-induced mice. At the end of the study, they determined that proinflammatory cytokine levels such as TNF-α and IL-6 decreased more after synbiotic administration compared to probiotic and prebiotic administrations. While the dominant bacterial phylum was "Proteobacteria" in the intestinal microbiota composition of the UC-induced group but nothing was administered, the "Bacteroidetes" phylum was the dominant microflora in the groups to which probiotics, prebiotics and synbiotics were administered. However, after the synbiotic administration, the "Firmicutes" phylum containing bacteria of the "*Lactobacillus*" genus, called beneficial bacteria, increased significantly compared to the probiotic and prebiotic administrations (p<0.05). As a result, in their study, Son et al. stated that the administration of the aforementioned synbiotics was quite effective in correcting the dysbiosis seen in the intestinal microbiota composition (41). In their recently published meta-analysis, Zhang et al. (2021) determined that there was a decrease in DAI scores after the use of probiotic strains belonging to the genus "*Lactobacillus*" and "*Bifidobacterium*" and prebiotics such as inulin, lactulose, FOS and GOS, and that this decrease was higher in the synbiotic administration in which these components were used together (37).

In studies in which synbiotics were used for therapeutic purposes in the treatment of UC, it was observed that they generally reduced proinflammatory cytokine levels and corrected the dysbiosis in the intestinal microbiota composition. From this perspective, the use of synbiotics is considered as a functional alternative method in the treatment of UC (42). However, the number of studies in the literature is still insufficient in terms of randomized controlled design and sample size. In addition, methodologically more detailed and advanced in vivo studies ahold be conducted to determine the dose levels of the synbiotic forms to be administered clearly, because the probiotic bacterial strains and prebiotic species used in synbiotic application show a wide range of distribution.

Fecal Microbiota Transplantation:

Clinical treatment of UC is usually carried out with pharmacological agents such as immunosuppressants and antibiotics. However, after a long-term use of these drugs, serious side effects can be seen in individuals, which leads to significant decreases in patients' quality of life. Therefore, various applications that can be an alternative to the pharmacological treatment of IBDs are being the subject of more and more studies every day. One of these innovative applications is FMT. In this procedure, feces samples obtained from healthy donors are administered to individuals with UC in various ways (e.g. enema or colonoscopy) after they undergo necessary procedures. The purpose of the FMT is to transform the intestinal microbiota composition, which exhibits dysbiotic character in the presence of UC, back to a healthy microbial composition because the presence of dysbiosis significantly increases the release level of inflammatory cytokines, which is the biggest obstacle to remission in UC (43).

Fecal microbiota transplantation first attracted the attention of the scientific world with the persistent diarrhea caused by the bacterium *"Clostridium difficile"* and usually seen in individuals using long-term antibiotics (44). In their randomized double-blind placebo-controlled study conducted with UC patients for 6 weeks, Moayyedi et al. (2015) administered microbiota samples obtained from healthy donors to those in the intervention group through FMT. At the end of the study, they stated that the remission rates of UC were 24% in the intervention group undergone FMT and 5% in the control group, and that the difference was statistically significant (45). On the other hand, in their phase-I study conducted with ten pediatric patients with UC aged 7-21 years, Kunde et al. (2013) performed FMT once a day for five days. In the pediatric patients with UC, the clinical remission rate was 78% one week after the application, and as high as 67% even one month after the application (46).

In their multicenter randomized double-blind placebo-controlled study, Paramsothy et al. (2017) performed FMT by increasing the dose number of FMT procedure (FMT for 8 weeks and 5 times a week) for the first time at a considerably higher rate compared to other studies, and they assessed how much this application reduced the incidence of remission and the intestinal microbiota composition in UC. To achieve their purpose, they took samples from the individuals in the intervention and control groups for microbiota analysis at the beginning, fourth and eighth weeks (end) of the study, and used various clinical scoring systems to determine the remission findings in UC prognosis. At the end of the study, clinical remission rate was 27% (n=11/41) in the individuals in the intervention group, but 8% (n=3/40) in the individuals in the control group (RR = 3.6, 95% CI = 1.1 – 11.9; p = 0.021). They found a positive correlation between clinical remission and *Barnesiella, Parabacteroides, Clostridium cluster IV* and *Ruminococcus* bacterial species. On the other hand, in individuals without clinical remission, the density of *Fusobacterium* and *Sutterella* bacteria was high (p<0.05). The most important finding in Paramsothy et al.'s study was that the dysbiosis in the intestinal microbiota composition in the UC in the fourth and eighth weeks of FMT improved, but that the reflection of this change to clinical remission only occurred in the eighth week (47).

In their randomized double-blind placebo-controlled study, Costello et al. (2019) investigated the effects of FMT procedure applied to patients with UC on clinical remission and gut microbiota composition. They administered FMT to the individuals in the intervention group to whom isolate obtained from healthy donors was given for the first 7 days. However, the individuals in the control group were administered a placebo product via enema. At the end of the eighth week, clinical remission was observed in 32% (n=12/38) of the individuals in the intervention group, and only in 9% (n=3/35) of the individuals in the control group (p<0.05). However, even in the analysis performed at the end of the study (in the 12th month), the positive metabolic effects of FMT continued in a significant portion of individuals (42%, n=5/12) with clinical remission findings at the eighth week. Bacterial species belonging to the genus "*Prevotella*" increased in the intestinal microbiota at the eighth week after FMT, and there was a relationship between clinical remission and bacterial species such as "*Anaerophilum pentosovorans*" (Firmicutes phylum) and "*Bacteroides coprophilus*" (Bacteroidetes phylum) (48). In a recent meta-analysis, the effect of FMT on clinical remission and response levels on IBD, such as UC and Chron's disease, was investigated. The results of the analysis of six randomized controlled trials (RCTs) demonstrated that FMT improved the clinical remission level (RR = 1.70, 95% CI = 1.12 – 2.56; p = 0.01) on IBD (49).

On the other hand, in several studies in the current literature, it was indicated that the FMT procedure performed to correct the dysbiosis in the treatment of UC leads neither to clinical remission at a sufficient level nor to significant increases in the DAI scores (14). In their randomized double-blind placebo-controlled phase-II studies, Rossen et al. (2015) administered isolates obtained from healthy donors to individuals with UC through FMT. Fecal microbiota transplantation was performed twice at the beginning of the study and 3 weeks later. The presence of clinical and endoscopic remission was analyzed at the 6th and 12th weeks of the study. The results of these analyses demonstrated that clinical and endoscopic remission rates determined at the sixth week were similar to those determined at the twelfth week (p>0.05). According to the results of intestinal microbiota analysis of the control and FMT groups, the density of *Clostridium clusters* IV and XIVa, known to show colitogenic activity, decreased in individuals with remission in both groups (50).

As a result, the FMT came to the forefront as an alternative therapeutic application in the treatment of UC due to its low cost and, more importantly, due to its a lot fewer side effects compared to pharmacological treatment (51). However, in a review of studies in the literature, it was observed that the number of randomized clinical controlled studies accepted as the gold standard in clinical decision making was limited. It is also noteworthy that the frequency and duration of administration in UC studies in which FMT is used for therapeutic purposes varies considerably. In the scientific world, there is a consensus that the bacterial population in the intestinal microbiota composition, accepted as one of the most important etiological factors of UC, decreases in terms of variety and

total amount. However, it has not yet been clarified in full detail whether there is a relationship between the change in the amount of composition of which bacterial genus or species in the intestinal microbiota composition, and the development of UC. Therefore, in order to reveal the efficacy of FMT promising hope in the treatment of UC clearly, more comprehensive and randomized controlled studies should be conducted.

In Table 1, randomized controlled studies with alternative therapeutic applications (probiotics,

Table 1. Randomized controlled trials with alternative therapeutic applications used in the treatment of UC

Study, Year	Study Type	Methods and Aims	Main Findings
Moayyedi et al. (2015)	Randomized placebo-controlled trial	The study aims to measure the effectiveness and reliability of the FMT procedure applied to UC patients. In this direction, the FMT procedure was applied once a week to two different groups of UC patients for 6 weeks: - Intervention group (n = 38): 50 ml of fecal sample solution obtained from healthy donors - Control group (n = 37): 50 ml water (placebo)	As a result of the study, it was determined that the clinical remission rate was 24% in the intervention group and 5% in the placebo group, and the difference between the two groups was found to be statistically significant (p<0.05). As a result of the applications, there was no significant difference between the groups in terms of side effects (p>0.05). Finally, it was observed that the bacterial diversity in the intestinal microbiota pattern of the intervention group was higher than that of the control group (p=0.02).
Rossen et al. (2015)	Randomized placebo-controlled trial	This study aims to examine the clinical remission rates of the FMT procedure and the changes in the intestinal microbiota pattern. In this direction, FMT was applied to UC patients who were divided into two groups, at the beginning of the study and in the third week, as follows: - Intervention group (n = 23): 500 ml of fecal sample solution obtained from healthy donors via nasoduodenal tube Control group (n = 25): 500 ml of stool sample solution obtained from UC patients' feces via nasoduodenal tube	As a result of the study, no significant difference was found between the intervention (30.4%) and control (20%) groups in terms of clinical remission rates in the analyzes performed at the sixth and twelfth weeks (p=0.51). In the analysis of the intestinal microbiota patterns of the individuals in the intervention group during the twelfth week, it was found that the density of *Clostridium clusters* IV and XIVa, which are known to show colitogenic activity, decreased.
Paramsothy et al. (2017)	Randomized placebo-controlled trial	The study aims to evaluate the effects of increasing the frequency of FMT procedures applied to UC patients on clinical remission rate and gut microbiota pattern. For this purpose, UC patients were divided into 2 groups and FMT was applied 5 times a week for 8 weeks: - Intervention group (n = 42): 150 ml of fecal sample solution obtained from healthy donors - Control group (n = 43): 150 ml of isotonic placebo solution	As a result of the study, it was found that the clinical remission rate was 27% in the intervention group and 8% in the control group (p=0.021). It was observed that there was no significant difference between the groups in terms of side effects related to the applications (p>0.05). It was determined that the diversity of bacterial species increased in the intervention group and there was a negative correlation between the bacteria belonging to the genus *Fusobacterium* and clinical remission levels.
Costello et al. (2019)	Randomized placebo-controlled trial	This study aims to test whether the effects of the FMT procedure applied in UC on clinical remission and intestinal microbiota persist for a long time. FMT procedure was applied to the following two groups formed for this purpose for 7 days, and then the scores of UC severity were evaluated at the end of the eighth week and twelfth month: - Intervention group (n = 38): 100 ml of fecal sample solution obtained from healthy donors - Control group (n = 35): 100 ml solution sample obtained from the own feces of UC patients	As a result of the study, it was observed that the clinical remission rate measured in the eighth week was 32% in the intervention group and 9% in the control group (p<0.05). In addition, it was found that the positive metabolic effect in question continued in the twelfth month in 42% of individuals with clinical remission findings in the eighth week. A negative correlation was found between *Anaerophilum pentosovorans* and *Bacteroides coprophilous* species and the severity of UC.

Table 1. Randomized controlled trials with alternative therapeutic applications used in the treatment of UC (Continued)

Study, Year	Study Type	Methods and Aims	Main Findings
Chen et al. (2020)	Randomized placebo-controlled trial	This study aims to determine the effects of a product consisting of a mixture of various probiotic strains (Probio-Fit) on the picture of UC when used in addition to the pharmacological agent currently used in the clinic. Accordingly, the patients were divided into two groups, and the following practices were performed twice a day for 12 weeks: - Placebo group (60 mg/kg/day) (n = 13): Mesalazine + Placebo - Intervention group (60 mg/kg/day) (n = 12): Mesalazine + Probio-Fit	As a result of the study, when the intervention group was compared with the placebo group; They found a decrease in disease activity index scores reflecting the severity of UC (p=0.043), while an increase in clinical remission rates (p=0.034). However, it was determined that the diversity and richness of the intestinal microbiota pattern of the intervention group and the bacterial species were higher than the placebo group. Finally, it was observed that the amounts of *Eubacterium ramulus* (p<0.05), *Pediococcus pentosaceus* (p<0.05), *Bacteroides fragilis* (p=0.02), and *Weisella cibaria* (p=0.04), which are known as beneficial bacteria species, were higher in the intervention group than in the placebo group.

prebiotics, synbiotics and fecal microbiota transplantation) in the treatment of UC are indicated.

Conclusion

In the medical treatment of UC, one of the most important subtypes of IBDs, generally, medications such as anti-inflammatories and antibiotics are used. Medicine therapy, usually carried out in the clinic to relieve symptoms, may cause serious side effects due to long-term use, which leads to significant decreases in patients' quality of life. In addition, the administration of pharmacological agents such as antibiotics in the treatment worsens the presence of dysbiosis in UC and adversely affects the course of the disease. Therefore, scientists intensively continue to search for applications which have the potential to be an alternative to pharmacological agents in the treatment of UC, without serious side effects and with lower costs. Among these applications, probiotic, prebiotic and synbiotic supplements and processes such as FMT come to the fore. Although there are studies claiming the opposite in the literature, the general opinion is that these supplements and FMT provide clinical remission in UC and make the intestinal microbiota composition healthy. However, in order for such a treatment method to be used routinely in the clinic, several variables such as dose, content and duration of use of these applications seem far from being standardized. Thus, more detailed and comprehensive studies should be carried out on the subject in the future.

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