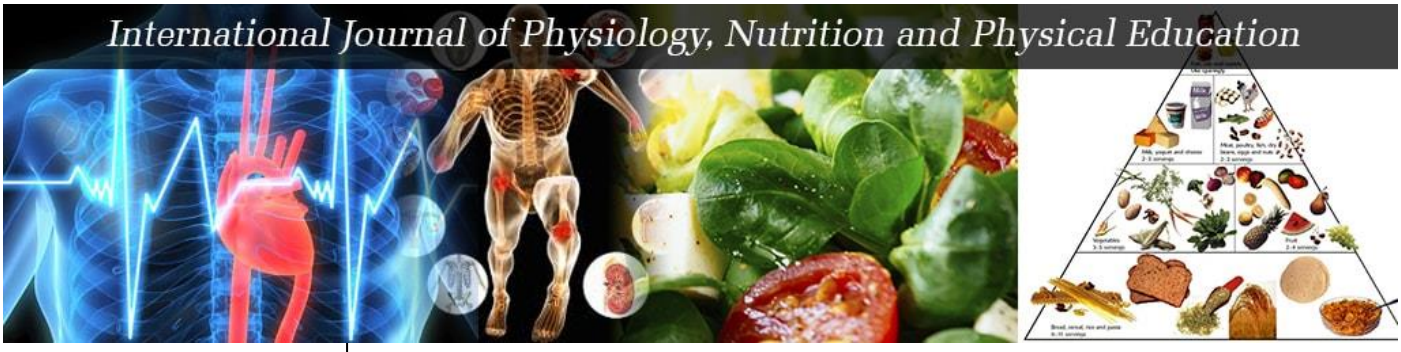

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Benefaction of probiotics in human gastro intestinal tract

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Abstract
In last two decades probiotic bacteria have become most popular due to continuously enlarging scientific research and evidences based on its beneficiary effects on human health. According to previous research work probiotics have documented health benefits outside the gastrointestinal tract; digestive health remains key benefits for probiotics. Recent advances in technology have made more concentrated in-depth analysis on the intestinal microbiota. Generally these probiotics will not only cure or prevent disease, but will mainly focus at maintaining health and reducing risk for disease. Along with the reducing risk factor these probiotics can exert health benefits in people suffering with diarrhoea, constipation, gastro intestinal mucositis and inflammatory diseases of the intestine. Even though maximal mode and mechanism of probiotic action is known, there remains a challenge to identify specific and mixed combinations of strains for explicit health benefits. Intestinal microbiota compositions and activity of genera's *Lactobacillus*, *Bifidobacterium* and *Saccharomyces* are identified and we may focus on new or existing health targets from new probiotics strains other than strains available in market. The main aim of this review is to update the probiotic bacteria beneficiary properties in gastrointestinal health.

Keywords: Benefaction, probiotics, human gastro intestinal, *Lactobacillus*

Introduction
Elie Metchnikoff first proposed the concept of probiotics in 20th century that ingested microorganism could confer health benefits to the host (NCCAM. 2012) [1]. Food and Agriculture Organization/World Health Organization working group and International Scientific Association for Probiotics and Prebiotics recently reaffirmed: live microorganisms that, when administered in adequate amounts, confer a health benefit on the host (Hill C *et al*., 2014, FAO/WHO 2002) [2, 3]. The definition of probiotics focuses on three major points: 1) viability of the microbes, 2) the dose amount 3) the registered health benefits.

Viability of Microbes
Maximum number of probiotics belongs to genera *Lactobacillus* and *Bifidobacterium* and some are *Saccharomyces* and other genera. But these strains require viability until the end of the shelf life. Consumption of probiotics is mainly under two forms: as a food and as a dietary supplement. In general foods having high water activity shows high fermentation capacity which lowers pH. Those foods should require freeze storage and will have limited shelf life (weeks, months or years). In dietary supplements, even though water activity is low the product has to be stored at ambient temperature conditions and shelf life is up to 2 years. Sufficient dose is needed to the host supplement until the end of the probiotic microbe shelf life. And this should be mentioned on the product, about the amount of viable microbes at the time of product manufacture.

Dose amount
Dose is also one of the important criteria in probiotic supplement. In general dose should be at least 10^9 CFU (Colony forming unit), as per the Health Canada dose may also have 10^7 CFU (Albers R *et al*., 2013) [4]. But usually dosage mainly depends on the specific strain and its combinations. Hence dosage amount have been documented to administrate health benefits to the host.

Health Benefits

Finally health benefits is another important factor in food supplement which are used to treat or prevent a broad range of human diseases, reducing risks and syndromes. Along with this probiotics have been proposed for future applications. Health benefit will be explained as an improvement in a clinical outcome which was not considered as change in the microbiota composition or certain immune markers (Glanville J *et al*., 2015) [5].

Safety of Probiotics

Even though safety is not mentioned in the probiotic definition it is evident that probiotics should be non pathogenic, documented, identification has to be carried out by the molecular and advanced techniques. Now-a-days this molecular identification is more cost effective so general population are moving towards the commercial strains. Lactobacillus and Bifidobacterium are non pathogenic and safe for the general population. For patients with poor health and immune status specific strain (commercial) should be provided based on risk consideration.

History of Probiotics

Function of gut microflora was completely unknown at the beginning stage of 20th century. Later Nobel Prize winner Metchnikoff in 1908 linked the health and stability to consumption of bacteria available in yoghurt (I.I. Metchnikoff and P. Chalmers Mitchell *et al.*, 1910, I.I. Metchnikoff 2004) [21, 22]. In 1907 he identified that bacteria responsible for yoghurt fermentation are *Lactobacillus bulgaricus* and *Streptococcus thermophilus* and this ingestion of yoghurt gives beneficiary effect in maintaining health. *Bifidobacteria* in breast-fed infants plays an important role in maintaining good health and clinical benefits by modulating the gut flora in infants against gastrointestinal disorders (Tisser H 1906) [23]. H. Cheplin in 1920s reported that *Lactobacillus acidophilus* from milk has therapeutic effects that aids in digestion mechanism (H. Cheplin and L. Rettger 1922) [24]. *Lactobacillus acidophilus Shirota* was first product later named as *L.casei Shirota* developedby Yakult Honsha Company, the researcher selected this strain of intestinal bacteria that could survive in gut (*L.casei* strain Shirota 1998) [25]. In 1950s for the treatment of scour (*Escherichia coli* infection) in pigs, probiotics drug was used which was recommended by United States Department of Agriculture (Orrhage *et al.*, 1994) [26]. Finally at the end of the decade, it was concluded that gut/intestinal microbiota have several health benefits, cure and protective against harmful pathogens (F. Guarner, J.R. Malagelada 2003) [27]. Foods containing *Lactobacillus acidophilus*, *Bifidobacterium* and *L.casei* provide health benefits when they were supplemented and it was recorded. Yoghurt starter cultures *Streptococcus thermophilus* and *L.delbrueckii ssp*. *bulgaricus* also shows some health benefits, even though they are natural survivals of the intestine. Serum cholesterol level was decreased when *Lactobacillus acidophilus* was added to the infant formula (Harrison *et al*. 1975) [28] and in adult human serum cholesterol level was in control (Gilliland *et al*. 1985; Buck and Gilliland 1994, and Gilliland and Walker 1989; Gill and Guarner 2004) [29, 30, 31, 32]. World Health Organization specified that probiotics are most important to develop immune defence system.

Mechanism of Probiotics

Mechanism of probiotics is not clear till now. Gastrointestinal tract plays main role which is an intermediate between the host and the environment. These intestinal epithelial cells have ability to differentiate between pathogenic and non pathogenic bacteria based on the presence of flagella (Borchers *et al*. 2009) [33]. Probiotics have multiple mode of action which include 1) Inhibiting the growth of pathogenic bacteria in intestinal and epithelial cell lines; 2) Probiotics grow by attaching to the colon and increase the barrier function of GI tract mucosa by helping in reducing risk of intestinal and food allergies; 3) Probiotics secrete antimicrobial compound bacteriocins; 4) They increase the activity of immunoglobulins mainly immunoglobulin A; 5) Probiotics increase the ability of interferon and develop peripheral blood monocytes; 6) Probiotics have capability to produce proteolytic enzymes which digest the bacterial toxins; 7) They potentiate intestinal immune response to viral infection; 8) Alteration of intestinal immune response by modulating cytokine profiles and control the inflammatory effects; 9) Modulation of microbial flora by acidification of the colon by nutrient dietary; 10) Intensification of epithelial barrier function; 11) Decrement of Visceral function, spinal afferent movement and stress reactions. (S Sonal *et al*., 2007; Borchers *et al*. 2009; Lin *et al*. 2008; Vanderpool *et al*. 2008; Lawton *et al*. 2007; Quigley and Flourie, 2007; Yan *et al*. 2007; Focareta *et al*. 2006; Makras *et al*. 2006; Roselli *et al*. 2006; Candela *et al*. 2005; Collado *et al*. 2005, 2007; Cotter *et al*. 2005; Matsumoto *et al*. 2005; Paton *et al*. 2005; Sherman *et al*. 2005; Smits *et al*. 2005; Sturm *et al*. 2005; Hart *et al*. 2004; Mukai *et al*. 2004; Pathmakanthan *et al*. 2004; Servin, 2004; McCarthy *et al*. 2003; Pena and Versalovic, 2003; Borruel *et al*. 2002) [33-57].

Health benefits of probiotics in Gastro intestinal tract

Stomach, small intestine and large intestine are the three major sections in gastro intestinal tract and every section has its own specific microorganisms (Savage, D. 1977, Simon, G.L. and Gorbach, S.L. 1984, Dethlefsen, L., *et al.*, 2006) [6-8]. In this aerobic gram-positive microorganisms (<10^3 CFU/g) are colonized majorly in stomach region and small intestine is inhabited by the following strains *Lactobacillus*, *Bifidobacterium*, *Bacteroides, and Streptococcus* (10^3 - 10^4 CFU/g). And finally the large intestine is owned by the genera *Bacteroides*, *Fusobacterium*, *Lactobacillus*, *Bifidobacterium*, and *Eubacterium* in large numbers (10^{11} - 10^{12} CFU/g). Many scientists communicated the effects of probiotic (LAB Montville, T.J. and Matthews, K. 2005) [8]. List of species involved are *Lactobacillus acidophilus, L. casei, L. johnsonii, L. fermentum, L. rhamnosus, L. plantarum, L. reuteri, L. salivarius, L. paracasei, L.delbrueckii subsp. bulgaricus, Saccharomyces boulardii, Streptococcus thermophilus, Bifidobacterium lactis, B. longum, and B. breve.* These probiotic strains probably exert a dual effect, prevention and reducing the risk of intestinal colonization with pathogenic microbes (Arvola, T *et al.*, 1999) [10]. Otherwise interact with the gut- associated lymphoid tissue (GALT) to block the inflammatory effects and improve the tolerating capability (Turcanu, V. and Lack, G. 2006) [11]. Based on distant and specific strain reaction the beneficiary effect of probiotics is examined (Ebel, B *et al.*, 2014) [12]. The Beneficiary effects which include treatment of acute diarrhoea associated with pathogenic strain rotavirus (Isolauri, E *et al.*, 1995), ulcerative colitis (Ishikawa, H *et al*., 2003, Kruis, W *et al.*, 2004) [13, 14], diarrhoea and infections caused by the another two most prominent pathogens *Clostridium difficile* and *Helicobacter pylori* (McFarland, L.V *et al*., 1994, Nista, E.C *et al*., 2004,

Wang, Y.W *et al*., 2004) [15-17]. Recent research studies registered that probiotics prevent antibiotic associated diarrhoea in children (Szajewska, H *et al*., 2006) and lactose digestion improvement (de Vrese, M *et al*., 2001). By using *Lactobacillus* and *Bifidobacterium* probiotics in the intestine reduces the effect of necrotizing enterocolitis in preterm infants (Lucas, A. and Cole, T.J. 1990) [18]. Some scientific reports suggested that *Lactbacilus rhamnosus* GG and *Bifidobacterium lactis* BB-12 are used for prevention and *Lactobacillus reuteri* SD2222 are recommended for treatment to obtain beneficiary effects to human health (Reid, G *et al*., 2003) [19]. By administration of probiotics to the babies <1500g, leads to reduction of the incidence and severity of necrotizing enterocolitis (Rohan, T. and Wainwright, L. 2014) [20]. In children abdominal pain related with functional gastrointestinal disorders (abdominal pain, vomiting and aerophagia) can be cured by giving supplement of *Lactobacillus rhamnosus* GG, *Lactobacillus reuteri* DSM 17938 and *Lactobacillus reuteri* VSL#3 provides best treatment. At last probiotics are good candidates to attain novel oral vectors for gastrointestinal functions and for successive treatments. Following literature clearly explains how probiotics are used in intestinal disorders and its functional activities.

Probiotic function in Intestinal bowel disorders

Probiotics theory recommends supplementation of the intestinal microbiota with specific type f microbes which has colonizing characteristics and boost up the health (Reid G *et al.*, 2011; Varankovich NV *et al.*, 2015, Pandey V *et al.*, 2015) [58-60]. Probiotics restore the balance required for intestinal microbiota, which helps in proper digestion and intestinal metabolic functions. Many researchers conducted studies on irritable bowel syndrome (IBS) (Ki Cha B *et al*., 2012; Kruis W *et al*., 2012; Pineton de Chambrun *et al*., 2015; Sisson G *et al*., 2014; Yoon JS *et al*., 2013; Yoon H *et al*., 2015; Yoon JS *et al*., 2014; Ducrotte P *et al*., 2012; Gawronska A *et al*., 2007; Francavilla R *et al*., 2010; Bauserman M and Michail S 2005) [61-72] and few worked on chronic idiopathic constipation (CIC) (Koebnick C *et al*., 2003; Waitzberg DL *et al*., 2013; Yang YX *et al*., 2008; Kim SE *et al*., 2015; Mazlyn MM *et al*., 2013; L SK Hilli L *et al*., 2006) [72-77], identification of mixtures of strains in functional diarrhea, functional abdominal pain (FAP) (Gawronska A *et al*., 2007; Francavilla R *et al*., 2010; L SK Hilli L *et al*., 2006; Kalman DS *et al*., 2009) [69, 70, 77].

In IBS five probiotic strains are having high efficiency and showing better data. Clinical studies have been well designed on *Bifidobacterium infantis* 35624 (O'Mahony L *et al*., 2005; Whorwell PJ *et al*., 2006) [78, 79]. In 77 patients with IBS, research observed that expressive decrement in the abdominal pain, bloating, bowel movement and regularization of interleukin levels in the patients by taking the *Bifidobacterium infantis* or *Lactobaillus salivarius* UCC4331 when correlated with the placebo (Whorwell PJ *et al*., 2006) [79]. Further studies also conducted in these strain by incrementing in pain at 4th week with *Bifidobacterium infantis* 35642 group versus placebo group (1.73 vs 1.48 respectively, $P<0.03$). Ki Cha B and along with the co-authors evaluated that significant improvement in producing competent relief of IBS over placebo and also increment of stool consistency in IBS-D patients when probiotic mixture containing *Lactobacillus plantarum*, *Lactobacillus rhamnosus*, *Bifidobacterium breve*, *Bifidobacterium lactis*, *Bifidobacterium longum* and *Streptococcus thermophiles* are supplemented to the patient during the study period (Ki Cha B *et al*., 2012) [80]. Based on the individual studies complete or total review in the IBS-C subgroup reports that some preliminary results showed that the fermented dairy products containing *Bifidobacterium lactis* DN-173010 along with *Streptococcus thermophilus* and *Lactobacillus bulgaricus* which are classical yogurt starter can activate gastrointestinal transit and increase distention and all IBS signs and symptoms severity after 4-week (Agrawal A *et al*. 2009) [81] and 6 week (Guyonnet D *et al*., 2007) [82] period of treatment.

Probiotics in ulcerative colitis

In last two decades several studies were conducted in UC comparing probiotic therapy with placebo or standard care. These studies can be divided into two groups; investigated induction of remission in active UC, and those that investigated maintenance of remission. Different probiotics strains are compared in different dosages, with different outcomes which were greatly differing in their design and studies.

Induction of remission in active ulcerative colitis

Based on the recent studies maximum research was done to evaluate with *E.coli Nissle* 1917 and VSL#3 (Nagasaki A *et al*., 2010) [83].

***E. coli Nissle* 1917**

Escherichia coli, anon pathogenic strain, prevent and reduce the growth of pathogenic bacteria. It slows down the colonic mucosal damage and decrease epithelial barrier function, which leads to increase in colonic healing (Chibbar R and Dieleman LA 2015) [84].

VSL#3

Eight bacterial strains *Streptococcus thermophiles*, *Bifidobacterium breve*, *Bifidobacterium infantus*, *Bifidobacterium longum*, *Lactobacillus acidophilus*, *Lactobacillus bulgaricus*, *Lactobacillus casei* and *Lactobacillus plantarum* are included in VSL#3. It maintains the host immune response, increase epithelial permeability and improves mucus production (Huynh HQ *et al*., 2009; Sood A *et al*., 2009) [85, 86]. Out of eight VSL#3 studies, six studies are with adult patients and two pediatric in patients with active UC. (Huynh HQ *et al*., 2009; Sood A *et al*., 2009; Bibiloni R *et al*., 2005; Miele E *et al*., 2009; Ng SC *et al*., 2005; Soo I *et al*., 2008; Tursi A *et al*., 2004;) [85-91].

Pancreatitis

In mechanism of infectious complication in cirrhosis, bacterial translocation is the major causative action in the late phase of severe acute pancreatitis where in severe sepsis and multiple organ failure. Over production of pro-inflammatory cytokines, bacterial over growth and /or distribute motility, mucosal barrier (Besselink MG *et al*., 2004; Van Santvoort HC *et al*., 2006) [93, 94] are the reasons for bacterial translocation which can be prevented by intake of probiotics. In patients with non-biliary pancreatitis, researcher observed that by usage of *Lactobacillus plantarum* 299 reduction in infection of pancreatic necrosis with live *Lactobacilli* (5%, n=22) than with heat killed *Lactobacilli* (30%, n=23). In another study when compared to placebo and with sham operation these *Lactobacillus plantarum* actively reduces the infection of pancreatic necrosis in experimental acute pancreatitis which was induced by isolation and ligation of the biliopancreatic duct (Mangiante G *et al*., 2001) [96].

Conclusion

From the past four decade, people are extensively using antibiotics to improve the growth and development and as a preventive process in human to control diseases and consequently, to improve their growth results. Now-a-days non pathogenic eco-friendly probiotics strains are introduced which acts as beneficiary to the host against disease resistance, enhance the growth and immunity development. Probiotic bacteria is broadly using in various GI and liver diseases, mostly for intestinal bacteria which when involved in their pathological effect. Administration of these probiotic to the host in intestinal, pancreatitis and chronic liver disorders is mostly based on the animal data and human trials have to be awaited. Different effect has been observing from different probiotic strain, further insight into disease entities. And role of probiotic strains is to be well known which is able to select well-characterized strains with specific health benefits.

Several probiotics are available at commercial and standardized level that can be used for human health development. But further research should be performed to use these probiotic in the reliable way, which is most advantageous and simplify to test the following criteria;

1. To study their mechanism of mucosal adhesion
2. Their clinical features of human health to be studied.
3. To identify the technical data like probiotic strain stability, viability in products and bacteriophage resistance.
4. To study their antibiotic resistance pattern.

Conflicts of interest

All authors have none to declare.

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