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PROBIOTICS IN ULCERATIVE COLITIS

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Abstract:
Probiotics are organisms which provide desired and beneficial effect on human health. With recent evidence implicating a disruption in the balance of the gastrointestinal microbiome and intestinal immunity as a potential trigger for inflammatory bowel disease (IBD), there has been growing interest in using probiotics as an adjunct to standard anti-inflammatory and immune suppressing therapy. The intestinal microbiota is one of the key players in the etiology of ulcerative colitis. Manipulation of this microflora with probiotics is an attractive strategy in the management of ulcerative colitis. Several intervention studies for both the induction and maintenance of remission in ulcerative colitis patients have been performed. Multiple probiotics and their formulations have been studied for both the induction and maintenance of remission of ulcerative colitis (UC); however, mainly Escherichia coli Nissle 1917 and VSL#3 have been shown to provide significant benefits for the prevention and treatment of mild to moderate UC. In general, probiotics show potential for therapeutic application in inflammatory bowel disease (IBD) and UC, with continued research and a movement towards carefully selected, individualized management based on an individual's specific microbiota composition and function.
Key words- *Probiotics, Inflammatory bowel disease (IBD), Ulcerative Colitis (UC).*

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INTRODUCTION:

Inflammatory bowel disease (IBD) is a general term for a group of chronic inflammatory disorders of unknown etiology involving the gastrointestinal tract. Chronic IBD is divided into two main groups, ulcerative colitis (UC), and Crohn's disease [1]. The prevalence of inflammatory bowel diseases, including ulcerative colitis, is generally higher, with an estimated of 250 cases per 100,000 individuals in western countries but is becoming common in rest of the world due to the adoption of western lifestyle [2]. Clinical and experimental studies suggest that the relative balance of aggressive and protective bacterial species is altered in ulcerative colitis (UC), Crohn's disease (CD), which are caused by overly aggressive immune responses of commensally enteric bacteria [3]. Ulcerative colitis is an inflammatory chronic disease primarily affecting the colonic mucosa; the extent of severity of colon involvement is variable. In its most limited from it may restricted to the distal rectum, while in its most extended form the entire colon is involved. However, 80% of the patients present with disease extending from the rectum to the splenic flexure, and only 20% have pan colitis [4]. Their cause is unknown, but genetic, immunologic, and environmental factors are involved [5]. The disease is the most prevalent gastrointestinal disease burdens in western societies and it has become more widespread; its rise in incidence has been reported in all age groups including early childhood [6]. Intestinal microflora play important role in development of IBD, there is currently some interest in altering the composition of the microflora towards a potentially more remedial community [7]. Probiotics are live and nonpathogenic organisms that confer health benefits beyond their nutritional value. In IBD, where changes in bacterial flora have been demonstrated, there is an increasing interest in modulating the flora with probiotic strains [8]. The microenvironment of the gut forms a good microbiota habitat, which has been demonstrated to affect many physiological conditions in earlier studies. Since intestinal microbiota is considered as an important organ of the human body in recent times, an increasing number of studies have linked this microenvironment to gastrointestinal diseases. Because the composition of the intestinal microbiota is stable over a period of time, many studies inferred the gut microbiota as potential predictor of health status and a target for therapeutic intervention. Moreover, it has been reported that intestinal microbiota has key role in inflammatory bowel diseases (IBD), including UC and Crohn's disease (CD) [9, 10]. The human gastrointestinal tract (GIT) houses the *gas-trointestinal microbiome*, a complex and dynamic microbial ecosystem, which is estimated to feature more than 400 different species of bacteria, [11] and which is responsible for important functions, including metabolic activities, trophic effects on the intestinal epithelium and interactions with the host immune system [12]. The intestinal microbiome is essential in the interaction between the intestinal epithelium and the mucosal immune system, and affects the development and homeostasis of normal mucosal immunity [13]. Probiotics (derived from Latin and Greek) means "for life" is defined in many ways. The recent accepted definition of probiotics is "live micro-organisms administered in adequate amounts which confer a beneficial physiological effect on the host." Joint FAO/WHO experts consultation report defines probiotics as: Live microorganisms which when administered in adequate amounts confer a health benefit on the host [14].

Ulcerative colitis

Ulcerative colitis is an idiopathic relapsing and remitting disease affecting the rectum and colon. Ulcerative colitis and Crohn's disease are two main type of inflammatory bowel disease. Despite some shared characteristic, these forms can be distinguished by differences in genetic predisposition, risk factors, and clinical, endoscopic, and histological features. The cause of inflammatory bowel disease is unknown. Genetically susceptible individuals seem to have a dysregulated mucosal immune response to commensally gut flora, which result in bowel inflammation [15].

Inflammation in ulcerative colitis is characterized by diarrhea, blood in stool, pain, weight loss, arthralgia, fever, loss of appetite, opthalmopathies, nausea, vomiting, abscesses, fistulae and lymph node swelling [16]. The disorder starts in the rectum and generally extends proximally in a continuous manner through the entire colon; however, some patient with proctitis or left-sided colitis might have a caecal path of inflammation. Disease distribution is stratified by the extent of the colonic involvement, from proctitis to left-sided colitis or extensive colitis [17].

Epidemiology

Ulcerative colitis is usually related with recurrent attacks with complete remission of symptoms in the interim. The disease is mostly observed in Caucasians than in Blacks or Orientals with an increased incidence (three to six fold) in Jewish. Both sexes are equally affected [16]. North America and Western Europe, although the incidence is increasing in Asia. The overall incidence is reported as 1.2 to 20.3 cases per 100,000 persons per year, with a prevalence of 7.6 to 245 cases per 100,000 per year [18, 19]. The exact

pathogenesis of UC is unknown, although there are a number of genetic and environmental factors that have been found to increase the risk of the disease [20].

History of probiotic

Recognition of the relationship between gut health and human disease may be traced back to Hippocrates (460–370BC) who stated: "All diseases begin in the gut." The Old Testament provided some of the earliest evidence suggesting that ingested bacteria play a key role in beneficial effect on health; it was stated that Abraham owed his longevity to the consumption of sour milk. Research in the modern era began with Theodor Escherich, who in1886 described the relationship of intestinal bacteria to the physiology of digestion in the infant. In 1892, Ludwig Doderlein proposed that microorganisms (*lactobacilli*) could be used to treat vaginal infections [21]. Eli Metchnikoff is considered the father of the probiotic concept. The Nobel Prize winner in Medicine in 1908, at the Pasteur Institute was the first who spotted the effect of what is called now Probiotic. He linked the health and longevity to the ingestion of bacteria present in yogurt [22, 23]. In 1907, he hypothesized that bacteria were involved in yogurt fermentation (*Lactobacillus bulgaricus* and *Streptococcus thermophilus*) suppression of putrefactive-type fermentations in intestinal flora and that consumption of these yogurts was important in maintaining health. He correlated the long life of Bulgarian peasants and their good health to yogurt intake which contained the Lactobacillus species and he simplified his conclusions to the public that, Probiotics could do an extra-job by digesting unusual components exactly like what happens in the ruminant animals which eat rough food composed of bulky vegetables [24]. In 1908, Henry Tissier, a pediatrician working at the Pasteur Institute in Paris report the finding of Y-shaped bacteria (which he named *Bifidus*) from the stool of a breast-fed infant. He observed that Bifidus was found in significant numbers in the stool of healthy infants, where as children with diarrhea had low concentrations of this organism. That organism could be used to treat infant diarrhea by displacing proteolytic bacteria from the gut. *Bifidus* was subsequently renamed *Bacillus acidophilus* because of its acid tolerance. In 1917, during World War I, Alfred Nissle pathogenic strain of *Escherichia coli* isolated from the stool of a soldier, in which few of soldier did not develop entero colitis during a severe outbreak of *Shigellosis*. This strain was named *E. coli* Nissle 1917 and was subsequently used to treat gastrointestinal salmonellosis and *shigellosis* [21]. Minoru Shirota recognized the therapeutic potential of using bacteria to modulate gastrointestinal micro flora. In1930, he succeeded in isolating and culturing a Lactobacillus strain capable of surviving the passage through the gastrointestinal tract. This bacterium was named which have been Shirota (later named *Lactobacillus casei* Shirota) [24]. Many of the publications define probiotics with reference to more or less same source. Most publications say that term probiotics is attributed to Lilly and Stillwell who had coined the term first in 1965. They defined probiotic as: a substance produced by one microorganism stimulating the growth of another microorganism. They understood a probiotic as opposite to an antibiotic. Parker (1974) gives a different overview: Organisms and substances which contribute to intestinal microbial balance. Most commonly, Kollath may be credited for the term 'probiotics'. In 1953, he coined probiotics as 'Probiotika', active substances that are essential for a healthy development of life [14]. Food and Agriculture Organization of the United Nations/ World Health Organization [25] endorsed by the International Scientific Association for Probiotics and Prebiotics [26], defined Probiotics as live microorganisms which, when administered in adequate amounts, provide a health benefit on the host'.

Probiotics

The word "probiotic" was derived from the Greek meaning "for life" or "in favor of life". Although it has had several different meanings or definitions over the years [27, 28, 29, 30], probiotics are now defined by a joint FAO/WHO working group as "live microorganisms which, when administered in adequate amounts, confer a good health benefit on the host" by improving its intestinal microbial balance [31, 32]. Theoretically, the word, probiotic, is only a generic term, and the commercial products may contain bacterial cultures, yeast cells, or both that stimulate the microorganisms capable of modifying the GIT environment to improve the health status and feed efficiency of the host [33]. Another scientific term, direct-fed microbials (DFM), are often used interchangeably with the term of probiotics, but in fact these 2 terms are not truly synonymous. Many probiotic products also contain enzymes and/or crude extracts in addition to live microorganisms. The Office of Regulatory Affairs of the US FDA and the Association of American Feed Control Officials (AAFCO) have defined DFM as feed "products that are purported to contain live (viable) microorganisms (bacteria and/or yeast)" [32] and the microorganisms should be those that are naturally occurring [34]. Probiotics may be ingested in the form of any food supplement or as drugs [35, 36, 37]. However, most commercial products are derived from food sources, especially cultured and fermented dairy products [38].

The term prebiotics was introduced by Gibson and Roberfroid in 1995 to describe food supplements that are non-digestible by the host but are able to exert beneficial effects by selective stimulation of growth or activity of microorganisms that are present in the intestine. Prebiotic substances are not hydrolysed nor absorbed in the gastrointestinal tract but are available as substrates for probiotics and the most commonly used ones at present are nondigestible fructo oligosaccharides. For practical reasons the combination of probiotics and prebiotics has been described as conbiotics by certain authors and as symbiotics by others [39, 40]. The probiotics are available in multiple formulations that may contain just one or a combination of several probiotics, whose quantity varies widely from one product to another. The micro-organisms that are most commonly used as probiotics belong to the group of lactic acid bacteria (*Lactobacillus*) and *Bifidobacterium*. These are important constituents of the normal human GI microbiota [41, 37]. Other probiotics that are less commonly used but are also being researched due to their possible probiotic functions are strains of *Streptococcus*, *Escherichia coli* (*E. coli*) and *Bacillus* [42, 38].Some non-pathogenic yeasts, such as *Saccha-romyces boulardii* (*S. boulardii*) (from *Litchi chinensis*, a tropical fruit originating in southern China that are not normally found in the GIT are also used [42, 43].

Sources of Probiotics

Many types of bacteria have probiotic properties, Yogurt is the most common source of probiotic. Yogurt consists of milk (usually from the cow, goat, or sheep) fermented by bacteria that modify lactose into lactic acid. Lactic acid is responsible for formation of yogurt its characteristics and also denatures and precipitates casein. Bioyoghurts are produced in a similar way, but bacteria used for fermentation are of different strains, usually *L. acidophilus* [14]. The most documented groups comprise of lactic acid bacteria (LAB) and bifidobacteria. While *L. casei* and *Lactobacillus acidophilus* survive in the acidic conditions of artificial gastric juice at pH 3.0 at 37°C, *Lactobacillus delbruekii* sp. *bulgaricus* does not. Strains of *Bifidobacterium* vary in their ability to survive transit through the stomach [44]. Fermented milk and fortified fruit juice are common sources of probiotics. Probiotics are also available in supplements consisting of freeze dried bacteria in tablets, capsules and powders. Selection of probiotic product depends on type of bacteria and type of beneficial effect expected. There are thousands of strains of probiotics and all of them show different beneficial effects (Fig 1) [14].

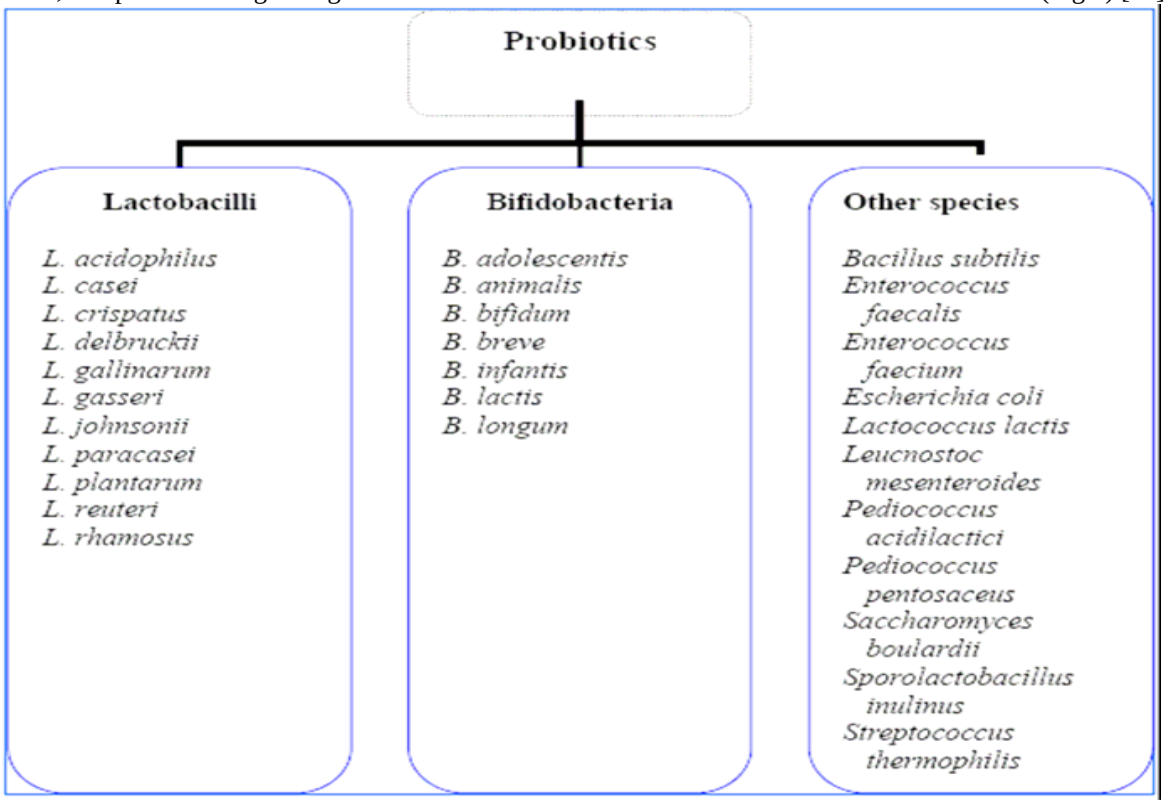

Fig. 1: Different types of bacteria which are recognized as probiotics [14].

Desirable Probiotic Properties

Probiotics have attained considerable interest and importance for a variety of medical conditions, and millions of people around the world consume probiotics daily for perceived health benefits. The initial screening and selection of probiotics also include testing of the phenotype and genotype stability, including plasmid stability; intestinal epithelial adhe-sion properties; protein and carbohydrate utilization patterns; production of antimicrobial substances; antibiotic resistance patterns; ability to inhibit known pathogens, spoilage organ-isms, or both; and immunogenicity [44]. In order for a potential probiotic strain to be able to exert its beneficial effects, it is expected to exhibit certain desirable properties.

(i) Acid and bile tolerance which seems to be crucial for oral administration,

(ii) Adhesion to mucosal and epithelial surfaces, an important property for successful immune modulation, competitive exclusion of pathogens, as well as prevention of pathogen adhesion and colonisation,

(iii) Antimicrobial activity against pathogenic bacteria,

(iv) Bile salt hydrolase activity [45, 46].

(v) Probiotic strain must be able to survive in the extremely harsh conditions of the digestive tract of the host, such as high acidity in the stomach and concentrated bile found in the small proximal of the intestine.

(vi) An effective probiotic should be capable of gastrointestinal tract transition.

(vii) Influencing metabolic activities like cholesterol assimilation, lactase activity and vitamin production, overcoming effects of peristalsis, and possessing the capacity for colonization.

(viii) In addition, it must also be safe, commercially feasible, and technologically compatible and must remain viable in storage while maintaining acceptable sensory attributes.

Mechanisms of Action of Probiotics

To understand the role that probiotics may have influencing health, it is important to have an appreciation of the roles of the normal intestinal microbiome (commensal microbiota). The human GI tract is host to over 500 bacterial species as well as a less well-described virome. These microbiota form a virtual bioreactor facilitating digestion, nutrient provision, and the shaping of our immune system [47]. Our intestinal bacteria weigh up to 1 kg and bacterial cells outnumber human cells by 10:1. The bacterial genome may outnumber the human genome by 100:1. Nutritional factors including several B vitamins, vitamin K, folate, and short-chain fatty acids are produced by these bacteria. Up to 10% of an individual's daily energy needs can be derived from the by-products of bacterial fermentation [48]. Beyond contributing to or modifying the metabolic and nutritional functions of the commensal microbiota, probiotic bacteria have several putative mechanisms by which they may confer specific beneficial effects. General categories include modulation of immune or sensory-motor function, enhancement of mucosal barrier function, and antipathogen effects. [49, 50]. Probiotics exert their beneficial effect via various and rather complicated mechanisms which seem to be unique for each strain. The activity of a given strain depends on a number of other factors, such as the presence of bacteria in the intestine and the kind of the disease in which the strain is being used [52]. The biological effects of probiotics can be categorised as follows (Fig. 2. and Table 1).

Antimicrobial effects:

The antimicrobial effects of probiotics are succeeded via [53]

• Production of inhibitory substances through modification of pH and production of bacteriocins, defensins, deconjugated bile acids, organic acids, and H2O2.

• Induction of heat shock proteins and endogenous antimicrobial peptides (mainly defensins) via activation of NF-κB, MAPK, and JNK. Since defensins are implicated in the pathogenesis of IBD, increased expression by probiotics provides a possible mechanism for clinical efficacy seen in certain IBD patients.

• Blocking of the sites of adhesion, because probiotics act as a competitive exclusion to bacterial adhesion sites thus impeding invasion by pathogenic bacteria [54, 55].

• Competition for essential nutrients by consuming nutrients that otherwise would be utilized by potentially harmful microorganisms and,

• Degradation of toxin receptor via inhibition of toxin expression in pathogens, such as in *Clostridium difficile*.

• Promotion of gut integrity this multi-function includes the following parameters:

• Enhancement of epithelial barrier function,

• Stabilization of tight junctions,

• Induction of mucin gene expression and up-regulation of mucus production [56],

• Enhancement of epithelial cell glycosylation,

• Stimulation of intestinal epithelial cell proliferation, intestinal mucin production, excretion of pancreatic enzymes and intestinal motility, and decrease epithelial cell apoptosis.

Table 1: Mechanisms of action of probiotics [68].

Antimicrobial effect	▪ Decreased colonization and invasion by pathogenic organisms ▪ Modification of pH ▪ Production of inhibitory substances ▪ Block of adhesion sites ▪ Competition for essential nutrients ▪ Degradation of toxin receptor
Restoration of gut integrity	▪ Restoration of intestinal permeability [64]. ▪ Up-regulation of T-betand enhancement of mucosal barrier function with up-regulation of tight junction molecules [65].
Modification of the host immune response	▪ Reduction of proinflammatory cytokine content on plasma and lymphocytes [55]. ▪ Decrease in the colonic concentration of IL-6, TNF-α and NF-kB p65, leukocyte recruitment, and decrease in colonic MPO activity [66]. ▪ Expansion of mucosal regulatory cells [67]

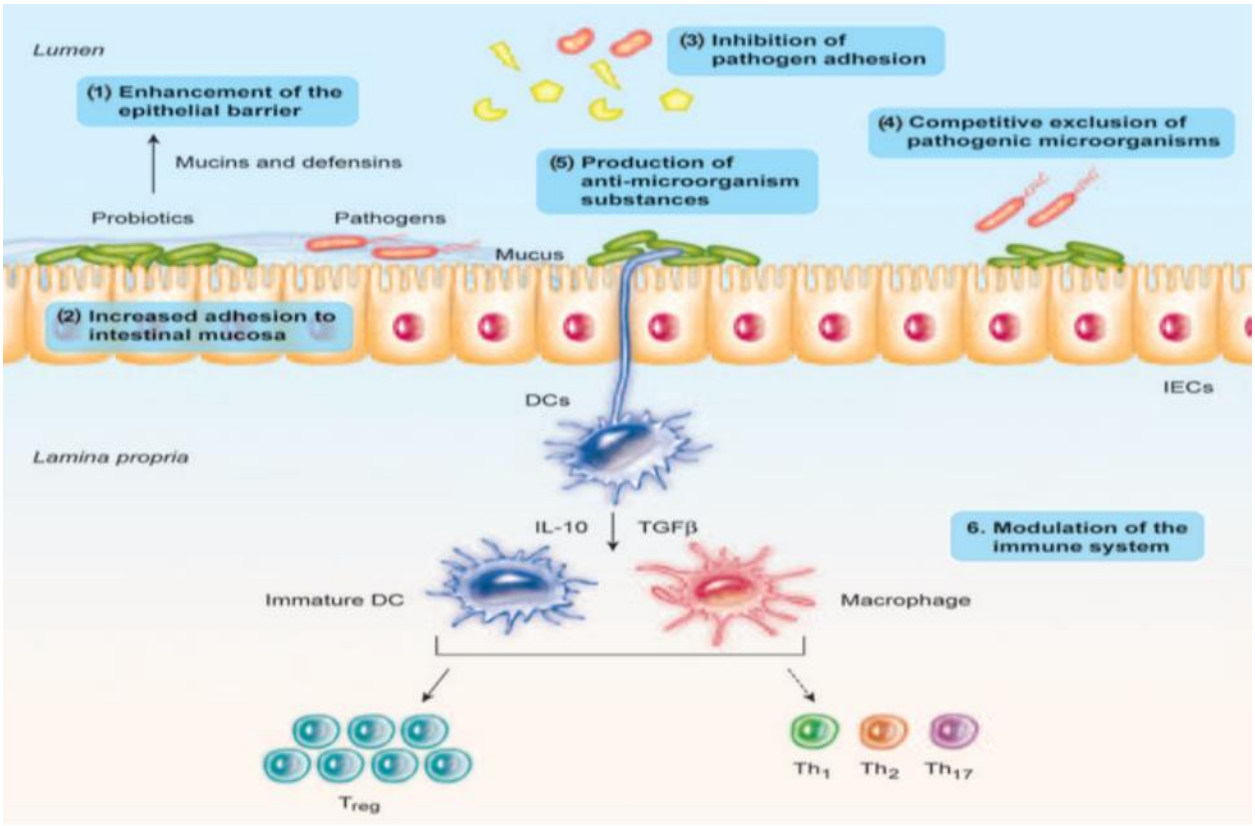

Fig. 2. Major mechanisms of action of probiotics [51].

Modulation of host immune responses:
The modulation of the host immune responses seems to be the most important action of probiotics. It has been shown that probiotics can actively interfere with regulatory and pro-inflammatory signalling pathways resulting in a reduction in Th-1 proinflammatory response and a greater T-regulatory anti-inflammatory response. Therefore, probiotics exert their immunomodulatory effects through enhancement of antibody production and natural killer cell activity,

modulation of dentritic cell phenotype and function, modulation of NF-κB and AP-1 pathways, modulation of apoptosis, induction of regulatory T-cells and PPAR-g, alteration of cytokines release, influence on the innate immune function including c-Jun NH2-terminal kinase, and inhibition of proteasome activity [57]. SCFA also participates in antiinflammatory mechanisms by modulating intracellular levels of calcium in neutrophils; inducing immune cells in inhibiting the expression of adhesion molecules, and chemokine production which in turn suppressed the recruitment of macrophages and neutrophils [58]. Again, SCFA (butyrate) acts as an inhibitor of histone deacetylases (HDI) and therefore can affect gene expression, arrest growth, induce antiinflammation and apoptosis [59]. Soluble products secreted or shed by probiotics also mediate important physiologic benefits; thus, viable bacteria are not necessarily required for all benefits [60, 61]. The mechanisms by which probiotics exert benefit varies by specific probiotic strain and likely depends on the clinical indication [62, 63]. Therefore, as with antibiotic prescribing, clinical use of probiotics should focus on matching the probiotic strain and dosage to the condition for which it has shown benefit in clinical trials. In the future, greater understanding of probiotic-specific mechanisms could allow for precise selection of a particular probiotic strain to target a patient's specific pathogenic defect and clinical problem.

GASTROINTESTINAL MICROBES AND IBD

The gut is a hollow tubular structure into which nutrient-rich food is pushed, processed, and absorbed, and then wastes are expelled as it occurs in even the most primitive hydra. This process occurs sequentially in the buccal cavity, esophagus, stomach, and intestines in humans. The large intestine offers a home for a large number of microbes called gut microbiota or/and commensal microflora. [69].The human gastrointestinal tract provides a suitable environment to a diverse microbial population, with more than 400 to 500 different species of bacteria currently identified. The gut microbiota refers to all microorganisms colonizing the gut, not only including bacteria but also other microbes such as fungi and viruses [70].The microbiota develops soon after birth, when the sterile gastrointestinal tract is colonized by successive waves of microorganisms. The individual gut microbiota is relatively stable over time and differs between subjects [71, 72]. The microbiota contains several critical functions that contribute to the overall health of the host. These functions include nutrient and mineral absorption, synthesis of vitamins and amino acids, production of short-chain fatty acids (SCFA), maintenance of structural integrity of the gut mucosal barrier, immunomodulation and protection against pathogens [70]. The exact etiology of IBD is not yet understood. The accepted hypothesis is that IBD is a dysregulated mucosal immune response to commensal gut microflora in a genetically susceptible individual. Many of the susceptibile genes are related to defective innate immunity and impaired primary defense systems against enteric bacteria. This further strengthens the continually evolving interaction between the gut microbiome and IBD. Several intestinal microorganisms ranging from bacterial, fungal, to viral species collectively make up the intestinal microbiota. Any change in the microbiota can lead to dysbiosis, which can precipitate pathologic changes such as chronic inflammation [73]. These distinct microbial populations have less stability and bacterial diversity of the microbiota. Specifically, there is less expansion of the Enterobacteriaceae, y-Proteobacteria such as Escherichia coli with parallel contraction of certain Clostridium subsets, such as Faealibacterium prausnitzii. Both of these species play important roles in maintaining the steady state of the gastrointestinal tract [74, 75]. The intestinal microbiota in IBD patients has a different composition compared to healthy individuals. In IBD microbial diversity is less, especially in regions of active inflammation, although total bacterial numbers are increased [72]. Several studies have magnified the importance of enteral microorganisms in the development and maintenance of IBD. Analysis of mucosal-associated and fecal bacteria reveals diminished commensal microbial diversity. In general, fewer *Firmicutes* and *Bacteroidetes* are found as well as a reduced diversity within these phyla [76]. A decrease in the phylum *Firmicutes* can mainly be attributed to a decreased bacterial load in different *Clostridium* classes, including for example the species *Faecalibacterium prausnitzii.* By contrast, within the phylum *Proteobacteria*, an increased number of *Enterobacteriaceae* is found. As such, *Escherichia coli*, one of the species within *Enterobacteriaceae*, comprise an increased proportion of the fecal and mucosa-associated microbiota in CD patients. In these patients, *Escherichia coli* is more frequently present within granulomas and adjacent to fistulae and ulcers [72, 77]. Conflicting results are reported regarding differences in microbial compositions between CD and UC patients. Some studies reported similar microbial changes, whereas others found disease specific alterations [77].

Probiotics in IBD

The incidence of IBD in a person may depend on the genetic aberrations, which stimulates the abnormal inflammatory response against intestinal microbiota.

The intestinal microbiome is also responsible for the continuation of the inflammatory response, and it is proven that the intestinal bacteria can penetrate the mucosa and strengthen the intestinal epithelial inflammation [78, 79]. Genetic factors as well as environmental triggers seem to play a substantial role, as the incidence of Crohn's disease is increasing, at least in the Western world. Among those environmental triggers, bacterial and viral organisms have been studied the most [80], but the dramatic changes regarding food production and consumption habits during the last century should be taken into account [81]. The most recent studies in IBD and experimental colitis indicate that normal resident luminal bacteria are a significant factor in the onset and chronicity of inflammation. Crohn's disease is known to occur in sites with the highest concentration of luminal bacteria, such as the colon and terminal ileum [82]. Giaffer *et al.* showed that the intestinal flora of patients with active Crohn's disease is considerably different from that of patients with quiescent disease, ulcerative colitis, or normal controls. In these individuals, the concentration of aerobic bacteria was elevated, especially *Escherichia coli*, and within the fraction of anaerobic bacteria bacteria, *Bacteroides fragilis* and *Bacteroides vulgatus* were increased. Additionally, in all patients with Crohn's disease, *Bifidobacteria* were decreased [82]. Although the search for clearly defined triggering factors in IBD continues, the protective qualities of probiotic bacteria may provide an innovative approach to treatment. Probiotics have been increasingly investigated in the induction and maintenance of remission for active and inactive IBD; however, there is a paucity of well-powered randomized-controlled trials. The available studies in the literature are variable in design, including the type and dosage of probiotic used, as well as the presence and choice of concomitant therapies, such as 5-ASA medications, and/or thiopurines. Specifically for UC, non–lactic acid bacteria probiotics, such as E. coli Nissle 1917 and the combination probiotic cocktail VSL#3 have been found to be the most beneficial, and have received "A" recommendations as per the American Recommendations [83, 84]. E. coli Nissle 1917 has been studied in both active and inactive UC. It has been shown to decrease myeloperoxidase activity and to decrease TNF-a, interferon (IFN)-g, and interleukin (IL)-10 levels. It reduces mucosal damage and colonic epithelial permeability, which thereby can improve healing of the colonic tissue. VSL#3 consists of 8 bacterial strains—*Lactobacillus acidophilus, Lactobacillus bulgaricus, Lactobacillus casei, Lactobacillus plantarum, Streptococcus thermophiles, Bifidobacterium breve, Bifidobacterium infantus, Bifidobacterium longum*. Like E. coli Nissle 1917, this probiotic mixture has been studied in both the induction and maintenance of remission for UC. It promotes the downregulation of IL-12 levels, attenuating the TH1 response, and lowers production of IFN-g. In addition, VSL#3 reduces apoptosis of colonic epithelial cells, downregulates T cell, B cell, and Toll cell receptor signaling, which decreases expression of TH1 transcription factors (TNF-a and its induced chemokines), and attenuates colonic expression of proinflammatory mediators such as IL-6, TNF-a, IFN-g, ultimately diminishing colonic neutrophil infiltration. It not only decreases the number of Enterococcus species, but also stimulates the amounts of Streptococci and Lactobacilli [83].

Probiotics in Ulcerative colitis.

In recent decades several intervention studies were performed in UC comparing probiotic therapy with placebo or standard care. Studies can be classified into the following two groups: those that investigated induction of remission in active UC, and those that investigated maintenance of remission. Several relatively small studies are available. However, these studies greatly differ in design, for example in regards to the presence and choice of concomitant therapies in the control groups. In the available studies, different probiotic strains were compared, in different dosages, with different primary outcomes. The variety within study designs limits the possibility to uniformly compare and pool the available data and prevented us from drawing firm conclusions with respect to probiotic use in UC.

Induction of remission in active ulcerative colitis

E coli Nissle 1917, a non-pathogenic strain of *Escherichia coli*, prevents and antagonizes colonization of pathogenic bacteria. It reduces colonic mucosal damage and decreases epithelial permeability, which may improve colonic healing [85]. Three studies investigated the beneficial effect of *E coli* Nissle 1917 in active UC [86, 87]. The first randomized controlled study compared *E coli* Nissle 1917 (10x1010 bacteria) with oral mesalamine (3x800 mg/d) in 116 patients receiving standard medical therapy and a 1-week course of gentamycine [87]. No statistical differences in remission rates and time to remission were found and the authors therefore concluded non-inferiority of *E coli* Nissle 1917 compared to mesalamine. A control group without mesalamine was not included in this study. Another dose-finding phase II trial (n=90) administered the same probiotic rectally and compared its effect with placebo [86]. A higher dose-dependent remission rate was found in the per protocol analysis for *E coli* Nissle

1917, although not confirmed in the intention to treat analysis. The latter could be explained by the high number of drop outs due to protocol violation or lack of efficacy. In contrast, the third study including 100 patients that compared *E coli* Nissle 1917 (5-50x109 colony-forming unit, CFU/d), Ciprofloxacin (2x500 mg/d) and placebo, showed the highest remission rates in the placebo group (p<0.05) [88]. Tursi et al [89] compared low-dose balsalazide 2.25 g/d plus VSL#3 900 billionCFU/d to concomitant 4.5 g/d balsalazide and mesalamine 2.4 g/d over 8 weeks in 90 patients with mild to moderate UC. Safety and efficacy were assessed clinically, endoscopically, and histologically. The combination therapy group was found to be statistically significantly superior to both the balsalazide and mesalamine groups (P<0.02). In addition, remission was achieved more quickly compared with the monotherapy patient populations, and in those with left-sided colitis versus subtotal or pancolitis. This study effectively demonstrated that lower 2.25 g/d doses of balsalazide in combination with a probiotic (VSL#3) had better results than the higher balzalazide dose required to maintain remission, and with better compliance rates. Although there were less adverse effects, these did not achieve statistical significance. The overall conclusion was that balsalazide plus VSL#3 was superior to mesalamine or balsalazide alone in mild to moderate left-sided or distal colitis. The same group also compared VSL#3 to placebo with concomitant 5-ASA/immuosuppressive therapies in 144 patients for 8 weeks. There was a statistically significant benefit in the VSL#3 group, with a decrease in the ulcerative colitis disease activity index (UCDAI) score of at least 50%, as well as a trend to a higher rate of remission achieved (P=0.069). There was a statistically significant decrease in rectal bleeding (P=0.010), but not in stool frequency or endoscopic scores. In addition, 5 patients in the placebo group worsened clinically. In this trial 3600 billionCFU/d, VSL#3 was used, to induce remission. It was therefore concluded that the used dose of VSL#3, in addition to standard therapy, could not only improve symptoms, but also delay the initiation of immunomodulatory agents. These findings were confirmed by Sood et al, [90] who compared VSL#3 twice daily to placebo over 6 weeks in 147 patients who were on concomitant mesalazine, azathioprine, or 6-mercaptopurine, with a primary endpoint of decrease in the UCDAI by 50% and who showed a significant benefit, (P<0.001). Remission rates at 12 weeks were 43% in the probiotics and 16% in the placebo group (P<0.001). The combination therapy group also had improved symptoms, demonstrating that VSL#3 enhances the anti-inflammatory properties of mesalamine. Bibiloni et al [91] used VSL#3 in a small open study with 34 patients with mild to moderate active UC over 6 weeks. With high-dose probiotics, 900 billion bacteria (4 sachets) twice daily, remission was achieved in 53% of patients, whereas 9% had no response and another 9% worsened (P<0.001). There were no biochemical or clinical adverse events noted (8 no adverse events were noted, aside from bloating). Miele et al [92] studied VSL#3 in the pediatrics population. A 1-year prospective, placebo-controlled, doubleblind trial was performed with 29 children, ranging from 1.7- to 16.1-year-old children (mean, 9.8 y) with newly diagnosed UC. They were given weight-based VSL#3 or placebo with concomitant therapy including glucocorticoids and mesalamine therapy. Endoscopic and histologic assessment occurred at baseline, 6, and 12 months, or at the time of relapse. All 29 participants responded to induction therapy, with 92.8% in the VSL#3 group and 36.4% in the placebo group achieving remission. This was statistically significant, P<0.001. In addition, only 21.4% of patients in the VSL#3 group relapsed at 1 year versus 73.3% in the placebo group (P=0.014). In addition, the VSL#3 group showed lower endoscopic and histologic scores at each timepoint compared with the control group. No adverse effects were noted in the VSL#3 group [83, 92]. This was one of the first randomized, placebo-controlled trials demonstrating the efficacy of probiotics in the management of induction and maintenance of UC in children. Multiple other probiotic formulations have been studied in the induction of UC, albeit mostly in uncontrolled and/or smaller studies. Tsuda et al conducted a small, open-label study using BIO-THREE, tablet formulation (9 tablets daily for a period of 4 weeks) in 20 patients with mild to moderate distal UC. This probiotic combination of *Streptococcus faecalis* T-110, *Clostridium butyricum* TO-A, and *Bacillus mesentericus* TO-A led to remission of disease in 45% of patients, response in 10%, no response in 40%, and worsening in only 5%. Fecal samples revealed an increase in bifidobacteria, although no bifidobacteria were administered within the probiotic supplement [93]. This improvement in intestinal microflora probably represents a consequence of the treatment altering the microbial environment perhaps by removal of competing pathogens. Ishikawa et al [94] compared bifidobacteria—fermented milk 100 mL/d as an adjunct to standard medical therapy versus a control group. Twenty-one patients were assessed over 1 year with routine blood work, colonoscopy, and examination of the fecal flora, including fecal organic acids. In the bifidobacteria—fermented milk group, 3/11 patients had an exacerbation of disease activity compared with 9/10 in the control group. This difference was statistically significant (P=0.0184)

[94]. The same authors also examined the symbiotic effects of a live B. breve strain Yakult and galacto-oligosaccharide in active UC. In this trial, 41 patients were assigned to either the synbiotic group with probiotic powder 1 g three times daily plus galacto-oligosaccharide 5.5 g once daily versus the control group. Colonoscopy at 1 year found that the synbiotic group had a significant improvement and reduced markers of inflammation [83, 94, 95]. Furrie et al [96] studied a synbiotic mixture of a probiotic *B. longum*, plus prebiotic, Synergy1, an inulinoligofructose prebiotic mixture. This was the first randomized-controlled trial using synbiotics in which 18 patients were included in this small 1-month double-blind, randomized control trial, which occurred over a 1-month span. Patients were maintained on their current therapeutic regimens, and randomized to either the synbiotic or placebo arm. Flexible sigmoidoscopy showed no significant difference, but there was decreased microscopic inflammation and increased regeneration of epithelial tissue, as well as significantly reduced mRNA levels of b-defensins 2, 3, 4, TNF-a, IL-1. Although this small sample size study demonstrated histologic improvement, the time to assess endoscopic mucosal healing within 4 weeks was likely too short. In addition, this study was not able to characterize the effect of concomitant therapies, and was hampered by the small number of patients in the placebo group who completed the trial. Larger, more controlled trials are needed to determine if there is a role for synbiotics. Guslandi et al [97] investigated the efficacy of the non-pathogenic yeast *Saccharomyces boulardii* in 25 patients with active UC patients of mild to moderate severity, and unsuitable for steroid therapy, in an open-label trial. Patients received additional treatment with *S. boulardii* 250 mg three times daily for 4 weeks during maintenance treatment with mesalazine. A significant reduction in UC disease severity index scores was observed, and 71% achieved endoscopical remission.

Maintenance of remission in ulcerative colitis

E. coli Nissle 1917 has been compared with both standard medical therapy and placebo for the maintenance of UC. Kruis et al [98] conducted a double-blind double-dummy study in which 120 patients in remission were randomized to mesalazine 500mg three times daily or to E. coli Nissle 1917 for 12 weeks. Endpoints of the trial included the clinical activity index, relapse rates, relapse-free times, and physician global assessment. The start and end clinical activity index scores showed no statistically significant benefit between the 2 groups. In addition, relapse rates and relapse-free time were similar. The same group then performed a larger trial over 12 months, assessing both clinical and endoscopic parameters. Subgroup analysis showed no differences. Both groups had a good safety profile and were well tolerated. It corroborated that E. coli Nissle 1917 is comparable with mesalamine, providing an alternative therapeutic option for the maintenance of UC. It is also more cost-effective and has less adverse effects versus standard medications [83, 99]. However, the chosen maintenance dose of 1.5 g daily mesalamine is lower than the recommended oral 5-ASA maintenance dose for UC in clinical practice. VSL#3 was investigated in a small RCT in a pediatric population including 29 children with newly diagnosed UC [100]. Fourteen received weight-based VSL#3 and after 1 year 3 patients (27.0%) relapsed (> 3 points increase in Lichtiger CAI). This relapse rate was significantly lower compared to the placebo group (11/15, 73.3%; p=0.014). Furthermore, a small uncontrolled open label study with VSL#3 was performed including 20 patients with inactive UC who were intolerant for 5-ASA [101]. Four patients relapsed, however the small uncontrolled setting did not allow meaningful conclusions from this trial. Alternative probiotic preparations for maintenance of remission have been trialed. This includes a study by Zocco et al, open-label trial of *LactoBacillus GG* as maintenance treatment in 187 UC patients with quiescent disease [102]. Patients were randomized to receive *L. GG*, mesalazine or *L. GG* plus mesalazine. Overall analysis showed no difference in relapse rate at 6 and 12 months among the three treatment groups. However, the treatment with *L. GG* appeared to be more effective than standard treatment with mesalazine in prolonging the relapse-free time. Cui et al [103] gave 30 patients sulfasalazine and glucocorticoids with BIFICO (bifid triple-viable capsule 1.26 g/d) for 8 weeks versus placebo. After 2 months of therapy, clinical, endoscopic, and histologic assessment it was found that only 3 patients (20%) in the BIFICO group relapsed compared with 14 (93.3%) in the placebo group, and this was a significant difference (P<0.01). There was also an increased amount of fecal Lactobacilli and Bifidobacteria in the BIFICO group. In addition, there was decreased NFkB DNA-binding activity and increased mRNA expression of anti-inflammatory cytokines (P<0.05)8 in the probiotics group. The authors [103] therefore concluded that this probiotic therapy was an effective adjunctive method for prevention of disease flares. Shanahan et al [104] conducted a prospective, randomized-controlled, double-blind placebocontrolled study with 157 patients and found no significant difference in maintenance of remission between Lactobacillus salivarius and Bifidobacterius infantis, when compared with placebo [83, 104]. However, this study

has been published only in abstract form so far. Wildt et al, A recently published study [105] investigated the effect of treatment with *LactoBacillus acidophilus, La-5,* and *Bifidobacterium animalis subsp. lactis BB-12* (Probio-Tec AB-25) to maintain remission in patients with UC. Thirty-two patients with left-sided UC were entered in a double-blind placebo-controlled study to Probio-Tec AB-25 (20 patients) or placebo (12 patients) for 52 weeks. The results revealed no significant differences, as 5 patients (25%) in the Probio-Tec AB-25 group and 1 patient (8%) in the placebo group maintained remission after 1 year of treatment. In this trial no significant clinical benefit of Probio-Tec AB-25 could be demonstrated in comparison with placebo for maintaining remission in patients with UC.

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