



AMERICAN JOURNAL OF PHARMTECH RESEARCH

Journal home page: <http://www.ajptr.com/>

Probiotics: For Stomach Disorders - An Evidence Based Review

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ABSTRACT

Probiotics are the live microbial feed supplement which benefitted the host when administered in a certain number. Probiotics have been within our domestic use for as long as people have eaten fermented milk, curd, butter milk, but their association with health benefits dates only from the turn of the last century, when Metchnikoff drew attention to the beneficial effects of some gut microflora on the host, and suggested that ingestion of fermented milk products ameliorated this so-called auto-intoxication. Species of *Lactobacillus*, *Bifidobacterium*, *Bacillus*, *Streptococcus*, *Lactococcus* and *Saccharomyces* are used as Probiotics. Probiotics are purposely used for their immunomodulatory, antilipidemic, antitoxin, antimicrobial and anti-allergic properties. There is an endless list of Probiotics properties. In spite of these properties Probiotics are immensely showing fruitful results against diarrhea and stomach disorders like Irritable bowel syndrome, Antibiotic associated diarrhea, Pancreatitis, *Clostridium difficile* infection, Radiation induced diarrhea, Traveler's diarrhea etc. It increases IgA level and other immunoglobulins secreted cells in the intestinal mucosa and stimulate local release of interferons. It facilitates antigen transport to underlying lymphoid cells, which serves to increase antigen uptake in Peyer's patches. Present review has been aimed to discuss the role of Probiotics in diarrhea which is very common in developing countries like India.

Keywords: Probiotics, Stomach disorders, Gastroenteritis, Irritable bowel disease

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Received 20 February 2012, Accepted 29 February 2012

INTRODUCTION

Diet, stress and modern medical practices have been important factors which influence on subjects overall health and nutrition. As a result of deficient or compromised microflora, the incidence of illnesses may be increased. These generally includes the gastrointestinal tract infections; constipation; irritable bowel syndrome (IBS); inflammatory bowel disease (IBD)- Crohn's disease and ulcerative colitis; food allergies; antibiotic-induced diarrhea; cardiovascular disease and certain cancers ^{1,2}.

The vast majority of the total cells in the body are present as bacteria in the colon, reaching 10^{12} for every gram of large intestinal contents. Under natural conditions, a protective gut microflora develops and there is no need for a bacterial supplement from outer source. But the changing food habits and lifestyle force us to take processed and sterile food, which affects our access too, and colonization, by certain type of bacteria. Moreover, we also consume antibacterial substances ranging from vinegar to antibiotics ³ Humans live in close association with vast numbers of micro-organisms present on the skin, in the mouth and in the gastro-intestinal tract. The greatest concentration of commensal organisms is found in the gastrointestinal tract, which has more than 400 m^2 of surface area. This constitutes the second largest surface area of the body after that of the respiratory tract. The primary function of the human gastrointestinal tract is digestion and absorption of nutrients and excretion of waste end products from the body. In recent years, however it has become accepted that the gastrointestinal tract performs some other vital functions which are essential to our well-being. The gastrointestinal tract of humans is host for a vast ecology of microbes and harbors more than 500 identified species that can be cultured and many bacteria that cannot be cultured and properly identified. These bacteria which are necessary for health and also they have the potentially contribute in the development of diseases by a variety of mechanisms ^{4,5}.

'Probiotics' term was used by Lilly and Stillwell⁶. These are substances that stimulate the growth of other microorganisms. Many definitions have been given to till date. Now the meaning of Probiotics has been changed as 'It is viable microbial agent that, when used for other organisms like animal or man, beneficially affects the host by improving the balance of the normal microbial communities'⁷. The important fruitful effects of Probiotics were first reported by Methnikoff in the early 1900s ⁸.

Probiotics microorganisms are nonpathogenic and are safe for consumption⁹. These produce secondary metabolites, such as sakacin, salivaricin, enterocin, formic acid, diacetyl, hydrogen

peroxide, acetoin and enzymes, such as α -galactosidase, α -glucosidase, nitroreductase and β -glucosidase. Adhesion properties such as α -enolase, which help them to bind to host surface. Interactions with the host epithelium, particularly in terms of prevention of pathogenic microorganisms¹⁰.

The purpose of this review is to discuss the role of Probiotics in diarrheal disease and stomach disorders and the mechanism behind their action.

PRESENT SCENARIO OF PROBIOTICS

Majority of Probiotics bacterial species comprises of *Lactobacillus* and *Bifidobacterium*. *L. casei*, *L. acidophilus*, *L. brevis*, *L. sporogenes*, *L. rhamnosus*, *L. delbrukii*, *L. plantarum*, *L. fermentum* and *B. bifidus*, *B. infantis*, *B. longum*, *B. animalis* are used severally these days a potent Probiotics. Though some genera of *Streptococcus*, *Leuconostoc* and *Propionibacterium* also used as Probiotics. *Sacharomyces* and *Aspergillus* are also exploited for their Probiotic properties^{11,12,13,14}.

Probiotics, should retain viability during storage and use, should have the capacity to survive and metabolize in the gut, and finally should have documented health effects. *L. rhamnosus* GG (LGG) was the first Probiotics, which received most clinical attention to date. The *Lactobacillus* strain used traditionally for fermentation by dairy industry was unable to implant the gut, so, *L. rhamnosus* strain GG was discovered in 1985, by developing a list of ideal qualities for Probiotics. *Lactobacillus rhamnosus* strain GG has proven beneficial effects on intestinal immunity. It increases the number of IgA and other immunoglobulins secreting cells in the intestinal mucosa, stimulates local release of interferons and facilitates antigen transport to underlying lymphoid cells, which serves to increase antigen uptake in Peyer's patches¹⁵. Amdekar *et al*, suggested that Probiotics can be a oral vaccine candidate against so many deadful disease like AIDS, Malaria, Trichomoniasis, Ischemic heart diseases and Infantile diarrhea. Oral vaccines are much better than the conventional vaccine used previously from 5-6 dacades Oral vaccines are easily administrable, efficient in treating thousands of patients and eliminate the problem associated with injections¹⁶.

Applications of Probiotics

The health effects attributed to the use of Probiotics are numerous. The following outcomes are well documented:(1) lower frequency and duration of diarrhea associated with antibiotics (*Clostridium difficile*), rotavirus infection, chemotherapy, and, to a lesser extent, traveler's

diarrhea; (2) stimulation of hummoral and cellular immunity; and (3) decrease in unfavorable metabolites, eg, ammonium and procancerogenic enzymes in the colon.

[I] Immunomodulation

Microflora in the gastrointestinal tract regulates the systemic and local immune responsiveness by affecting the development of gut associated lymphoid tissue (GALT) at an early age¹⁷. Microbial colonisation leads to maturation of the hummoral immune mechanisms, particularly circulation of the IgA and IgM-secreting cells. The balance of the different T helper (T_H) subsets is particularly important in mucosal immunity. After priming, memory B and T cells migrate to effector sites. This is followed by active proliferation, local induction of certain cytokines and production of secretory antibodies (IgA). Upon antigen exposure, immune cells of a host respond and release cytokines. Which shows further subsequent immune responses? One of the major mechanisms by which the GALT maintains homeostasis is via local cytokines regulation, particularly TGF- β -associated low-dose tolerance immunity.

Malfunctioning of the immune system in ageing, stress and infectious diseases (e.g. AIDS), and in the undernourished is well established. The above deficiencies can be overcome by immunomodulation using suitable natural and chemical agents and/or products like Probiotics. Currently, available immunostimulatory products are associated with dreadful side-effects¹⁸. The development of natural products with immunomodulatory properties, devoid of side-effects, is therefore important for large population groups with impaired immune function¹⁹. *Lactobacilli* which adhere to the gut walls are capable of activating the macrophages.

[II] Anticancerous properties

Probiotics can be used as anticancerous agents. Gut bacteria like *Escherichia coli* and *Chlostridium perfringens* produced certain enzymes like nitroreductanse and β -Glucuronidase which convert some procarcinogens into carcinogens²⁰. *Lactobacillus* may also prevent the initiation and promotion of cancer. *Lactobacillus* has been used against the colon cancer. Probable mechanisms by which Lactic Acid Bacteria inhibit colon cancer may include alteration of the metabolic activities of gut microbes, changes in physicochemical conditions in the colon binding and degradation of potential carcinogens²¹. Probiotics also stimulate apoptosis through end-product formation.

[III] Probiotics for antilipidemic properties

Probiotics have been shown cholesterol lowering properties. Several studies attempted but the reason behind the antilipidemic property of Probiotics is still unknown. Lowering of cholesterol is due to co-precipitation of cholesterol with deconjugated bile salts at pH <6²². Bile salt

deconjugation results in the reduction of serum cholesterol level. Metabolism of cholesterol and bile salt is closely linked. Cholesterol is the precursor for synthesis of bile salts (water-soluble excretory end product). Bile salts are deconjugated during enterohepatic circulation (EHC) by bile salt hydrolase (BSH) (E.C.3.5.1.24). The free bile acids as well as glycine and taurine, are not so easily reabsorbed and are excreted in the faeces. Thus, loss in bile salts increases the catabolism of cholesterol to bile acids, resulting in lower cholesterol levels²³.

[IV] Probiotics as antimicrobials

Evidence has been obtained that the introduction of probiotics into the intestine results in the inhibition of conventional organisms or potential pathogens through a variety of mechanisms. These factors include decrease luminal pH, secrete bactericidal proteins (bacteriocins) and inhibit bacterial adhesion to epithelial cells. In addition, there is evidence that probiotics interfere with the production of defensins in the intestinal crypts that, as already mentioned, have antibacterial properties at this site. An important example of the antimicrobial effect of probiotics is the effect of the *Lactobacillus* species on *Helicobacter pylori* infection of the gastric mucosa²⁴. Hydrogen peroxide, lactic acid and pyroglutamate are the important antimicrobial in addition to bacteriocin. Antimicrobial properties of Probiotics are very well known against *E. coli*, *Yersinia enterocolitica* and *Salmonella typhimurium*, *Vibrio alginolyticus*^{25, 26, 27, 28, 29}.

Probiotics also produces substances that lower down the growth of viruses. Studies have shown that *L. rhamnosus* GR-1 and *L. fermentum* RC-14 can inactivate adenovirus and the vesicular stomatitis virus within minutes³⁰. The findings of experiments have suggested that *Lactobacillus* given at high concentrations is viricidal for HIV-1³¹.

[V] Antitoxin effect

Probiotics change the toxin molecules through an enzymatic reaction³². Their roles against the *Chlostridium difficle* and Cholera toxin has been well documented^{33, 34, 35}. These produced hydrolases like Proteases and lipases which destroy the toxins and activate intestinal receptors to produce IgG and IgA.

[VI] Probiotics in allergy

Allergy is an adverse immune reaction to a molecule called allergen (particle of foreign nature) in our environment, which is normally harmless to the non-allergic person. Allergic disorders are common in pediatric age group. While the exact etiology is unclear, evidence is mounting to incriminate environmental factors and an aberrant gut microbiota with a shift of the Th1/Th2 balance towards a Th2 response. This leads to activation of Th2 cytokines and the release of interleukin-4 (IL-4), IL-5 and IL-13 as well as IgE production. Probiotics modulate the immune

system back to a Th1 response. Several *in vitro* studies performed have suggested their role in treating allergic disorders. Human trials demonstrate a limited benefit for the use of probiotics in atopic dermatitis in a preventive as well as a therapeutic capacity³⁶.

Probiotics therapeutic potential in allergic disorders is due to the fact that they have been shown to reduce inflammatory cytokines (IL-6, TNF- α) and improve intestinal permeability *in vitro*. Such effects can be used in treating allergic disorders. Therefore, several studies have been designed to examine the efficacy of Probiotics in many allergic conditions, such as eczema, allergic rhinitis, asthma and food allergies^{37, 38, 39}.

THE USE OF PROBIOTICS AS A MAGIC BULLET

Diarrheal situation and stomach disorders are very common in Asia subcontinent. Diarrhea occurs world-wide and causes 4% of all deaths and 5% of health loss to disability. These gastrointestinal infections kill around 2.2 million people globally each year, mostly children in developing countries.

Colonies of bacteria in the intestine are called “microflora”. While a normal microflora is associated with good health, changes in intestinal health are associated with weakened immune function. An imbalance in the natural microflora is frequently associated with various disease states such as yeast infections and colon cancer.

Oral ingestion of probiotic bacteria helps support and modifies the composition and metabolic activities of the large intestine microflora. Microflora of the large intestine assist digestion through fermentation (lowering the pH of the intestine, making it more acidic and inhospitable to invading species); protect against disease causing bacteria; and stimulate the development of certain immune system components. Lactic acid bacteria have a central role in the gut flora enabling them to influence the composition of the flora for health benefits. Probiotic bacteria need to be ingested regularly for their health-promoting effects to persist.

[A] Inflammatory Bowel Disease (IBD) –

IBD is the inflammation of the gastro-intestinal tract followed by severe watery and bloody diarrhea and abdominal pain. It is an emerging disease that affects 20 out of 100,000 genetically susceptible people in Europe and North America. The most common manifestations of IBD are Crohn's disease and ulcerative colitis. In ulcerative colitis (UC) the inflammatory response is confined to the mucosa and submucosa of the colon with clear demarcations. In Crohn's disease (CD), the entire gastrointestinal tract can be involved and the inflammation can extend through the intestinal wall from mucosa to serosa. While the exact causes are unclear, IBD is known to

be the result of an overactive immune response that is linked to an imbalance of the normal types of bacteria found in the gut. It is now generally accepted that the intestinal bacterial flora contributes significantly to the pathogenesis of inflammatory bowel disease (IBD) along with mucosal immune dysregulation and genetic susceptibility.

The intestinal bacterial flora is thought to be an important factor in the development and recurrence of IBD. Current treatment of IBD relies mainly on anti-inflammatory drugs, immunomodulators, nutritional supplements and surgery. The human gastrointestinal tract contains about 10^{14} bacteria, with small numbers in the stomach ($<10^3$ / mL) and 10^{11} - 10^{13} / mL in the colon.

Because of the evidence implicating the intestinal bacterial flora in IBD, various attempts have been made to modify the flora with Probiotics. Both *Lactobacillus* species and *Bifidobacterium* species are frequently used in IBD.

Various studies have been performed in case of IBD to detect the beneficial effect of Probiotics. In a study, animals with experimental colitis orally or rectally administered *Lactobacilli* have yielded improvements. In IL-10 deficient mice, *Lactobacillus plantarum* 299v prevented onset of disease and reduced established colitis⁴⁰. *L. reuteri* (R2LC) attenuated the development of colitis in IL-10 deficient mice, in acetic-acid treated rats, and in methotrexate treated rats; *L. salivarius* UCC118 decreased mucosal inflammatory activity in IL-10 deficient mice; finally, a multispecies probiotic (VSL#3) given to IL-10 deficient mice with established colitis normalized gut barrier function, reduced pro-inflammatory cytokines and lessened histological disease^{41,42,43}. The probiotic cocktail VSL#3 has been demonstrated to induce dendritic cell secretion of IL-10 while attenuating T-cell production of IFN- γ ⁴⁴. Probiotic effects on epithelial cell function have been demonstrated in vitro and in vivo⁴⁵.

Further studies examined the effect of *B. infantis* 35624 on early inflammation in IL-10^{-/-} mice and wild-type mice of the same genetic background. Pronounced changes occurred in the Peyer's patch following probiotic consumption, with IFN- γ reduced in both wild-type and IL-10^{-/-} mice. Interestingly, following in vitro stimulation with a pathogen, IFN- γ was enhanced in wild-type mice but reduced in IL-10^{-/-} mice⁴⁶. These bacteria reduce the number of pathogenic bacteria in the colon. These good bacteria increased the secretion of IgA which could promote the gut immunological barrier⁴⁷. There is an increased level of th₂ (IL-4 and IL-10) cytokines and decreased in th₁ (IL-2 and IL-12) cytokines⁴⁸. These are anti-inflammatory and pro-inflammatory cytokines respectively.

In addition to indirectly influencing gut flora and stimulating immune responses, the Probiotic strains themselves produce antimicrobial peptides. Bacteriocin production is often associated with Probiotic strains. Production of different classes of bacteriocins confers a competitive survival advantage in colonisation and therefore these molecules are most relevant within the intestinal flora⁴⁹.

[B] Peptic ulcer-

Peptic ulcer is a chronic inflammation of stomach and duodenum. Peptic ulcers result from the breakdown of the lining of the stomach and duodenum caused by *Helicobacter pylori*, which burrows in between the cells and weakens the gastrointestinal tissues. Many new therapeutic strategies are being studied to improve the eradication of *H. pylori*. The use of probiotics in the field of *H. pylori* infection has become an important adjunct treatment to lessen side effects of prescribed treatment, especially as antibiotics not only eradicate *H. pylori*, but also eliminate many beneficial bacterial strains from the body.

Nonimmunological barriers such as the acidity of the stomach and the gastric mucosal barrier represent a first line of defense against pathogenic bacteria. It has been suggested that the intake of probiotics strengthens this barrier by producing antimicrobial substances, competing with *H. pylori* for adhesion receptors, stimulating mucin production and stabilizing the gut mucosal barrier. Probiotics may inhibit *H. pylori* growth by secreting antibacterial substances. Certain *lactobacilli* synthesize antimicrobial compounds related to the bacteriocin family. Other known substances secreted by these bacteria are the endproducts of lactic acid fermentation, such as lactic and acetic acids, and hydrogen peroxide⁵⁰. The production of relatively large amounts of lactate by *lactobacilli* has been implicated as an inhibitory factor of *H. pylori* by some authors. Some Probiotic bacteria exert their antiadhesion properties by secreting the antimicrobial agents^{51,52}.

The inflammatory response to gastric *H. pylori* infection is characterized by the release of various inflammatory mediators such as chemokines and cytokines. The cytokine response is initially manifested by the release of interleukin 8 (IL-8), which leads to the migration of neutrophils and monocytes to the mucosa. Monocytes and dendritic cells in the lamina propria produce tumor necrosis factor α (TNF- α) as well as IL-1 and IL-6⁵³. IL-1 and IL-6 stimulate CD41 T cells (type 1), and these produce a variety of cytokines including IL-4, IL-5, IL-6, and IFN- γ . This response is unable to clear the infection and sustains inflammation⁵⁴. Probiotics may provide a novel approach to the management of *H. pylori* infection.

[C] *Clostridium difficile* infection:

Clostridium difficile is the leading cause of nosocomially acquired intestinal infection. *C. difficile* has been associated with symptomatic diarrhea since it was identified as the pathogen responsible for pseudomembranous colitis. *C. difficile* is a spore-forming bacterium which is probably most commonly 'caught' through the mouth often in hospitals, especially after the use of antibiotics. It can result in syndromes of varying severity including transient diarrhea, a carrier status, a mild colitis-like illness, pseudomembranous colitis, and even toxic megacolon with possible mortality. Most affected patients can respond to medical therapy including discontinuation of the responsible antibiotic. It is not the antibiotic that causes the infection but rather the antibiotic use weakens the defense of the bowel bacteria so permitting *C. difficile* to implant in the bowel⁵⁵.

Most patients will respond to antibiotic therapy with metronidazole or vancomycin, but up to 20% of patients will develop recurrent episodes of *C. difficile* diarrhea or colitis⁵⁶. *C. difficile* associated diarrhea seems to be increasing in incidence, severity, and associated mortality. So a protective therapy is must. Studies conducted with *S. boulardii*. and *Lactobacillus* suggested that *C. difficile* associated diarrhea was prevented with their use^{57,58,59,60}. There are many mechanisms responsible for the probiotic action against the *C. difficile*. Most probiotics colonize the gut temporarily, producing bactericidal acids and peptides and promoting "competition" among microbes by competing for nutrients and epithelial adhesion. These effects appear to reduce the favorability of the environment for *C. difficile*. Bacteria in probiotic preparations produce acids that lower the pH of the local gut environment as well as toxins that inhibit the growth of other bacteria⁶¹. *S. boulardii* has been shown in vitro to secrete a protease that inhibits binding of enterotoxin A⁶², and *Lactococcus lactis* has been shown to secrete a cationic peptide that has antimicrobial activity against several strains of *C. difficile* in vitro. Probiotics may be capable of interfering with the binding of *C. difficile* toxins A and B to intestinal epithelial cells. In animal models, probiotic strains have been shown to inhibit adhesion and decrease invasion by pathogenic organisms of the colonic epithelium⁶³. Specifically, *Lactobacilli* increase expression of intestinal mucins and decrease bacterial translocatio. Several probiotic preparations including *Lactobacillus rhamnosus* GG, *Bifidobacterium breve*, and *Streptococcus thermophilus* have been shown in animal models to stabilize gut permeability⁶⁴.

Probiotics are responsible for immunomodulation by stimulating toll like Receptor, and upregulating cytokine expression in dendritic cells and peripheral blood monocytes and enhanced phagocytic activit^{65, 66, 67}.

[D] Lactose intolerance:

Lactose intolerance, also called lactase deficiency is the inability to digest and metabolize lactose, a sugar found in milk. It is caused by a lack of the enzyme lactase in the digestive system, required to break down lactose. Disaccharides cannot be absorbed through the wall of the small intestine into the bloodstream, so in the absence of lactase, lactose present in ingested dairy products remains uncleaved and passes in colon. It results in symptoms including abdominal pain, bloating, flatulence, diarrhea, nausea, and acid reflux. Yogurt and other conventional starter cultures and probiotic bacteria in fermented and unfermented milk products improve lactose digestion and eliminate symptoms of intolerance in lactose maldigesters. Although many Probiotic strains have some lactase activity, they normally promote lactose hydrolysis in the small intestine less effectively than do conventional yogurt cultures.

Probiotic bacteria are known to improve lactose digestion and the symptoms of lactose intolerance. Many probiotic bacteria including *Lactobacillus bulgaricus* and *Streptococcus thermophilus* actually produce lactase themselves⁶⁸. These lactic acid bacteria produce β -galactosidase (lactase), which can survive passage through the stomach and is released by bile salts into the small intestine, where lactose digestion occurs⁶⁹. Various studies have shown that supplementing with probiotic bacteria improves the ability of patients to tolerate lactose. Non-fermented milk containing either *Lactobacillus acidophilus* or *Lactobacillus bulgaricus* were given to patients who were lactose maldigesters and their degree of maldigestion monitored using a breath hydrogen test⁷⁰.

[E] Traveler's diarrhea:

TD is a condition characterized by a marked increase in the frequency of unformed bowel movements and is commonly accompanied by abdominal cramps, urgency, nausea, bloating, vomiting, fever, and malaise. Usually it begins abruptly, occurs during travel or soon after returning home, and is generally self-limiting. The onset of TD is usually within the first week of travel, but can occur at any time during the visit and even after returning home.

Antibiotics are effective prophylaxis but are not recommended for widespread use and there is thus a need for cost-effective alternative treatments. Several studies were performed with the use of probiotics. Among the five double blind, controlled trial reported, only one trial showed significant benefit using *Saccharomyces boulardii*⁷¹.

[F] Radiation induced diarrhea:

Almost all regimens of radiation therapy may disturb the colonization resistance of the indigenous gut flora. This is the main mechanism underlying the pathophysiology of acute

radiation-induced enteritis and colitis, which are a common and potentially severe complication among cancer patients treated with radiation therapy. Attempts to treat this complication with antibiotics, sucralfate, anti-inflammatory drugs such as mesalazine and balsalazide, glutamine, octreotide, proteolytic enzymes, and hyperbaric oxygen have so far provided inconclusive clinical results with failure of treatment occurring in a substantial proportion of patients⁷².

Furthermore, prophylactic use of sucralfate does not reduce the burden of radiation induced bowel toxicity but rather, is associated with more severe gastrointestinal symptoms including bleeding and fecal incontinence.

Previous studies showed a protective effect of probiotic administration after radiation therapy, and probiotic may play an important role in the pathogenesis of radiation enteropathy^{73,74,75}. These studies indicate that probiotics may decrease the risk of accumulated reactive oxygen species (ROS) in host organisms and could potentially be used as probiotic food supplements to reduce oxidative stress.

Thus, the administration of probiotics during RT could ultimately allow patients to receive a greater cumulative radiation tumour dose, thereby increasing the effectiveness of radiotherapy on tumours.

[G] Antibiotic-associated diarrhea (AAD):

Its usually results from an imbalance in the colonic microbiota caused by antibiotic therapy. Microbiota alteration changes carbohydrate metabolism with decreased short-chain fatty acid absorption and an osmotic diarrhea as a result. It is well known that antibiotic therapy can disrupt the homeostatic balance in the gut flora, causing an overgrowth of pathogenic microbes relative to beneficial flora. This allows pathogenic bacteria to colonize the gut and gain access to the GI mucosa, precipitating diarrhea and predisposing patients to fluid and electrolyte disturbances. Probiotics with specific strains of beneficial bacteria and yeast aim to restore that balance⁷⁶.

These bacteria liberate acid in the gut and lower luminal pH, which suppresses the growth of pathogenic flora. Probiotics also decrease colonization of pathogenic organisms in the gut by secreting hydrogen peroxide and organic acids that are locally toxic to pathogenic bacteria and may competitively block microbial adhesion to the gut epithelium.

Numerous studies conducted on antibiotic associated diarrhea suggested that they showed better conditions in subjects^{77, 78, 79}.

S. boulardii, *L. rhamnosus* strain GG, *L. acidophilus* and *L. bulgaricus*, *B. longum*, *B. lactis* are the important candidates which have been used now a day's against antibiotic associated diarrhea.

[H] Nosocomial and day-care center diarrhea:

Respiratory tract infections and gastrointestinal infections like diarrhea are more common in children attending day-care centres than in children at home or in family care. Nosocomial diarrhea may prolong hospital stay and increase medical costs. It is commonly caused by Rotavirus and less frequently by *C. difficile*.

[I] Pancreatitis:

Pancreatitis means an inflammation of the pancreas. Pancreas secretes digestive enzymes into the small intestine through a tube called the pancreatic duct. These enzymes help digest fats, proteins, and carbohydrates in food. In pancreatitis, the enzymes that help digest fats, proteins and carbohydrates in food become active inside the pancreas and start digesting the pancreas. Since commensal bacteria are believed to be a crucial part of host homeostasis, recent studies have looked at effects of probiotics in recreating equilibrium^{80, 81}. Colonization of the lower gastrointestinal tract and oropharynx with gram-negative organisms often precedes contamination of the inflamed pancreas. Study performed on human subjects who received *L. plantarum* 299v had shown less severity of pancreatic^{82, 83}.

[J] Irritable Bowel Syndrome

IBS is a syndrome lasting for more than 3 months and may present with either constipation or diarrhea associated with abdominal pain. Irritable bowel syndrome (IBS) is one of the most common functional gastrointestinal disorders with a prevalence of 3 to 15% in the general population. Several controlled trials of probiotics in irritable bowel syndrome (IBS). Several controlled trials of probiotics in irritable bowel syndrome (IBS) have been performed^{84,85}. The pathophysiology of IBS is still not well understood. Several factors such as motor and sensory dysfunction, immune mechanisms and psychological factors are suggested to play a role⁸⁶.

Currently available IBS therapies are mainly symptom orientated (e.g. anti-diarrheals for diarrhea, laxatives for constipation or smooth muscle relaxants for pain) and often are of limited efficacy regarding the overall complaints. Other treatment strategies, such as antidepressants for pain relief, are inadequate for long term management due to their side effect profiles.

Alteration of the colonic flora with administration of probiotics may modify fermentation processes and hence gas production, colonic transit and fluid fluxes. In fact, abdominal bloating, distension or flatulence, which are dominant symptoms in many IBS patients, have been shown to improve significantly by probiotic treatment in several placebo controlled trials^{87,88}. Several bacteria have been tested for example *Streptococcus faecium*, *Lactobacillus plantarum*, *Lactobacillus salivarius*, *B. breve* and *B. infantis*.

How Probiotics Reduce The Duration Of Diarrhea And Stomach Disorders?

Several potential mechanisms have been proposed to reduce the time of diarrhea and relieving stomach disorders. Not a single mechanism is responsible for that or we can predict that a combination of responses prevents or help the patient.

Competitive blockage of receptor site is responsible for the blockade of pathogen by probiotic bacteria⁸⁹. Surface layer proteins from probiotic bacteria are responsible for this adhenrence⁹⁰.

Goblet cells are present as a lining on the whole gut epithelium. These cells have the glycosylated mucins over it to inhibit bacterial and viral pathogens⁹¹. Out of the total 18 glycosylated mucins, MUC2 is abundantly present on the gut epithelium. These provide hydrophobicity and proteolytic resistance to the mucins. This layer provides protects gut by shielding from potentially harmful foreign particles and molecules, while acting as a lubricant for intestinal motility. The mucus is the first barrier that intestinal bacteria meet, and pathogens must penetrate it to reach the epithelial cells during infection. Probiotic bacteria increased the mucus secretion⁹².

Another important mechanism is the enhance in immune response. Approximately 80% of the Plasma cells are found in mucosa. Payer's patches are the important site of sIgA. sIgA protects the intestinal epithelium against colonization or invasion by binding antigens on pathogens. This is important in maintaining gut homeostasis by preventing overgrowth of the enteric microflora. sIgA can protect intracellular pathogens by binding and neutralizing viral or bacterial components during transcytosis of the epithelium⁹³. Antibody mediated cell mediated cytotoxicity, opsonization, generation of bactericidal superoxide, pro-inflammatory and anti-inflammatory cytokines signaling are the immunomodulatory properties governed by Probiotics⁹⁴.

Probiotics secrete antimicrobial for example bacteriocins and microcins which are peptides having bacteriostatic or bacteriocidal effect. Bacteriocins disrupts the cell wal by creating the spores⁹⁵. Microcins are responsible for the inner cell structure like DNA, RNA and protein synthesis enzymes⁹⁶. Hydrogen peroxides is also secreted as antimicrobial agent against the pathogen [Figure. 1].

How probiotic bacteria sum up the loss of rehydration induced due to diarrhea is still a questionnaire. More detailed mechanistic research is warranted to understand the mechanism behind the know probiotic strains reduce the duration of diarrhea in conjunction with rehydration therapy.

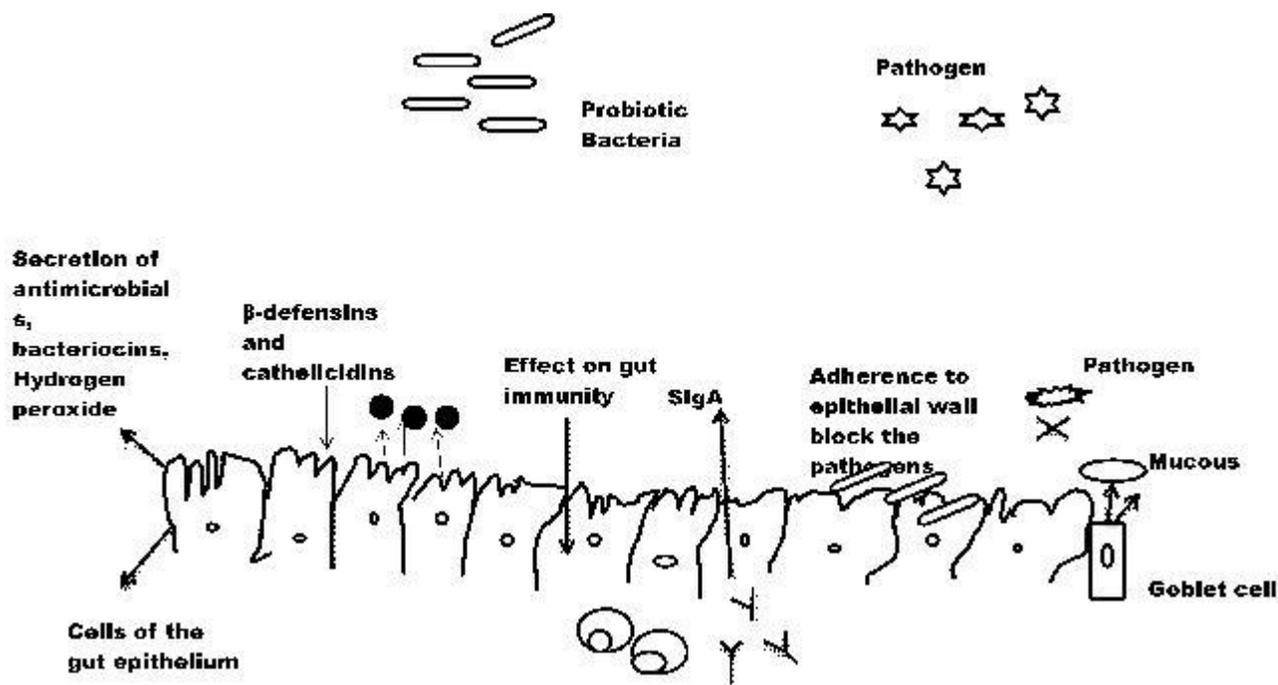


Fig. 1: This is a multifactorial approach regarding the protection of Probiotics from diarrheal and stomach diseases. Probiotic can increase the mucin production from goblet cells. Secretes defensins, bacteriocinas, microcins and other antimicrobial agents. Modulation of gut immunity by secreting IgA. These antibodies limits epithelial colonization by binding pathogens and their antigens. Thus contributing to gut homeostatis. Probiotics compete for the adherence with pathogen preventing detrimental colonization.

FUTURE PERSPECTIVES: SOLVING DISORDERS USING PROBIOTICS

Probiotics mediated therapy has already made its way in the treatment of various conditions- Infectious, inflammatory, neoplastic and allergic. The increasing use of Probiotics is linked to the concept of 'naturalness', which fulfills the desire of customers to take medicines free from side effects that is largely true for Probiotics. The areas of Probiotics and intestinal microflora are becoming more and more fascinating as we realize their significance and the interesting mechanisms by which they exert benefit to the host. Much more research is needed to aid in the full understanding of how these organisms play a role in gastrointestinal and systemic conditions that afflict children and adults, how the immune system interacts with such bacteria, and what constitutes a healthy microbial milieu in individual gastrointestinal disorders. Several important

criteria and standards regarding quality and reliability have to be met. This review article will prove a right step towards stimulating further research where immunologists, microbiologists, and gastroenterologists can collaborate.

Author's contribution:

SA wrote the manuscript. VS helped in critical reading and helpful discussion. All the authors approved the manuscript.

Conflict of interests:

There are nonfinancial competing interests (political, personal, religious, ideological, academic, intellectual, commercial, or any other) to declare in relation to this manuscript.

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