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Probiotic Microorganisms in Diet and Their Effect on Inflammatory Bowel Disease (Ulcerative Colitis)

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Abstract: *A group of inflammatory diseases that affect the colon and small intestine are called inflammatory bowel diseases (IBD), and Ulcerative colitis (UC) and Crohn's disease (CD) are two common types. These diseases increase the risk of colon cancer, inflammation of the joints, eyes, and skin and increase the risk of a blood clot in the arteries.Researches have indicated that a variety of factors, such as diet, genetics, intestinal flora, etc., are effective in getting infected by the mentioned disease, which affects the large intestine. Conventional synthetic drugs for reducing the inflammation and also for the treatment of this disease have serious and more side effects for the consumer, causing researchers to seek alternative treatment methods with fewer side effects. Studies have demonstrated that probiotic microorganisms can exhibit anti-inflammatory properties through various mechanisms. The present review showed that the major mechanism of probiotics for coping with inflammatory bowel disease is related to the consolidation of the epithelial barrier and the production and secretion of interleukins.*

Keywords— Diet; Inflammatory Bowel Disease; Microorganism; Probiotic; Ulcerative Colitis

1. INTRODUCTION

Probiotics are commensal organisms that have positive effects on the health of the consumer in the case of being consumed in sufficient quantities. Probiotics are usually catalase-negative gram-positive lactic acid bacteria that have no spores and can tolerate acidic conditions. These bacteria are fermenters, and lactic acid is their major end product in sugar fermentation [1]. On the other hand, there are prebiotics that are not living dissimilar to probiotics; however, they are non-digestible nutrition (usually oligosaccharides or polysaccharides) that effectively influence the health of the host by selectively stimulating the growth and activity of some bacterial species. More precisely, prebiotics implies to the component that was selectively fermented and provided specific changes in the composition and/or activity of gastrointestinal microbiota that ultimately leads to beneficial effects on the health of the host. Prebiotics should not be hydrolyzed by human intestinal enzymes but should be selectively fermented by harmless and beneficial bacteria to lead to positive impacts on the health of the host. The combination of probiotics and prebiotics is called synbiotic [2,3].

In order to have excellent performance and efficiency and to be part of the probiotic family as a whole, probiotic bacteria need to be of human origin and possess Generally Recognized as Safe status (GRAS). They also need to be resistant against acid and bile, capable of adhering to intestinal cells and remaining stable in the intestine for a long time. These types of microorganisms must be able to resist pathogenic bacteria and regulate the immune response [4]. Most of the microorganisms which are used as probiotics are bacteria derived from human, animal, and food sources. The types *Lactobacillus* and *Bifidobacterium* include most probiotic species; however, other bacterial strains such as *Enterococcus*, *Streptococcus*, and *Escherichia* have been employed in many cases. *Saccharomyces boulardii* fungus is the most common non-bacterial probiotic, which is isolated from Chinese lychee fruit [5].

2. METHODS AND MATERIALS

2.1 Methods

The present article is the result of investigating articles and books related to the topic and keywords of research in various databases such as Google Scholar, Science Direct, PubMed, Medline, and other related databases. Inflammatory bowel diseases are divided into two common types of ulcerative colitis and Crohn's disease. It should be noted that the purpose of this study is to evaluate the tests and studies on ulcerative colitis in these databases.

3. RESULTS AND DISCUSSION

3.1 Probiotic Sources: Foods or Probiotic Supplements

Dairy and fruit are considered to be the main sources of probiotic bacteria [6]. Fermented foods are excellent sources of probiotic microorganisms that can be used to enter probiotics to dietary. Yogurt, which is one of the most consumed dairy products, is obtained from the fermentation of milk by various bacteria and mainly lactic acid bacteria and bifidobacteria [7]. Kefir is a fermented probiotic drink made from milk. The fermentation of milk begins after the addition of Kefir grains to the milk. It should be noted that the cause of fermentation is the lactic acid bacteria and yeast found in kefir grains. Compared to yogurt, kefir is a richer source of probiotics [8]. Sauerkraut is a fermented product

derived from the fermentation of headed cabbage by lactic acid bacteria; in addition to being an excellent source of probiotics, it also contains lutein and zeaxanthin antioxidants [9]. Tempeh is obtained from the fermentation of soybeans by *Rhizopus* fungi such as *Rhizopus oligosporus* and *Rhizopus oryzae*. This product, also known as vegetarian burgers, is a good source of vitamin B12 and minerals other than probiotics [10,11]. Kimchi is a traditional Korean dish made from the fermentation of various vegetables, and cabbage is usually the main component of Kimchi. This product contains some lactic acid bacteria, the most important of which is *Lactobacillus kimchii* [12,13]. Miso is a traditional Japanese dish that is made from the fermentation of soybeans with *Aspergillus oryzae* (kōji) fungi combined with salt. This product is a valuable source of probiotics and fiber. Although the products, as mentioned earlier, may come from particular cultures and every single of which be considered as traditional food of a specific country, they are known and consumed throughout the world today. Due to the variety of foods that include probiotic microorganisms, the use of probiotic-containing supplements was not recommended except under specific conditions and as a substitute for probiotics present in foods. Most supplements on the market are labeled in milligrams (mgs), but probiotic supplements are labeled in colony-forming units (CFUs). In general, it is expected that a bottle containing probiotic supplements to possess ≥ 10 billion CFU. However, investigations have indicated that only one sample of fermented vegetables contains 10 trillion CFU of probiotic microorganisms [14]. In addition, probiotic foods naturally possess more pragmatic "super food" benefits than probiotic supplements. On the other hand, due to the lack of established regulatory laws, probiotic supplements are not regulated, and the exact number of CFUs in these products is questionable [15].

3.2 Inflammatory Bowel Diseases

A group of inflammatory diseases that affect the colon and small intestine are called inflammatory bowel diseases (IBD), and Ulcerative colitis (UC) and Crohn's disease (CD) are two common types. These diseases increase the risk of colon cancer, inflammation of the joints, eyes, and skin and increase the risk of a blood clot in the arteries.

3.2.1 Effects of probiotics on IBD

surface active compounds including surface layer protein, lipoteichoic acid, lipopolysaccharide, and heat-killed antigen, molecular metabolites such as bacteriocin, vitamins, short-chain fatty acids, and long-chain fatty acids, antihistamine production, γ-aminobutyric acid, citrullination, biohydrogenation property such as the production of conjugated linoleic acid, with properties such as being antioxidant and cholesterol assimilation. The production of beta-galactosidase, immunomodulation, pathogen suppression, competition with pathogens and harmful microorganisms for grabbing food and space are some factors that have made it possible to recommend and emphasize the use of probiotic microorganisms in the diet [16-24]. Stopping the production and maintenance of microbiota has been recognized as a key factor in the development of diseases in individuals. In particular, it can be said that this factor causes individuals to expose to local inflammation. The results of previous researches have indicated that probiotic microorganisms, whether living or dead, can regulate the microbial composition of the intestine to restore the lost microbiota and reduce the inflammation and its consequences. Probiotic microflora-mediated therapy is referred to as a new therapeutic method for inflammatory diseases. Probiotics are of the most important components of functional foods. These microorganisms regulate the intestinal microflora and keep homeostasis stable in the gastrointestinal tract. Probiotics are also involved in the normalization of intestinal colonization [25]. In most cases, the study of the correlation between probiotics and their effects on the health of the host is related to three functional fields of the gut microbiota, including metabolic effects, protective effects, and trophic effects [3].

Evidence shows that probiotic bacteria in different species and strains may be applied as an anti-inflammatory agent in some chronic inflammatory diseases depending on their way of usage [26]. According to conducted studies, anti-inflammatory properties are of the important effects of probiotics on the host body. Several in vitro studies were performed by intestinal cells to confirm these properties. The anti-inflammatory properties of probiotic strains were determined in an investigation conducted by Kwon et al. by an ex-vivo screening method [27]. Probiotics regulate the inflammation in the host body in different ways. The primary purpose of probiotics is to enhance the function of the epithelial barrier [28]. The effect of probiotic microorganisms on the function of epithelial cells has been demonstrated in vivo and in vitro [29]. In the context of IBD, anti-inflammatory bacteria may transmit signals to the gastrointestinal epithelium and mucosal regulatory T cells or dendritic cells [30]. Consolidation of intestinal defense barriers can be an important factor in the treatment of IBD. Regulatory signals may also be transmitted between the commensal flora and the epithelial and subepithelial segments of the mucous membrane and may be part of the process of consolidation of intestinal defense barriers. Researches have indicated that non-pathogenic microorganisms such as probiotics can demonstrate counterbalance epithelial responses by regulating cytokine transcription factors compared to invasive bacteria [31]. Some probiotic strains can apply their effects by stimulating the signaling pathways of intestinal epithelial cells (IEC), such as blocking the activity of NF-κB (nuclear factor kappa-light-chain-enhancer of activated B cells), the change of MAPK/ERK pathway, PI3K and Akt activation and also dependent pathway of PPAR-γ or PPARG (Peroxisome proliferator-activated receptor gamma) [32].

Different probiotic strains can stimulate the production of cytokines and chemokines to cope with inflammatory diseases [33]. In a study by Di Giacinto et al. [34] on mice, it was identified that probiotic bacteria might prevent the mice from being exposed to chemically induced intestinal inflammation by induction of the Regulatory T cell lymphocyte. The answer to the question of whether a specific probiotic strain is capable of this in humans is still unclear, but in vitro data and indirect evidence from clinical studies suggest that consumption of certain probiotics may increase the production of IL-10 and transforming growth factor beta (TGF-β) [35,36]. A study performed by Mohamadzadeh et al. [37] indicated that some probiotic strains force dendritic cells to express higher levels of Interleukin 12 (IL-12) and Interleukin 18 (IL-18). An investigation by Rigby et al. [38] showed that Bifidobacterium longum could induce murine colonic dendritic cells to produce Interleukin 12 (IL-12)) and Interleukin 10 (IL-10). It is worth noting that besides the fact that the living strains of probiotic microorganisms have many health benefits for the host, the cellular components of the dead probiotic strains also affect the health of the host [16]. A study by Vinderola et al. [39] showed that gram-positive strains of living or dead probiotics such as Lactobacillus casei and Lactobacillus helveticus were able to stimulate the production of Interleukin 6 (IL-6) in intestinal epithelial cells of mice. In an investigation conducted by Van Baarlen et al. [40], it was revealed that polysaccharide A (PSA) can be extracted from probiotic strains of human origin such as Bacteroides fragilis and may lead to the expression of Interleukin 10 (IL-10) from regulators FOXP3 (forkhead box P3), CD4 (cluster of differentiation 4), and T cells.

3.3 Ulcerative colitis disease

UC, which is categorized as an inflammatory bowel disease, can affect different parts of the bowel. In most cases, it is reported that this disease affects the large intestine. Glucocorticoids are compounds of the type of corticosteroids that are prescribed to reduce inflammation for many diseases, including UC. Mineralocorticoids are other types of corticosteroids that can show anti-inflammatory properties. The important point about this steroid compound is its side effects that can include metabolic and anterior pituitary disorders. The use of chemical drugs is a common way for the treatment of IBDs that work by suppressing the immune system or modulating the inflammatory response. Chronic use of antibiotics to treat IBD is associated with negative side effects and the risk of bacterial resistance. Probiotics have a lower risk of side effects and can be considered as a suitable option for use in the treatment of IBD by changing the intestinal flora and modulating the immune response [41].

3.3.1 Effects of probiotics on UC

In order to increase the impact of probiotics on experiments conducted on animal models, researchers have combined the therapy by probiotics with prebiotics and antibiotics or engineered probiotic strains to secrete anti-inflammatory mediators [41].

Mesalazine is one of the common chemical drugs for the treatment and prevention of mild to moderate cases of IBD, including UC and CD. In a random and double-blind clinical trial conducted by Kruis et al.[42] on 120 patients with colitis, the prescription of edible *Escherichia coli* (*E. coli* strain Nissle 1917) was done as a maintenance treatment. The results showed no significant difference in the relapse rates of patients who have consumed Escherichia coli or mesalazine so that the relapse rates were equal to 11.3% and 16.0%, respectively, in the mesalazine-treated group and the group of patients treated by Escherichia coli. In another trial by Rembacken et al. [43], 116 patients with colitis were examined in two groups by prescribing mesalazine and Escherichia coli. The relapse rate was significantly higher than the predicted of researchers in both groups. The relapse rates for the patients treated with mesalazine was approximately 73% and for the patients treated with Escherichia coli was equal to 67%. It can be concluded from these experiments that the use of probiotic microorganisms in the treatment of colitis can be as effective as the use of the chemical drug mesalazine. In a non-blinded designed trial by Ishikawa et al. [44], the effect of *Bifidobacterium* of fermented milk was evaluated in 21 patients who were on the recovery process with standard drugs (mesalazine and other drugs). Results of trials indicated that patients who had consumed Supplement containing bifidobacteria during the 12-month trial period had fewer relapses compared to others. Several published studies confirmed the effect of probiotics on UC in animals. In these cases, Interleukin-10 (IL-10) was extensively studied in mice. IL-10 destroys advanced murine colitis during usual colonization in flora [45]. In previous studies, it has been proved that genetically engineered bacteria for the local administration of a therapeutic agent such as IL-10 are effective in the treatment and prevention of UC in humans [46]. Oral consumption of lactose prebiotic results in increasing the levels of Lactobacillus species and rectal swabbing with *Lactobacillus reuteri* (*L. reuteri*) results in the return of *Lactobacillus* levels to normal status. Overall, these factors lead to the attenuation of UC [47]. The prebiotic inulin and a combination of probiotics such as *Lactobacillus acidophilus* La5, *Lactobacillus delbrueckii* subsp. *bulgaricus*, *Bifidobacterium* BB-12, and *Streptococcus thermophilus* significantly reduce the inflammation in the human leukocyte antigen (HLA-B27). This combined effect was increased by the addition of metronidazole, indicating a synergistic effect of the combination of probiotics and antibiotics in the treatment of colitis [48]. In a study by Fernandez et al. [49], it was found out that the probiotic strains *Lactobacillus salivarius* Ls-33 can be a protective agent against UC in trials on the mice due to possessing peptidoglycan and through NLR-peptidoglycan interactions. Several published studies have investigated the performance and effectiveness of *Lactobacillus casei* strain GG in the treatment of IBDs. In

this regard, Malin et al. [50] reported that in pediatric Crohn's Disease, the consumption of Lactobacillus casei GG is associated with increased levels of immunoglobulin A (IgA), which can enhance the intestinal defense barriers. The components isolated from the probiotic cell may also have therapeutic benefits. According to researches, bacterial DNA possesses reinforcing effects on the immune system, so that in an investigation, the bacterial DNA was employed to reduce colitis in mice [51]. After the treatment of UC, the patient may be at the risk of inflammation of the ileal pouch. In an open-labeled study, it was found that this condition, called pouchitis, can be treated with *Lactobacillus* GG and fructooligosaccharide. It should be noted that patients have reported beneficial effects of the probiotic-prebiotics, which were prescribed as antibiotic supplements [52].

4. CONCLUSION

Although probiotics have shown great potential in treating and controlling inflammatory diseases, besides the many benefits of probiotic microorganisms, there are potential challenges, and further studies are required to find suitable solutions to them. In general, these problems were not significant to overshadow the extensive impact of these microorganisms on inflammatory diseases, including IBD. With the increasing number of studies in this field, a brighter future can be envisioned for the treatment of inflammatory diseases with probiotics.

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