PROBIOTICS AND ITS EFFECTS ON GASTROINTESTINAL INFECTIONS: AN OVERVIEW

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Abstract
Probiotic are live microorganism which when administrated in adequate amount confers health benefit on human. Among the different microbial types, probiotics have been used most potentially as therapeutic agents and explored extensively. Probiotics belong to normal flora of gastrointestinal and urogenital tract. This review elucidate the natural and evolutionary history of probiotics over its importance in gastrointestinal infections and therapeutic application. Gastrointestinal microflora has strong prospective in scientific, veterinary and medical research. There are several studies based published in the literature on importance of probiotics in gastrointestinal disease in scientific world. Already, there is an image of dairy product to appear as an excellent mean for inventing nutritious food. Moreover, such dairy products provide beneficial affects to the host by improving survival and functioning the implantation of live microbial dietary supplements in the gastrointestinal tract. Although by stimulating the growth or activating the catabolism of one or more health promoting bacteria in the gastrointestinal tract, it is possible to improve the microbial balance in the gut.

***Keywords*: Probiotics, Prebiotics, Synbiotics, Microorganisms, Gastrointestinal tract (GIT), Infectious disease, Health benefits.**

Abbreviations: **LABs/LAB**, Lactic Acid Bacteria; **FAO**, Food and Agriculture Organization; **WHO**, World Health Organization; **GIT** Gastrointestinal tract; **SCFAs**, Short chain fatty acids; **GOS**, Galacto-oligo-saccharide; **IBD**, Inflammatory Bowel Disorder; **IBS**, Irritable bowel syndrome.

1. INTRODUCTION

The bioavailability of the rising trend of antibiotics in the 1950s ensured various attempts for controlled clinical trials as a pharmaceutical which were used as therapeutic agents and growth stimulants (Podolsky, S. H. 2010). Thus, this emphasized that the use of antibiotics as growth promotors fixed a context in development of resistance population of bacteria which used antibiotics made therapies difficult. The Swann Committee in 1969, restricted the use of antibiotics as a growth promoting factor for animal feeds. Because subsequent use of antibiotics for farm animals resulted in various side effects. Alternative use of antibiotics does not have a prolong benefit on man and animal. As the upgrading evolution of antibiotics, subsequently probiotics were regarded as the microbial growth stimulating factors for other microorganism. So the emerging trend in use of probiotics came into picture in the world (R Fuller, 1989). However applications in feeds are less documented. Thus, probiotics are now being considered to fulfill this role. As a result, already some farmers are indulged to the use of probiotics in preference to antibiotics (Di Gioia, D., & Biavati, B. (Eds.). 2018).

Probiotics are present in dairy as well as non-dairy products. Usually, they are consumed after the antibiotic therapy to cure some illness, as a relevance to destroy both the useful and targeted harmful intestinal microbial flora present in the digestive tract (Soccol et.al, 2010). Consequently, probiotics are found in rich and healthy habitat in association with food, feeds, plant, animal and humans. At present probiotics are extensively studied due to the economic importance, the metabolism, genetics and phylogeny (Duar et.al, 2017).The probiotic benefits are mostly concerned with gastrointestinal tract (GIT), immune and urogenital system. Nevertheless the major research focus today is on the intestinal microbial flora and the human gut tissues which emphasize that the microbial flora present in the gut act as a key factor which influence both the local and systematic immune response (Hill et al., 2014; Vandenplas et.al, 2015). However, recent research studies are pushing probiotic application towards other areas such as metabolic syndrome (obesity, diabetes, cardiovascular disease, etc.), psychotropic activity through the gut-brain axis, and antimutagenic or anti-cancerous activities (Aggarwal et.al, 2013; Zoumpopoulou et al., 2018). At the same time, exploring rich microbial diversity, finding for new strains are all used for alleviation of several medical condition besides perceived health benefit, their safety is of paramount importance (Diwas Pradhan et.al, 2019).

2. DEFINITION

2.1 Probiotics

A probiotic can be defined as a "viable microbial supplements with live organism and that have beneficial effect on the host". The term 'probiotic' was originally derived from the Latin word 'pro' (for) and Greek word 'bios' (life), thereby, means 'for life'. In 1953, Werner Kollath first introduced 'probiotics'. In 1974, Parker's definition was "Organism and substances which contribute to intestinal balance". Until Fuller in 1989, first defined 'probiotics' as "A live microbial feed supplement which beneficially affects the host animal by improving its intestinal balance".

Over the years, the word probiotics has been used in many ways. The World Health Organization (WHO) and Food and Drug Administration (FDA), defines briefly as, "Live microorganisms that, when administered in adequate amounts, confer a health benefit on the host." (WHO/FDA, 2002). Thus, to define a microorganism as probiotic, the microorganism should be of human origin, possess health benefits and clinical evidence, must not show any transferable resistance to antibiotics, must have a spectrum of non-pathogenicity, neither toxic nor allergic, resist in favorable conditions in the colorectal tract, must survive and have a desired viability in a food commodity throughout its storage and lifespan (Sadeka Choudhury Moni et al, 2014).

2.2 Prebiotics

The prebiotic concept is much alike to be young, and was first introduced by Gibson and Roberfroid in 1995, so as defined prebiotic "Non-digestible food ingredients that beneficially affect the host by selectively stimulating the growth and/or activity of one or a limited number of bacterial species already resident in the colon, and thus attempt to improve host health" (Gibson et.al, 1995). Some of the out listed prebiotics are oligosaccharides such as lactulose, galacto-oligosaccharides, inulin, fructo-oligosaccharides and other more promising non-digestible food carbohydrates are some of well-known examples of prebiotics (Ranadheera et.al, 2010). However, there are large number of other non-digestible oligosaccharides were less rigorous studies have been applied are gluco-oligosaccharides, glycol-oligosaccharides, lactitol, isomalto-oligosaccharides, xylo-oligosaccharides, stachyose, raffinose and sucrose thermal oligosaccharides have also been investigated (Gaggìa et.al, 2010).

2.3 Synbiotic

One approach which occurred for future research is synbiotic, a combination of both probiotic and prebiotic in a single product. The combination of probiotics and prebiotic enhances the survival and activity of microorganism. Although, this combination show synergistic effect (Nagpal et.al. 2012). Synbiotics is defined as "a mixture of a probiotic and a prebiotic that beneficially affects the host by improving the survival and the implantation of live microbial dietary supplements in the gastrointestinal tract, by selectively stimulating the growth and/or by activating the metabolism of one or a limited number of health-promoting bacteria and thus improving host welfare' (Gibson et.al, 1995).

3. HISTORY

Probiotics has a broad history up to date since its discovery. Whereas the science of probiotics is still young and rapidly expanding. Instantly, the finding for probiotics took place right from the evidences based on the fermentation of milk i.e. fermented milk or what we know today is yogurt. Thus, fermented milk was considered as a medicine by the Hippocrates (Oberman H, 1985).

The 20th century gave birth to probiotics. Russian bacteriologist Dr. Eli Metchnikoff noble price winner who use to work in the Pasteur Institute, France gave the first evidence on the beneficial effects of fermented milk i.e. yogurt. Thus, gave an appropriate understanding for the microbiological aspect of fermented milk. Through his finding, it was observed that the microorganism present in the yogurt have beneficial effects on health. They have ability to produce lactic acid, called as lactic acid producing bacteria (LAB) (Lourens-Hattingh et.al 2001). He gave a brief attribute that this lactic acid producing bacteria have the ability to inhibit the toxin producing anaerobes, spore-formers and pathogenic microbes in the gastrointestinal tract. Also enlisted that sour milk and other dairy products contain Bulgarians which has longevity in health. Certainly, identified '*Bulgarian Bacillus*' and later named as '*Lactobacillus bulgaricus*' a single strain from the species of *lactobacilli* (R Fuller, 1989). The yogurt today produced use *L. delbrueckii subsp. Bulgaricus* and *Streptococcus salivarius subsp. thermophiles* (Oskar Adolffson et.al 2020).

Over a period of time, Rettger in 1920 suggested that *Bulgarian Bacillus* could not survive for long and a new strain *Lactobacillus acidophilus* which was/is predominantly used in preparation for fermented products. It was an isolate from intestine. In 1899, Tessier at Pasteur Institute, isolated *Bifidobacterium* from human stool sample of breast feeding infants (Ishibashi et.al, 1993).

Moreover, many studies are been carried out for more health benefits and claims for use of probiotics. Often, various studies on new finding strains from the above species are carried out.

4. HOST GUT MICROBIOTA METABOLIC INTERACTION

The interaction of immunity and activity of gut microbiota is codeveloped from the time of birth within the host. This complex interplay depend on the host genome, nutrition and lifestyle. The microbiota shapes the immune system and in turn the immune system shapes the composition of the microbiota (Hooper et.al, 2002).

Bacterial antagonism is established until the gut acquires the whole microbial flora. This help to protect the host against proliferation of alimentary and potential pathogen like *Clostridium, Enterobacteria* or *Campylobacteria* which are toxigenic (Roy Fuller, 1992). The visualization of probiotics like *Lactobacillus paracasei* and *Lactobacillus rhamnosus* show trans-genomic metabolic effects which have been measured and mapped in germ-free mice colonized with human baby flora. Probiotic modulation of symbiotic gut microbial-host metabolic interactions includes biofuels, ceacal short chain fatty acids (SCFA), hepatic lipid metabolism which stimulates glycolysis, amino acid metabolism, exogenous and endogenous metabolism which influence etiology and development of several disease etc. (Martin et.al, 2008).

5. COMPOSITIONAL STRAINS OF PROBIOTICS

As these bacteria, produce lactic acid and show bifidogenic effects (Sadeka Choudhury et.al 2014). The type of probiotic preparation will depend on their intended use. They can be used in various form such as pelleted feeds or products in form of pastes, powder, granules etc. (R Fuller 1989).

Currently used species of probiotic bacteria's are *L. bulgaricus, L. acidophilus, L. casei, L. helveticus, L. lactis, L. salivarius, L. plantarum, Streptococcus thermophilus, Enterococcus faecium, Ent. faecalis, Bifidobacterium* spp. and *E. coli.* The other bacterial genera which are used as probiotics are *Leuconostoc, Pedicoccus, Propionibacterium* and some *Bacillus.* (Pradhan et.al, 2020). Fungus are also used as probiotics from the golden era, species of yeast namely *Saccharomyces cerevisiae* and *Candida pintolopesii* and species of moulds such as *Aspergillus niger* and *A. oryzae* are also been used (Sen et.al, 2020).

Table1. Commonly used probiotic microorganism and corresponding species

Probiotics Genera	Species Involved
Lactobacillus	*L. plantarum, L. paracasei, L. acidophilus , L. casei, L. rhamnosus, L. crispatus, L. gasseri , L. reuteri, L. bulgaricus*
Bifidobacterium	*B. longum, B. catenulatum , B. breve, B. animalis, B. bifidum*
Streptococcus	*S. sanguis, S. oralis, S. mitis, S. thermophilus, S. salivarius*
Bacillus	*B. coagulans, B. subtilis, B. laterosporus*
Lactococcus	*L. lactis subsp. cremoris (Streptococcus cremoris), L. lactis subsp. lactis*
Leuconostoc	*L. citreum, L. lactis, L. mesenteroides*
Enterococcus	*Ent. faecium*
Pediococcus	*P. acidilactici, P. pentosaceus subsp. pentosaceous*
Propionibacterium	*P. jensenii, P. freudenreichii*
Peptostreptococcus	*P. productus*
Saccharomyces	*S. cerevisiae (S. boulardii), S. pastorianus (S. carlsbergensis)*
Candida	*C. pintolopesii*
Kluyveromyces	*K. fragilis K. marxianus*
Aspergillus	*A. niger* and *A. oryzae*

6. CHARACTERISTICS OF GOOD PROBIOTIC

The good features of probiotics are been enlisted in the table 2. Although we do not know the minimum dose for preparation, the preparation must contain viable amount of cells possessed by the species on the label. Of course, it should be non-pathogenic and have less adverse effects on health of any sort. The beneficial effects should be in the form of growth promotors and increase resistance to disease. In order to survive, colonize and show metabolic activity it should harbor resistance to gastric juice, bile, pH, organic acids and all the other antibacterial influence present in the intestine. Should persist in the GIT and show adhesion to epithelium or mucus. It should acquire modulation of immune responses and exert antagonism towards pathogenic bacteria. However, by feeding large number of viable cells continuously (i.e. yoghurt contains non-intestinal bacteria which do not grow) may result in large number in the lower intestine. Consequently, by restricted dosing with intestinal strain may result in colonizing the gut and become self-replicating. For this, it should be remembered that the characteristics of the strain must survive growth on a large scale and its preparation should be prepared in such a way as to retain its viability under storage and field conditions (R. Fuller, 1989; Gaggìa et.al 2010).

Table 2. Features of good probiotics

Expected characteristics and safety criteria of probiotics.

• Non-toxic and non-pathogenic
• Accurate taxonomic identification
• Normal inhabitant of the targeted species
• Present as viable cells, preferably in large numbers, although we do not know the minimum effective dose
• Capable of exerting a beneficial effect on host i.e. increase growth and resistance to disease
• Survival, colonization and being metabolically active in the targeted site, which implies:
  ○ Resistance to gastric juice and bile
  ○ Resistance to low pH and organic acids
  ○ Persistence in the GIT
  ○ Adhesion to epithelium or mucus
  ○ Competition with the resident microbiota
• Production of antimicrobial substances
• Antagonism towards pathogenic bacteria
• Modulation of immune responses
• Ability to exert at least one scientifically-supported health-promoting properties
• Genetically stability
• Amenability of the strain and stability of the desired characteristics during processing, storage, delivery and field conditions for long period
• Viability at high populations
• Desirable organoleptic and technological properties when included in industrial processes

7. ROLE OF PROBIOTICS

The probiotics play a magnificent role in our day to day life. There are many evidences on the health and clinical proclaimed benefits of probiotics. Currently, due to the search process and strategies there have been many more research carried on applications of probiotics. The table 3 enlist the intestinal functions assigned to probiotics and prebiotics in the upper and lower gastrointestinal tract (Gaggìa et.al 2010).

Table 3. Intestinal functions assigned to probiotics and prebiotics.

Probiotics, Dietary fibers and gastrointestinal functions	
• Effects on upper GI tract	○ Resistance to digestion ○ Retarded gastric emptying ○ Increased oro-caecal transit time ○ Reduced glucose absorption and low glycemic index ○ Hyperplasia of the small intestinal epithelium ○ Stimulation of secretion of intestinal hormonal peptides
• Effects on lower GI tract	○ Acting as food for colonic microbiota ○ Acting as substrates for colonic fermentation ○ Production of fermentation end products (mainly SCFAs) ○ Stimulation of saccharolytic fermentation ○ Acidification of the colonic content ○ Hyperplasia of the colonic epithelium ○ Stimulation of secretion of colonic hormonal peptides ○ Bulking effect on stool production ○ Regularization of stool production (frequency and consistence) ○ Acceleration of ceco-anal transit

8. EFFECTS ON HUMAN GUT

8.1 Irritable bowel syndrome

Irritable bowel syndrome (IBS) is a problem all over the world. This problem can led to destructive and erratic fluidized movements in the stomach. The syndrome can be controlled by prebiotics and probiotics utilization and consumption. The major symptoms are constipation (IBS-c), abdominal pain (IBS-ab pain) and diarrhea (IBS-d) (Floch, M. H. 2018).

A review study which mainly focuses on irritable bowel syndrome witnesses improvement in abdominal distention and severity of symptoms after 4-6 week on demonstration of *B lactis DN-173 010* in 312 constipated patients (Agrawal et.al 2009). Also multispecies probiotic effect on 49 IBS patients were observed when they were administrated with a mixture of probiotics for 4 weeks. Later it was observed that primary efficacy end-point was proportion of participants whose IBS symptoms were sustainably relieved. Thus, feacal analysis revealed that *B. lactis, L. rhamnosus* and *S. thermophiles* had significant effects (Yoon J. S, 2003). During IBS symptoms the number of facultative anaerobes such as *klebsiella spp.* and *Enterococci* is higher than *lactobacillus* and *bifidobacteria*. Administration of probiotics prevents intestinal microbiota, show improvement in pain and flatulence and hence reduces caecal and feacal yeast proliferation in IBS patients treated with antibiotics (Madden, J. A. 2004).

8.2 Inflammatory Bowel Disorder

Inflammatory Bowel Disorder (IBD) is also known as functional bowel disorder (FBD) are the gastrointestinal disorders most commonly seen by the gastroenterologists and primary physicians. This is caused by alteration in the intestinal microbiota with pathogenic microbes. The most common symptoms are functional bloating, diarrhea and constipation during unspecified inflammatory bowel disorder. The complex community of microorganism in the gastrointestinal tract reside more than 1000 different types of bacterial species which can reach a viable count up to 10 log bacteria per gram of luminal content. The most predominant are *Firmicutes, Bacteriodetes* followed by *Proteobacteria* and *Actinobacteria* in the intestinal colon (Keren Hod 2016).

The following are the inflammatory bowel disorders (IBD):

8.2.1 Ulcerative colitis

Anatomical level of microorganism which shows invasion and adherence to develop inflammation at a particular site are most frequently affected by ulcerative colitis. VSL#3 probiotic-mixture induces remission in patients with active ulcerative colitis (Floch, M. H. 2018.).

In a study, 32 patients were treated with VSL#3 for 6 weeks for active ulcerative colitis. The therapy was measured using Ulcerative Colitis Disease index (UCDI) (Bibiloni et.al, 2005). In total, 327 patients were recruited for receiving either 200mg probiotic drug or 500mg mesalazine drug for 12 months on daily basis. Thus, the effectiveness of probiotic *Escherichia coli Nissle 1917* shows efficacy and safety in maintaining remission of ulcerative colitis in equivalent to standard mesalazine (Kruis et.al, 2004). The symbiotic effect of administration of *B. breve* in Yakult and galacto-oligo-saccharide (GOS) improved clinical condition for ulcerative colitis. A large scale randomized study for 41 mild and moderate ulcerative colitis patients was carried out, 1gm probiotic and 5.5gm of GOS was ingested on daily basis. The significant symbiotic effect resulted feacal count of *Bacteroidaceae* and feacal pH was reduced (Ishikawa et.al, 2011).

8.2.2 Crohn's disease

Crohn's disease is clearly classified among the chronic inflammatory bowel disorders. Indiscriminate repression of intestinal bacteria which are harmful with antibiotics can have an adverse side effects. An investigation on the efficacy on *Lactobacillus rhamnosus strain GG* on 45

patients was carried out for 12 months. The manipulation of enteric microflora with probiotic compound made possible in reducing the endoscopic recurrence rate for Crohn's disease (Prantera et.al, 2002). The increased mucosal tumor necrosis factor α play an important role in pathogenesis for intestinal inflammation during Crohn's disease. The effect of bacteria on TNF- α release was investigated by obtaining ileal specimen for 10 patients with Crohn's disease. Cocultures of *Lactobacillus casei DN-114001* and *L. bulgaricus LB10* reduced the CD4 cells as well as TNF- α expression among intraepithelial lymphocytes from crohn disease mucosa (Borruel et.al, 2002). *Saccharomyces cerevisiae subsp. boulardii* is a non-pathogenic yeast and reported to protect against infection caused by *Clostridium difficile* and cholera toxin. A remission trails on 35 patients with 1gm mesalamine or preparation of *S. boulardii* was carried. Results showed that the yeast culture can maintain treatment for crohn's disease (Guslandi et.al, 2000).

8.2.3 Pouchitis

The etiology of pouchitis after ileal pouch-anal anastomosis (IPAA) is unknown in entire colon and rectum. Although its manifestation resembles non-specific inflammatory bowel disease which evokes extra intestinal manifestation (EIM). A significant determination for pouchitis can be identified on basis of chronic ulcerative colitis. Total proctocolectomy can cure gastrointestinal symptoms of ulcerative colitis and pouchitis (Lohmuller et.al, 1990). Pouchitis is an inflammation in ileal reservoir or "pouch" and develop in patients who undergo surgical procedures. Bacteriological studies reveal that increased level of *Clostridium prifringens* in the colorectal tract causes pouchitis (Floch, M. H. 2018).

High dose of VSL#3 or *streptococcus thermopiles* and *Bifidobacterium* can be used for the treatment of active pouchitis. Some non-pathogenic strains of *E.coli* are also been used. (Gionchetti et.al, 2007).

8.3 Acute Infectious Diarrhea

An increased level of defecation i.e. three or more times per day or 200gm of stool per day lasting for less than 14 days results in nausea, vomiting, abdominal cramping, clinically significant systemic symptoms or malnutrition is known as 'acute diarrhea'. The causative agent for diarrhea are *salmonella, shigella, campylobacter* etc. There are some enterotoxigenic, enteropathogenic, enteroaggregative and enteroinvasive strains of *E.coli, Clostridium prifringens, Staphylococcus aureus, Bacillus cereus* etc. (Thielman et.al, 2004).

A meta-analysis on prevention of acute infectious diarrhea was carried out with consistent effects of *lactobacillus* species of *L. rhamnosus GG* and *L. plantarum strain 299v* in infants and children in comparative placebo-controlled trails (Szajewska et.al, 2001). A study on infectious diarrhea was carried out for children up to 4-60 months, diarrheal stool samples were examined with *Rotavirus, Adenovirus, Entamoeba histolytic, Salmonella, Shigella, Campylobacter, Clostridium difficile, Cryptosporidium* and some parasites. The role of *B. lactis B94* plus 900mg inulin as a synbiotic play significant role in treatment for shorten duration acute watery diarrhea (Islek et.al, 2014).

9. CONCLUSION

The use of probiotics is now leading above the bench mark. Scientific evidence indicates that an unbalanced intestinal microbiota can contribute in development of many diseases and infections. Thus, the emerging health claims and guidelines for a beneficial probiotics depends on the selection of strain with species specification. The role of probiotics organism in various health issues have witnessed as a merging tool. The preventive cure for several infectious disease has made probiotic the wholesomeness part of life. The combination of probiotic and dietary fibers show symbiotic effects. Thus, the advance in gut microbiota interaction in host, emphasize the overall prospective for a healthy host immune system. Also, the mechanism behind these health effects are being elucidated through *in vitro* and *in vivo* animal studies which are formulated on the selection criteria for probiotics. Also a personalized approach towards incorporation of probiotics in food or pharmaceutical formulation is noteworthy. However, particular focus on potential benefits for healthy consumers still need further investigation for proposed beneficial effects.

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