



A Review on Usage of Probiotic in Treatment of Different Diseases

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Abstract

Probiotic bacteria offer many health advantages in addition to basic nutritional value. They collaborate to keep the delicate balance. Balance between the immune system and the digestive system. When this equilibrium is upset, illness and inflammation occur. By remaining to the mucosa, healthy beneficial microflora competed with harmful bacteria to limit inflammation and excessive immune system stimulation. The growth of pathogenic bacteria is prevented, disease processes are changed, and broad inflammatory disorders are prevented in a healthy gastrointestinal tract with sufficient mucus production and optimal bacterial colonization. Prevents the overgrowth of pathogenic bacteria, modulates disease processes, and prevents widespread inflammatory disorders. The understanding of the function of probiotics in the maintenance of health and their importance in preventing disease serves to enhance the overall health of patients. With increasing understanding that beneficial microbes are required for health maintenance and disease prevention, probiotics may be commonly used as a therapeutic tool by health care practitioners in the not-too-distant future. This article presents a review of probiotics in health maintenance and disease prevention.

Keywords: Probiotic, Gut, Colon, Fuction, etc

Introduction

Microbiologists discovered in the late nineteenth century that the microbes that lived in the gastrointestinal tracts of healthy people differed from that found in patients. Probiotics are the beneficial bacteria found in the gastrointestinal tract. Probiotic a word derived from Latin and Greek meaning literally "for life" has been defined in many ways since it was first coined 50 years ago ^[1]. The most recent understanding is that "defined, live microorganisms administered in adequate amounts that confer an appealing physiological effect on the host" are the best

option ^[2]. Probiotics are frequently microorganisms found in the normal human gut flora, such as lactobacilli and bifidobacteria, which develop lactate and short-chain fatty acids like acetate and butyrate as products of metabolism. Certain strains of Probiotics while it may initially seem unusual to think that consuming a great deal of live bacteria might improve health and help prevent and treat disease, the value of probiotics is quickly becoming clear. (For example, *Lactobacillus rhamnosus* GG, *L plantarum* 299v, *L casei*Shirota and *L*

johnsonii La1) have well defined and proven clinical effects for the treatment and/or prevention of diseases of intestinal and extraintestinal origin. These effects have been extensively reviewed recently [3,4].

Lactic acid producing bacteria (LAB) have been used, unwittingly, for centuries to preserve food (for example, sauerkraut), and most countries developed their own characteristic type of fermented milk [5]. The first deliberate use of LAB for health reasons was by Metchnikoff early in the 20th century as a possible antidote to the aging process, proposed by him to be at least partly due to toxins produced by putrefactive intestinal bacteria (that is, not LAB). After some initial enthusiasm, interest waned [6] and Probiotics did not gain popular until the last decade of the 20th century, after the public started accepting the idea of functional foods (defined as "foods that provide physiological benefits or decrease the risk of chronic diseases, over and above their basic nutritional value"). Finding that germ-free animals exceed their conventional counterparts in the 1950s supported Metchnikoff's ideas that gut flora contribute in a certain way to aging [7]. Probiotics have

become widely available, extensively obtained, and identified to everyone as part of bio yoghurts and dietary supplements. Probiotic yoghurts and milks were bought by Europeans cost almost \$900 million in 1997, and this industry is growing rapidly [8]. Probiotics are a more recent concept; they were only made public a little more than ten years ago [9]. They are chemicals that act as growth-promoting substrates for the host's intrinsic Probiotic bacteria, which are typically oligosaccharides. Prebiotics are chosen because non-probiotic gut flora like *Escherichia coli* and *Bacteroides* spp. cannot digest them and do not break them down. Prebiotics can be found naturally in breast milk and some plants (such Jerusalem artichokes and onions) as well as synthetically as fructo- or galactose-based oligosaccharides, or FOS and GOS [10]. It can also be combined with a probiotic to create a synbiotic and added to food. This review's objective is to describe how consuming probiotics and maybe prebiotics may benefit elderly persons in connection to Constipation, under nutrition, and a deteriorating immune system are three problems that are frequently present.

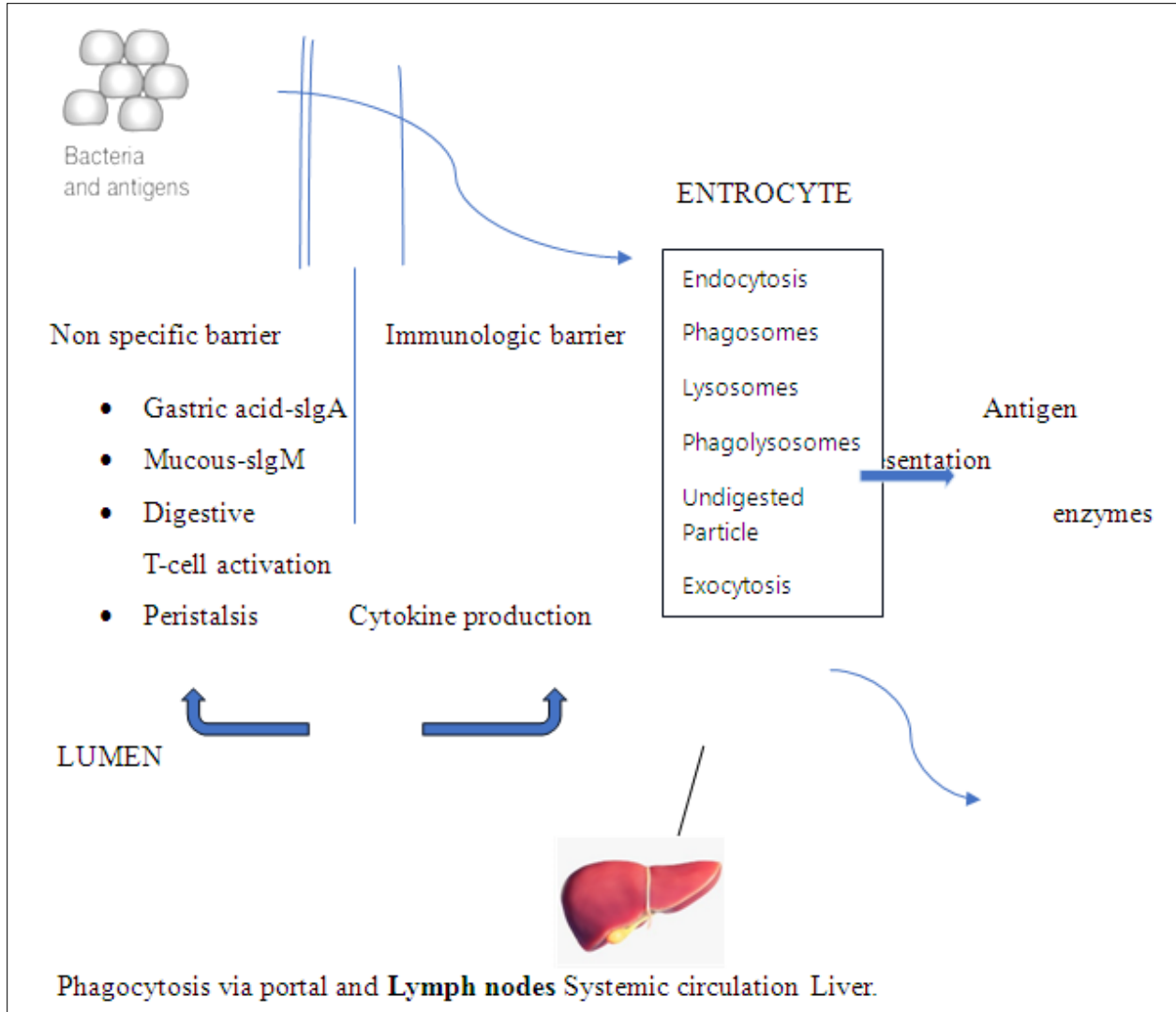


Figure No. 1: Barriers to Antigenic Absorption in the Intestine

Colonization

The gastrointestinal (GI) tract of humans has a variety of protective and immunological barriers. The epithelial layer, the mucous layer, and the peristalsis and desquamation mechanics, and activities of secretory IgA that all have an effect on bacterial connection is seen in Figure.1^[11]. Following connection, Colony-forming bacteria cannot combine with the epithelium layer's eukaryotic cells of the host, It serves as a

crucial defense against invasion^[12] The barrier's sound composition and effective operation are necessary for the host human's wellness. In this intricate system, the careful balance between the microbiota of the digestive tract and the operationally kept up.

The gastrointestinal tract is sterile until a baby is delivered and develops vaginal and fecal bacteria.^[13] Feeding helps to improve the microflora population in the newborn GI tract. The breast-fed infant has a 90%

Bifidobacterium colonial population, with a small amount of Enterobacteriaceae and Enterococci, but hardly any Bacteroides, Staphylococci, Lactobacilli, or Clostridia. In contrast, the infant that is bottle-fed does not have Bifidobacterium predominance. Bifidobacteria, Clostridia, Lactobacilli, Bacteroides, Streptococci, and enterics infect breast-fed infants who are then shifted to cow's milk or solid meals [14].

Along the length of the gastrointestinal tract, the diversity and abundance of native microflora increase [11, 15]. Due to enhanced intestinal motility and saliva production, which efficiently transport bacteria down the intestine and stop significant numbers from clinging to mucosal surfaces, the upper GI tract has substantially less bacteria than the lower GI tract. Additionally, stomach growth is inhibited by gastric acid. Less than 10⁵ colony forming units (cfu) per milliliter (mL) is the norm for the upper intestine's relatively scant flora. up to the mid-ileum, where the Increase in population to 10⁷ cfu/mL of contents indicating a shift toward the flora that heavily populates the colon [11, 12].

Lactobacillus plantarum, L. rhamnosus, L. reuteri, and L. agilis all display advantageous traits in probiotics colonizing the human gut. [13] However, persons who live in industrialized countries are rare carriers of these Lactobacilli species. In contrast to Africa and Asia, where virtually all of the population is colonized with beneficial Lactobacilli species, just 25% of the general population in the United States carries L. plantarum. The most important factor is that Lactobacilli are dramatically underrepresented in the Western diet

The following requirements must be satisfied in order for something to be considered a beneficial microflora:

1. It must be resistant to acid and bile;
2. It must be metabolically active in the GI tract;
3. It must be able to adhere to the GI tract;
4. It must have antimicrobial activity toward pathogenic bacteria; and
5. It must lower colon pH [11, 16, 17]. In this environment, there are several species of Lactobacilli and Bifidobacterium that have complicated enzymes and roles that could either improve or impair the host's health [18]. There is a chance for subsequent dysfunction and disease when there are changes to the gastrointestinal barrier or the microbiota of the gut. For instance, a high level of a single bacteria species may disturb the gut's environment and cause a loss of beneficial characteristics.

Digestive, gastrointestinal, and/or immunological function may be damaged by an overgrowth of one bacterial species as well as microflora imbalances put on by an interrupted mucosal layer [19]. Additionally, a damaged epithelium layer can make it easy for microorganisms to infect the human host. This breach has the potential to cause an inflammatory reaction in the host, which could further affect normal function.

Function of the Gut

The ability of the gut to function normally is influenced by the microflora that it is colonized with. Short-chain fatty acids (SCFAs), polyamines, vitamins, antioxidants, and amino acids are examples of commensal microflora byproducts that support digestive tract health [20, 16, 18]. For instance, the primary source of energy for colonocytes in the large

intestine is the SCFA butyric acid, which is produced during carbohydrate fermentation. Additionally, the pathogenesis of Enterobacteriaceae, *S. aureus*, and Enterococci present in fermented foods can be prevented by *Lactobacillus* species, which can also maintain antioxidants and vitamins, eliminate harmful food components, and prevent food degradation.

Probiotics influence the immune system in addition to the GI tract's indigenous flora [21-24]. Both cellular and humoral immunity are improved by lactobacilli [25]. The immune system is stimulated by lactic acid-producing bacteria in a variety of ways, including macrophages' phagocytic activity.

After receiving a rotavirus vaccine, *Lactobacillus* GG increases IgA seroconversion and induces IgM-secreting cells, which improves the immune system's response to vaccinations [23]. Administration of

Lactobacillus GG also improves IgA response to rotavirus [13]. These studies corroborate probiotics' beneficial effects on innate and acquired immune augmentation, which are most likely due to their capacity to attach to the gut epithelium. After binding, the complement system, reticuloendothelial system, and antibody synthesis are all stimulated. Bacterial-epithelial cross-talk refers to the interaction between probiotics and epithelial cells [23]. In a different trial, adults receiving the typhoid vaccine had their antibody response improved by *Lactobacillus* GG [25].

Saccharomyces boulardii's activation of the reticuloendothelial system and complement cascade is another instance of a probiotic increasing the immune response [17]. It is obvious that the connection between commensal gut flora and the gut-associated immune system is crucial to maintaining healthy immunological function.

Table No.1a: Activity of Specific Probiotics

Microflora	Associated Action	Reference
Bacteroides species	Chronic gastritis, arthritis, and chronic juvenile arthritis have enhanced bacterial urease activity.	25
Bifidobacterium animalis	Reduces the spread of <i>Candida albicans</i> throughout the body in euthymic or athymic beige mice.	11
Bifidobacteria species	Neonatal necrotizing enterocolitis is less common.	51
<i>Enterococcus faecium</i> SF 68 or <i>Escherichia faecium</i> SF 68	a. Reduced duration of gastroenteritis-related acute diarrhea. b. Not helpful for diarrhea related to <i>Vibrio cholerae</i> and <i>Escherichia coli</i> .	a. 35, 52. b. 11, 53.
<i>Escherichia coli</i> nonpathogenic strain(serotype	As successful as mesalamine at keeping ulcerative colitis in remission	54

O6:D5:H1)		
Lactobacillus strains	<p>a. Number of organisms, primarily Lactobacillus strains, has been shown to be effective in treating pouchitis</p> <p>b. Lactose digestion has improved, reducing diarrhea and intolerance symptoms in people who are lactose intolerant, children who have diarrhea, and people with short bowel syndrome.</p>	<p>a. 25,40</p> <p>b.35</p>
actobacillus strains	<p>Intolerance symptoms in people who are lactose intolerant, children who have diarrhea, and people with short bowel syndrome.</p> <p>c. Microbial interference therapy, which employs non-pathogenic microorganisms as an adjuvant to antibiotics and as a means of eradicating pathogens</p> <p>d. Enhanced mucosal immune response, mucin secretion, and disease prevention</p>	<p>c.16</p> <p>d.34,40,55</p>
Lactobacillus acidophilus	<p>a. Significant reduced of diarrhea in patients of pelvic irradiation</p> <p>b. Reduced Candida albicans systemic dissemination in euthymic or athymic beige mice</p> <p>c. reduced polyps, adenomas, and colon cancer in experimental animals.</p> <p>d. Avoided urogenital infection and subsequent exposure to E. coli, K. pneumoniae, and P. aeruginosa, three uropathogens</p> <p>e. Reduced serum cholesterol levels.</p>	<p>a.35</p> <p>b.32</p> <p>c.44</p> <p>d.56</p> <p>e.18</p>
Lactobacillus GG	<p>a. decreased period of time or risk of rotavirus diarrhoea</p> <p>b. reduced polyps, adenomas, and colon cancer in experimental animals</p> <p>c. decreased period time in acute diarrhea most of many times caused by gastroenteritis</p> <p>d. it decreases diarrheal disease in formula-fed toddlers</p> <p>e. decreased occur of Clostridium difficile diarrhea</p> <p>f. Children who get antibiotics concurrently experience less diarrhea not caused by Clostridium difficile.</p> <p>g. decreased risk of traveler's diarrhea</p> <p>h. Decreased severity of pneumonia in children with cystic fibrosis.</p> <p>i. Reduceses Candida albicans systemic dissemination in euthymic or athymic beige mice</p> <p>j. increaces IgA-specific antibody secreting cells to rotavirus and decrease the period of time of diarrhea</p> <p>k. Increased IgA secretion in Crohn's disease</p>	<p>a.25,35</p> <p>b.44</p> <p>c.35</p> <p>d.25</p> <p>e.25</p> <p>f.25</p> <p>g.35</p> <p>h.25</p> <p>i.11</p> <p>j.11</p> <p>k.11</p>

	<p>l. prevented chronic, recurring vaginitis .</p> <p>m. Vaginal suppositories containing lactobacillus are beneficial at reducing the frequency of current UTIs.</p> <p>n. decrease food allergies and atopic dermatitis.</p> <p>O .Children with atopic dermatitis produces more interleukin-10.</p>	<p>l.13</p> <p>m.13</p> <p>n.14</p> <p>o.29</p>
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Table No.1b: Activity of Specific Probiotics (continued)

Microflora	Associated Action	Reference
Lactobacillusfermentum strain KLD	No effect -Traveler’sdiarrhea	35
Lactobacillus plantarum	the development and storage of vital vitamins, minerals, and antioxidants; the elimination of harmful ingredients from food; the preservation of food against degradation; and the elimination of infections such Enterobacteriaceae, S. aureus, and Enterococci.	16
Lactobacillus plantarum (299v and DSM 9843)	<p>a. reduced incidence of diarrhea in daycare facilities when medication is only given to half the kids .</p> <p>b. particularly efficient at reducing inflammation in inflammatory bowel diseases, such as pouchitis, small bowel bacterial overgrowth in children, and enterocolitis in rats.</p> <p>c. Irritable bowel syndrome pain and constipation are lessened.</p> <p>d. Reduced discomfort, bloating, and flatulence in a controlled trial for irritable bowel syndrome</p> <p>e. positive impact on children with HIV/AIDS' immunity</p>	<p>a.25</p> <p>b.25,40</p> <p>c.13</p> <p>d.57</p> <p>e.</p>
Lactobacillus reuterIrritable bowel syndrome pain and	<p>a. shortened the acute gastroenteritis period</p> <p>b. Reduced systemic Candida albicans spread in euthymic or athymic beige mice.</p>	<p>a.35</p> <p>b.11</p> <p>c.11</p>

constipation are lessened	c. Protected rats from developing colitis brought on by acetic acid and methotrexate, respectively. d. less acute diarrhea	d.65
Lactobacillus rhamnosus (HN001)	enhanced cellular immunity in a controlled experiment in healthy adults	58
Lactobacillus salivarius	lactic acid secretion suppressed and eliminated Helicobacter pylori in tissue cultures and animal models	60
Saccharomycesboulardii (yeast)	a. decreased recurrence of diarrhea caused by Clostridium difficile. b. Antibiotic-associated diarrhea risk and/or duration lowered as a result of effects on C. difficile and Klebsiellaoxytoca. c. shortened the acute gastroenteritis's duration. d.decreased only functional diarrhea, but had no effect on IBS's other symptoms. e. Reduced length of diarrhea brought on by tube feedings f. Ineffective for treating bacterial overgrowth in the small intestine. g.may lessen persistent diarrhea brought caused by HIV h. infant diarrhea i. extends the period when Crohn's disease is in remission . j. In pretreated mice, elevated IgA anti-toxin A responses.	a.63,64 b.35 c.35 d.35 e.35 f.35 g.35 h.61 i.62 j.59
Saccharomyces cerevisiae (ayeast containing sucrase)	Infants with a deficit in sucrase showed improved sucrose load digestion.	35

Probiotics in Specific Disorders



Figure No. 2: Probiotics in Specific Disorders

Allergies / Eczema

Probiotic bacteria play a critical role in reducing inflammation linked to hypersensitive reactions in atopic eczema and food allergy patients [22, 27]. When given during pregnancy, *Lactobacillus rhamnosus* GG reduced the occurrence of eczema in infants at risk by 50% [27]. The first bacteria to colonize the sterile GI tract in newborn children may create a permanent niche and have long-lasting effects on immune control and the future emergence of atopic illnesses. After a one-month experiment with *Lactobacillus* GG-fortified hydrolyzed whey formula, significant improvements in dermatitis were seen in infants with pre-existing eczema. Probiotics, according to the scientists, may improve the gut's endogenous barrier mechanisms and reduce intestinal

inflammation, making them an effective tool for treating food allergies [22].

In both animal and human trials, related investigations have validated the beneficial impact probiotics have on the immune system [28, 29]. Probiotics reduced an inflammatory reaction brought on by milk in people who were only minimally hypersensitive [28]. This was discovered to be secondary to the inhibition of elevated receptor expression in neutrophils and monocytes. It's interesting to note that participants in the same study who were not milk sensitive did not experience receptor down-regulation when taking probiotics.

Additionally, probiotics have been shown to increase the levels of anti-inflammatory cytokines in atopic children, including interleukin 10.30 this is perceived as having

immunostimulatory effects in healthy participants and immunoinflammatory response down-regulation effects in hypersensitive sufferers.

Similar to this, probiotics have been shown to support mucosal degradation of antigens in animal models by promoting the breakdown of macromolecules [30].

- **HIV/Compromised Immunity;**

A study looking at the supplementation of *Lactobacillus plantarum* 299v in infants congenitally exposed to HIV provides additional proof of the beneficial effects of probiotics on the immune system [31]. Children with HIV infections typically have spells of diarrhea and malnutrition that may be caused by bacterial overgrowth. 17 HIV-positive kids were randomly assigned to either *Lactobacillus plantarum* 299v or a placebo. Within two weeks, *Lactobacillus plantarum* 299v colonization took place in the therapy group; however it did not survive once treatment stopped. Negative incidents were not reported. In subsequent visits, changes in height and weight were observed. The transformation in one patient from total anergy to a normal immune response was noticed by the authors as evidence of a notable enhancement in immune response. These facts point to *L. Plantarum* 299v can be safely administered to impaired hosts, may in fact enhance immunological response, and may enhance growth and development.

Additional evidence of boosted immunity and greater infection resistance has been shown in both animals and people. *Lactobacillus* sp. and *Bifidobacteria* reduced diffused systemic *Candida albicans* in the immunodeficient

euthymic mouse model [32]. Additionally, when *Lactobacillus* GG was given to kids with cystic fibrosis, the severity of their pneumonia was found to be less severe in a placebo-controlled trial. It's likely that increased mucin cell activity and an improved immune response are related to protection from respiratory diseases. It seems promising to utilize probiotics more frequently in people who have impaired immune systems.

Hepatic Disease

There has been a puzzling case report published that demonstrates the impact of a high potency, multicultured probiotic supplement in liver cirrhosis [33]. *Streptococcus faecum*, bacterial B *Lactobacillus acidophilus*, *Lactobacillus plantarum*, *Lactobacillus casei*, and *Lactobacillus debrueckii*bulgaricus are among the 1011 bacteria per gram present in the probiotic formulation known as VSL #3. Oral bacteriotherapy, according to the scientists, may improve microbial balance, lower portal pressure, and reduce bleeding risk. A 76-year-old male patient with cirrhosis and esophageal varices received the probiotic preparation for one month, followed by a one-month washout period and a second one-month cycle of treatment. The blood flow and velocity in the superior mesenteric, splenic, and portal veins were observed at baseline and during therapy. After one month of therapy, the mean blood velocity and flow in the portal vein significantly increased; however, after the conclusion of the washout period, both parameters recovered to their pre-treatment levels. Blood flow and velocity in the portal vein were once more significantly higher than they were at baseline following a second

cycle of treatment. Urea-splitting bacteria are overpopulated in the microflora of patients with liver cirrhosis. To reduce the generation of mediators implicated in the pathophysiology of hepatic encephalopathy, portal hypertension, and variceal hemorrhage, oral antibiotics are frequently given as a result. Probiotics should be given instead of antibiotics, the author's advice, and they show that doing so might be a secure way to control portal pressure. They come to the conclusion that not all bacteria should be considered as pathogenic in liver cirrhosis and portal hypertension [33].

Diarrhea

Probiotics have a number of well-known applications, including treating diarrheal illnesses. There is a major potential benefit in controlling antibiotic-associated diarrhoea as well as the prevention and management of acute viral and bacterial diarrhoea. It has been demonstrated that a number of particular strains, including *Lactobacillus* GG, *L. reuteri*, *Saccharomyces boulardii*, *Bifidobacterium* species, and others, have a considerable beneficial effect on diarrhoea [11,34,25,35,36,37]. With regard to children, although there are many different strains of probiotics, doses, and populations in these studies that make generalizations difficult, it is clear that probiotic agents are becoming an important tool in the treatment of gastrointestinal problems in infants and children.

Probiotics appear to be helpful for viral diarrhoea, presumably by boosting secretory IgA and reducing viral shedding, despite the fact that gastroenteritis as the source of acute diarrhoea may in some circumstances recover.

Acute diarrheal disorders including rotavirus infection, traveler's diarrhoea, and more serious bacterial infections like *Clostridium difficile* have all been successfully treated with probiotics [11, 25, 35, 36, 38]. Studies on *Saccharomyces boulardii* and *Lactobacillus* species are important because they suggest a beneficial effect in *C. difficile*-related diseases [25, 39, 40, 41, 42]. The symptom complex in populations with small bowel bacterial overgrowth, especially those with short bowel syndrome, was found to be successfully alleviated by *Lactobacillus* species [25, 43]. However, *Saccharomyces boulardii* failed to completely eradicate the excess of small bowel intestinal bacteria in a seven-day, double-blind, randomized trial involving ten participants [35].

Probiotic substances prevent dysbiotic organisms from adhering to intestinal epithelial cells, according to in vitro research. It is hypothesized that this inhibition is achieved by the capacity to upregulate the expression of the intestinal mucins MUC2 and MUC3 [34]. The first step of the multi-stage process of bacterial-to-epithelial cell binding is defined by the initial engagement of the bacteria with the enterocyte layer. Probiotics boost the development of intestinal mucus, which inhibits enteropathogen adhesion. A tiny structural change in the bacterial ligand that interferes with proper attachment to the receptor is known as steric hindrance. The attachment may also be blocked by competing inhibition for attachment sites on mucins that imitate bacterial attachment sites on epithelial cells. It is yet unclear if enhancing the innate defense systems in the gastrointestinal tract, including

mucin synthesis, is preventative or therapeutic. It is also in childrens, adult etc.

Probiotics for Diarrhea



Figure No.3: Probiotic for Diarrhoea

Colon Cancer

In experimental models of colon cancer, probiotics have been found to have additional effects on the GI tract [44, 25]. Many chemicals, some of which may be carcinogenic and some of which may be anticarcinogenic, are produced when bacteria break down certain food components. The Production of such chemicals may be considerably influenced by the composition of the intestinal flora [45]. In fact, in animal experiments, individuals who received Lactobacillus strains had lower rates of colon tumor development [44, 25]. Several kinds of lactic acid-producing bacteria seem to inhibit the initial critical stage of carcinogenesis, which could ultimately operate as a proto oncogene or inactivate tumor suppressor genes, from being induced by carcinogenic chemicals. It has been demonstrated that administering Lactobacillus GG reduces the

activity of several bacterial enzymes, including tryptic, urease, fecalglycocholic hydrolase, and glucuronidase [46]. Reductions in glucuronidase, nitroreductase, and azoreductase, all of which may contribute to the activation of procarcinogens in the large intestine, are of special concern. These results will need to be confirmed in human trials.

Inflammatory Bowel Disease

Probiotic combination therapy have reportedly been shown to help people with inflammatory bowel disease.[47] During the course of the experiment, 26 patients who were given VSL #3 at a dose of 6 grams per day for a year had their clinical status evaluated. According to the authors, 75% of the patients maintained remission during treatment.

Patients with Crohn's disease who take Saccharomyces boulardii had longer

remission times and experience fewer relapses.^[48] Patients in 32 patients randomized to receive either 3 g daily mesalamine or 2 g daily mesalamine with *Saccharomyces boulardii* for those with established Crohn's disease who were in remission. Only one of the 16 patients in the probiotic arm relapsed compared to six of the 16 individuals in the pharmaceutical-only arm. It has been noted that *Lactobacillus GG* and *Saccharomyces boulardii* both raise the gut's levels of secretory IgA. There is a lot of interest in the ongoing research into probiotic usage in inflammatory bowel illness^[49, 50].

Conclusion

The theory that oral probiotic therapy may be helpful in a variety of illnesses both inside and outside the gastrointestinal tract is supported by the most recent research. Probiotics have been shown to have direct effects on the GI tract, including the up-regulation of immunoglobulins like IgA, the suppression of pro-inflammatory cytokines, and improved gut barrier integrity. Exciting new research suggests that probiotics have indirect, systemic effects for a wide range of illnesses, including atopic disease, immunological dysfunction, and vaginal infections.

References

1. Kollath W. *Ernaehrung und Zahnsystem. Deutsche Zahnärz Z* 1953; 8(11):7–16.
2. Reid G, Sanders ME, Gaskins HR, et al. *New scientific paradigms for probiotics and prebiotics. J Clin Gastroenterol* 2003; 36:105–18.
3. Marteau PR. *Probiotics in clinical conditions. Clin Rev Allergy Immunol* 2002;22:255–73
4. Ouwehand AC, Salminen S, Isolauri E. *Probiotics: an overview of beneficial effects. Antonie van Leeuwenhoek* 2002; 82:279–89.
5. Tamime AY. *Fermented milks: a historical food with modern applications a review. Eur J Clin Nutr* 2002; 56(suppl 4):S2–15.
6. Bibel DJ. *Elie Metchnikoff's bacillus of long life. ASM News* 1988;54:661–5
7. R, ed. *Probiotics the Fuller R. History and development of probiotics. In: Fuller scientific basis. London: Chapman and Hall, 1992:1–8.*
8. Stanton C, Gardiner G, Meehan H, et al. *Market potential for probiotics. Am J Clin Nutr* 2001; 73(suppl):476S–83.
9. Gibson GR, Roberfoid MB. *Dietary modulation of the human colonic microbiota: introducing the concept of prebiotics. J Nutr* 1995; 125:1401–12.
10. Rastall RA, Gibson GR. *Prebiotic oligosaccharides: evaluation of biological activities and potential future developments. In: Tannock GW, ed. Probiotics and prebiotics: where are we going? Wymondham: Caister Academic Press, 2002:107–48.*
11. Gionchetti P, Rizzello F, Venturi A, Campieri M. *Probiotics in infective diarrhoea and inflammatory bowel diseases. J Gastroenterol Hepatol* 2000; 15:489-493.
12. Walker WA. *Role of nutrients and bacterial colonization in the development of intestinal host defense. J Pediatr Gastroenterol Nutr* 2000; 30:S2-S7.
13. Vander hoof JA, Young RJ. *Use of probiotics in childhood gastrointestinal disorders. J Pediatr Gastroenterol Nutr* 1998; 27:323-332.
14. Levy J. *The effects of antibiotic use on gastrointestinal function. Am J Gastroenterol* 2000; 95:S8-S10.
15. Gorbach SL, Goldin BR. *Nutrition and the gastrointestinal microflora. Nutr Rev* 1992; 50:378-381.
16. Bengmark S. *Colonic food: pre- and probiotics. Am J Gastroenterol* 2000; 95:S5-S7.
17. Sarem- Damerджи L, Sarem F, Marchal L, Nicolas JP. *In vitro colonization ability of human colon*

- mucosa by exogenous Lactobacillus strains. FEMS Microbiol Lett* 1995; 131:133-137.
18. Percival M. Choosing a probiotic supplement. *Clin Nutr Insights* 1997; 6:1-4.
 19. Walker WA. Role of nutrients and bacterial colonization in the development of intestinal host defense. *J Pediatr Gastroenterol Nutr* 2000; 30:S2-S7.
 20. McFarland LV. Beneficial microbes: health or hazard? *Eur J GastroenterolHepatol* 2000; 12:1069-1071.
 21. Gorbach SL. Probiotics and gastrointestinal health. *Am J Gastroenterol* 2000; 95:S2-S4.
 22. Majamaa H, Isolauri E. Probiotics: a novel approach in the management of food allergy. *J Allergy Clin Immunol* 1997; 99:179-185.
 23. Walker WA. Role of nutrients and bacterial colonization in the development of intestinal host defense. *J PediatrGastroenterolNutr* 2000; 30:S2-S7.
 24. Hooper LV, Gordon JI. Commensal host bacterial relationships in the gut. *Science* 2001; 292:1115-1118.
 25. Vander hoof JA. Probiotics: future directions. *Am J Clin Nutr* 2001; 73:1152S-1155S.
 26. Vander hoof JA, Young RJ. Use of probiotics in childhood gastrointestinal disorders. *J PediatrGastroenterolNutr* 1998; 27:323-332.
 27. Murch SH. Toll of allergy reduced by probiotics. *Lancet* 2001; 357:1057-1059.
 28. Pelto L, Isolauri E, Lilius EM, et al. Probiotic bacteria down-regulate the milk-induced inflammatory response in milk-hypersensitive subjects but have an immunostimulatory effect in healthy subjects. *Clin Exp Allergy* 1998; 28:1474-1479.
 29. Pessi T, Sutas Y, Hurme M, Isolauri E. Interleukin-10 generation in atopic children following oral *Lactobacillus rhamnosus* GG. *ClinExp Allergy* 2000;30:1804-1808
 30. Pessi T, Sutas Y, Marttinen A, Isolauri E. Probiotics reinforce mucosal degradation of antigens in rats: implications for therapeutic use of probiotics. *J Nutr* 1998; 128:2313-2318.
 31. Cunningham-Rundles S, Ahrne S, Bengmark S, et al. Probiotics and immune response. *Am J Gastroenterol* 2000; 95:S22-S25.
 32. Wagner RD, Warner T, Roberts L, et al. Colonization of congenitally immunodeficient mice with probiotic bacteria. *Infect Immun* 1997; 65:3345-3351.
 33. De Santis A, Famularo G, De Simone C. Probiotics for the hemodynamic alterations of patients with liver cirrhosis. *Am J Gastroenterol* 2000; 95:323-324
 34. Mack DR, Michail S, Wei S, et al. Probiotics inhibit enteropathogenic *E. coli* adherence in vitro by inducing intestinal mucin gene expression. *Am J Physiol* 1999; 276:G941 G950.
 35. Marteau PR, de Vrese M, Cellier CJ, Schrezenmeir J. Protection from gastrointestinal diseases with the use of probiotics. *Am J Clin Nutr* 2001; 73:430S-436S.
 36. Saavedra JM, Bauman NA, Oung I, et al. Feeding of *Bifidobacterium bifidum* and *Streptococcus thermophilus* to infants in hospital for prevention of diarrhea and shedding of rotavirus. *Lancet* 1994; 344:1046 1049.
 37. Szajewska H, Kotowska M, Mrukowicz JZ, et al. Efficacy of *Lactobacillus GG* in prevention of nosocomial diarrhea in infants. *J Pediatr* 2001; 138:361-365.
 38. Pochapin M. The effect of probiotics on *Clostridium difficile* diarrhea. *Am J Gastroenterol* 2000; 95:S11-S13.
 39. Schultz M, Sartor RB. Probiotics and inflammatory bowel diseases. *Am J Gastroenterol* 2000; 95:S19-S21.
 40. Gorbach SL, Chang TW, Goldin B. Successful treatment of relapsing *Clostridium difficile* colitis with *Lactobacillus GG*. *Lancet* 1987; 2:1519.
 41. Surawicz CM, Mc Farland LV, Greenberg RN, et al. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomycesboulardii*. *Clin Infect Dis* 2000; 31:1012-1017.
 42. Vander hoof JA, Young RJ, Murray N, Kaufman SS. Treatment strategies for small bowel bacterial overgrowth in short bowel syndrome. *J Pediatr Gastroenterol Nutr* 1998; 27:155-160.
 43. Gorbach SL, Goldin BR. Nutrition and the gastrointestinal microflora. *Nutr Rev* 1992; 50:378-381.
 44. Moore WE, Moore LH. Intestinal floras of populations that have a high risk of colon cancer. *Appl Environ Microbiol* 1995; 61:3202 3207.

45. Gorbach SL. Probiotics and gastrointestinal health. *Am J Gastroenterol* 2000; 95:S2-S4.
46. Campieri M, Gionchetti P. Probiotics in inflammatory bowel disease: new insight to pathogenesis or a possible therapeutic alternative? *Gastroenterology* 1999; 116:1246-1249.
47. Guslandi M, Mezzi G, Sorghi M, Testoni PA. *Saccharomyces boulardii* in maintenance treatment of Crohn's disease. *Dig Dis Sci* 2000; 45:1462-1464.
48. Steidler L, Hans W, Schotte L, et al. Treatment of murine colitis by *Lactococcus lactis* secreting interleukin-10. *Science* 2000; 289:1352-1355.
49. Shanahan F. Inflammatory bowel disease: immunodiagnostics, immunotherapeutics, and eotherapeutics. *Gastroenterology* 2001;120:622-635.
50. Caplan MS, Jilling T. Neonatal necrotizing enterocolitis: possible role of probiotic supplementation. *J Pediatr Gastroenterol Nutr* 2000; 30:S18-S22.
51. Wunderlich PF, Braun L, Fumagalli I, et al. Double-blind report on the efficacy of lactic acid-producing *Enterococcus SF68* in the prevention of antibiotic-associated diarrhoea, and in the treatment of acute diarrhoea. *J Int Med Res* 1989; 17:333-338.
52. Mitra AK, Rabbani GH. A double-blind, controlled trial of bioflorin (*Streptococcus faecium SF68*) in adults with acute diarrhea due to *Vibrio cholerae* and enterotoxigenic *Escherichia coli*. *Gastroenterology* 1990; 99:1149-1152.
53. Rembacken BJ, Snelling AM, Hawkey PM, et al. Non-pathogenic *Escherichia coli* versus mesalazine for the treatment of ulcerative colitis: a randomised trial. *Lancet* 1999;354:635-639.
54. Floch MH, Moussa K. Probiotics and dietary fiber: the clinical coming of age of intestinal microecology. *J Clin Gastroenterol Nutr* 1997; 27:99-100.
55. Sanders ME, Klaenhammer TR. Invited review: the scientific basis of *Lactobacillus acidophilus* NCFM functionality as a probiotic. *Dairy Sci* 2001; 84:319-331.
56. Nobaek S, Johansson ML, Molin G, et al. Alteration of intestinal microflora is associated with reduction in abdominal bloating and pain in patients with irritable bowel syndrome. *Am J Gastroenterol* 2000; 95:1231-1238.
57. Systemic immunity-enhancing effects in healthy subjects following dietary consumption of the lactic acid bacterium *Lactobacillus rhamnosus* HN001. *J Am Coll Nutr* 2001; 20:149-156.
58. Qamar A, Aboudola S, Warny M, et al. *Saccharomyces boulardii* stimulates intestinal immunoglobulin A immune response to *Clostridium difficile* toxin A in mice. *Infect Immun* 2001; 69:2762-2765.
59. Aiba Y, Suzuki N, Kabir AM et al. Lactic acid-mediated suppression of *Helicobacter pylori* by the oral administration of *Lactobacillus salivarius* as a probiotic in a gnotobiotic murine model. *Am J Gastroenterol* 1998; 93:2097-2101.
60. Saavedra J. Probiotics and infectious diarrhea. *Am J Gastroenterol* 2000;95:S16-S18.
61. Guslandi M, Mezzi G, Sorghi M, Testoni PA. *Saccharomyces boulardii* in maintenance treatment of Crohn's disease. *Dig Dis Sci* 2000; 45:1462-1464.
62. Pochapin M. The effect of probiotics on *Clostridium difficile* diarrhea. *Am J Gastroenterol* 2000; 95:S11-S13.
63. Surawicz CM, McFarland LV, Greenberg RN, et al. The search for a better treatment for recurrent *Clostridium difficile* disease: use of high-dose vancomycin combined with *Saccharomyces boulardii*. *Clin Infect Dis* 2000; 31:1012-1017.
64. Sheih YH, Chiang BL, Wang LH, et al. Systemic immunity-enhancing effects in healthy subjects following dietary consumption of the lactic acid bacterium *Lactobacillus rhamnosus* HN001. *J Am Coll Nutr* 2001; 20:149-156.