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Research Article

Probiotics: A Comprehensive Review on the Impact of Gut Imuno-Modulation

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ABSTRACT

Although the host by itself develops an immune response against the invading pathogen, it is not always sufficient to get rid of the bacterium completely. Evidence indicates that gut microbiota has a major impact on host immunity. Gut is a key player in immune health which constantly gets exposed to numerous toxins. The gut microbiota comprises of more than 400 species of bacteria. This wide range of bacterial species provides a symbiotic relationship between the gut and immune cells of the body. Current research has shown the potential of probiotic in the gut health and bowel diseases. Effects of probiotics have been observed in the enhancement of both innate and adaptive immunity. While there is a considerable amount of studies on the characterization and formulation of probiotics, there is still a translational gap that owes to the challenges that confront during a disease symptom. This chapter will discuss on the fundamental issue relating to the gut health and host immune response influenced by probiotic strains.

Keywords: *Probiotics; Immunity; Beneficial microorganism; Health; Gut microbiota*

INTRODUCTION

The concept of human microbiome and the ecological community present in symbiosis with host was first led by Lederberg and McCray in the year 2001[1]. The microbial community present in the gut is dynamic and majorly comprises of bacteria and firmicuites. This leads to a potential chance for the host to acquire a large array of disease ranging from a simple irritation in bowel to metabolic disorder [2]. The introduction of beneficial organism has complemented a lot to the health of the host. The discovery of probiotics was first proposed by Elie Metchnikoff, while she observed a prominent connection between longevity of Bulgarian population to ingestion of fermented milk [3].These beneficial microorganisms also termed as 'probiotics' includes strains such as *Lactobacillus, Bifidobacterium* and also, some *Propionibacterium.* The probiotics were earlier classified according to morphology and phenotyp as genera *Betabacterium, Betacoccus, Microbacterium, Streptobacterium, Streptococcus, Termobacterium, Tetracoccus*. However, the only strain that is retained is *Streptococcus*, whereas most of the others have been categorized into *Bifdobacterium*, *Lactobacillus* and *Enterococcus sp*. Owing to its lactic acid fermentation process from the sugar substrate, the probiotics are termed as lactic acid bacteria (LAB). Developing a consortium of different probiotics has been successful in the past few years. These probiotics has also increased the punch of treatments in multiple disease symptoms (Figure 1).

Figure 1: Activities of probiotics

Probiotic intervention has a promising effect on immune function by altering the imbalance in intestinal homeostasis. Since the advent of probiotics, it has been marketed widely and consumed as a dietary supplement. Modulation of host immunity is also credited as the most claimed benefits of consumption of probiotics.

Host factors have been shown to modulate the genes associated with probiotic bacteria [4]. Multiple mechanisms have been conferred in association with the beneficial effects of probiotics, particularly involving gene expression regulation in

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various tissues [5]. Major mechanisms that influence human health are preventing the host from pathogenic bacteria, modulation of immune system, activation of barrier function and metabolic function [6]. Albeit the increasing evidence on the regulation of host immune system, the fate of probiotics after ingestion and the molecular mechanism is still unknown and has a big lacuna in the study area. This review emphasizes on the molecular targets for the probiotics that exert host immune responses, and mechanisms of probiotics in deterrence and cure of various disease.

MOLECULAR MECHANISMS OF PROBIOTICS

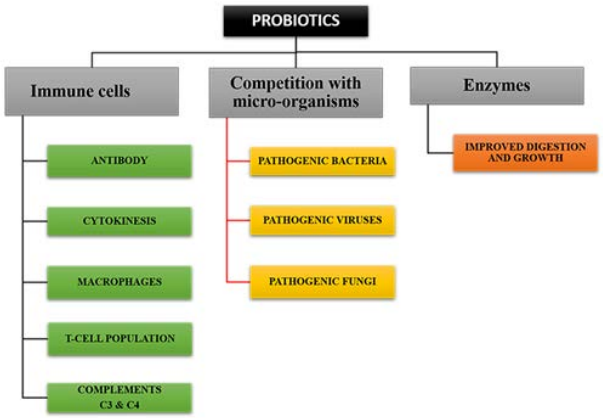
Probiotics impact on intestinal mucosa

One of the largest interfaces between the host, environment and the immune cells in human body is the gastrointestinal tract (GIT) that is spread up to 250-400 m2 of the total body space. The intake of food along with a large quantity of microorganisms from the ecosystem imposes a colossal risk on gut integrity. The body houses at least 1000 different species of microorganisms including bacteria, archaea, viruses, and other eukaryotic microbes known and holds 150 times additional microbial genes in comparison to the entire human genome. To maintain the gut integrity there needs a balance in the composition of microbial population.

The paradigm shift of gut microbiota

The impact of human health in terms of gut microbiota was focused in the past two decades. The physiological processes such as strengthening and shaping the intestinal epithelium, generating energy, and regulating host immunity aid the host by the presence and the mixture of microbial niche. Any disturbances in these functions will lead to disruption of the microbial composition creating dysbiosis [7]. The microbial composition determines the immune competence exhibited by the host. Ever since the birth, the GIT is prone to colonization of microorganism, especially bacteria, and has a high risk of illness, which subsequently provides an opportunity for antibiotic treatment causing chaotic shifts in the microbiota. Inclusion of probiotic diets confers healthy microbial population in the gut, modulates immune system, strengthens immune system by nutrition utilization and resistance against infection [8,9] (Figure 2). In spite of all these advantages, there is very less research evidence for consumption of specific probiotics.

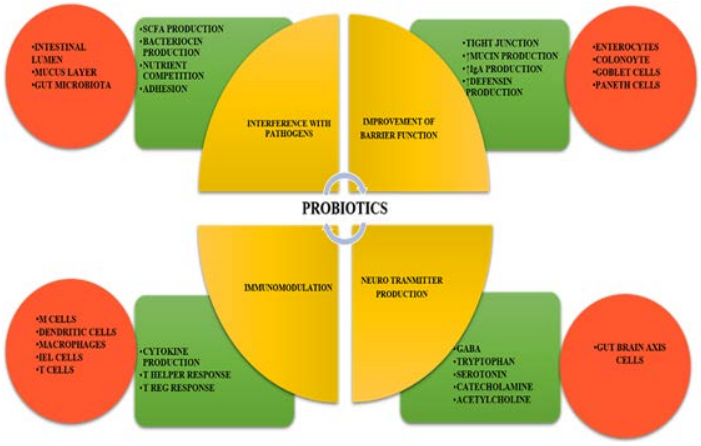
Figure 2: Flow chart for probiotics



At the first instance, study suggests that probiotics display inflammatory effects to reflect the immune response between host and its microbiota through a process mediated by toll like receptors [10]. *Bifidobacterium longum spp longum* 35624 is detailed for its anti-inflammatory effects associated with a containment of proinflammatory and inhibition of anti-inflammatory cytokines in animal model [11]. A recent study has also revealed another species of *Bifidobacterium* demonstrated that nativeness of the probiotic strain has a greater influence on ecological functioning [12]. Other than *Bifidobacterium*, probiotic strain Lactobacillus casei Zhang (LcZ) isolated from a fermented dairy product, koumiss, has the capacity to easen tropomycin induced food allergy caused by shell fish and has demonstrated the involvement of the tolerogenic immune cells in NF-ΔB signaling pathway [13].

The prime mechanism of action exhibited by probiotics in the intestinal mucosa are (i) competition of probiotics with pathogenic bacteria for the nutrition and adhesion sites, (ii) strengthening of epithelial lining (iii) immunomodulation, and (iv) influence on other organs of the body through stimulation of neurotransmitter [14] (Figure 3). High adherence property of probiotics aids in limiting the access of pathogens to enter the intestinal epithelium of the host cell surfaces which is primarily used for initiating the process of attack [15]. Along with that, probiotics produce antimicrobial substances such as bacteriocins which highly impacts on clinical strains. An additional benefit rendered by bacteriocins is its minimum level toxicity in oral mucosa when treated to host. Undeniably, many bacteriocins produced by LAB's, specifically, have been consumed in fermented foods as regular diet for generations. Involvement protein coding genes responsible for biochemical pathways can also be provided by probiotic bacteria, which in turn help in degradation of complex carbon or vitamin source and other essential molecules production. Certain receptor family like Toll-like receptors, Nod-like receptors or C-type lectin receptors, and RIG-I-like receptors present on immune and epithelial cells aids in favourable effects of probiotics. Interaction of these receptors with pattern recognition receptors play a pivotal role in maturation of antigen presenting cells, that in turn influence the effector cells like (Th1, Th2, or Th17) or regulatory (Treg). The important factor is that Treg is directly proportional to the functioning of intestinal homeostasis.

Figure 3: Types of probiotics



Achieving a positive effect on health through probiotics can happen by different actions such as inducing the immune response, amelioration of the nutritional state of the host, or those derived from the change of the gut microbiota. There has been a lot of preclinical studies on changes in gut environment composition of mice due to an introduction of probiotic bacteria. Few other studies have shown that probiotics can cause an alteration in definite bacterial populations, neither or nor with the help of

metabolic changes. Recent metagenomic approaches has facilitated in identifying the fecal bacterial population through the RNA sequencing of ingested *Lactobacillus rhamnosus, Lactobacillus paracasei or Bifidobacterium breve* strains [5]. Multispecies probiotic supplementation for Irritable bowel syndrome (IBS) was also reported to fluctuate the clostridium population and was related to alleviation of gastrointestinal symptoms. In this regard, a major finding in future probiotic research will be to utilize novel microbial cultivation strategies linked with healthy conditions in humans, which can be a whooping growth for the food and pharma industry.

Probiotics impact on autoimmune disorders

A considerable number of trials in humans and animals have been investigated to recognize the probiotic potential for inflammatory such as glomerulonephritis, hepatitis, ulcerative colitis and autoimmune diseases such as Rheumatoid arthritis (RA), multiple sclerosis, inflammatory bowel disease. There are two main routes for the immune system to be damaged in healthy individuals.

(i) Nullifying the effect of dysfunctional lymphocytes in the thymus before self-destruction of body cells

(ii) Inability of the immune system to interact with antigens, because of dysfunctional lymphocytes released into the mainstream.

The bout of inflammatory cells on differ in diverse autoimmune disorders. In Diabetes mellitus, the autoimmune system attacks the β cells of the pancreas activating an inflammatory reaction, thereby destructing the insulin production. A similar mechanism occurs in rheumatoid arthritis, the muscles and bones are deteriorated by the antibodies by forming a complex with globulin. In Graves' disease, Thyroid Stimulating Hormones Receptors antibodies are produced against the thyroid protein thyroglobulin, which results in the increase in thyroid synthesis and accompanying symptoms. One another example is Rheumatoid arthritis, a systemic autoimmune disease that leads to chronic inflammation in bone joints. The causatives of rheumatoid arthritis are Human leukocyte antigen (HLA) and environmental factors. Dysbiosis is considered to be a common symptom caused by the environmental factors and has consistently demonstrated a connection between the intestinal population and systemic immunity. In a study done by Zamani et al, the probiotic supplementation has shown significant difference in rheumatoid arthritis patients when compared to the placebo effect. Another report by Alipour et al. displayed that L. casei 01 supplementation decreased tender and swollen joint counts, affected the interleukin production and also diminished the levels of serum high-sensitivity C-reactive protein. Similar study by Mohammed et al. showed that treatment with probiotics decreased the proinflammatory cytokine IL-6 in rheumatoid arthritis patients than to their placebo-treated controls.

Multiple Sclerosis (MS) is a long-term disease that targets the central nervous system and its characterized under autoimmune disease. Many individuals with MS develop fatigue, sensory loss, and visual and mobility difficulties. Evidence has revealed that the use of probiotics could improve the gut microbial community, increase mucus-secretion, and also prevent the destruction of tight junction proteins via a decrease in the amount of lipopolysaccharides (LPS). Many autoimmune and inflammatory diseases have shown optimistic response to probiotic remedies. Thus, evolving evidence suggests a relationship between altered intestinal microbiota and rheumatoid arthritis, and we foresee that further studies will be needed to delineate the microbiota profiles which might contribute to RA and the potential for treatment with adjuvant probiotics.

Probiotics impact on Cancer

Probiotics has also been proven to enhance health boosting effects in chronic diseases such as cancer. The association between cancer cells and probiotics was first established in rats by Goldln and Gorbach, 1980. Even though cancer is considered as a multifactorial disease, they unanimously depend on the genetic factors and immunological factors related to the gut bacteria. Moreover, the stochastic piling of mutations, together with the cellular genomic instability, epigenetics, transcriptional and post-transcriptional intracellular changes, can pave way to the development of a molecularly varied bulk tumour to cancer cell clones, making it differentially sensitive to anticancer therapies.

A small change in diet can substantially eliminating the cancer cell proliferation. This is achieved by inhibiting the cell to cell communication, which is one of the most vital tools for the survival of cancer cell by introducing the probiotic bacteria. There are lots of reports that emphasizes on the effects of probiotic treatments in preventing the progression of several types of cancers including colorectal, liver, breast, bladder, colon, and cervical (Table 1). A reduction of procarcinogenic enzymes was found in colonic carcinogenesis in animal models. Given the diversity of inflammatory and immune response the fate of ingested bacteria in gastrointestinal tract is unspecified. A variety of chemical compounds produced by gut bacteria which affect intestinal cells, might transform into malignant carcinogenic metabolites. These pathogenic microorganisms induce alterations in epithelial-mesenchymal transition breaching the barrier. This aids the malignant cancer cell escape through the immune system and metastasize in various organs causing tumor promoting inflammation. The advent of metagenomics combined with Next Generation Sequencing (NGS) studies highlights the dual role of the gastro-intestinal microbiome suggesting it could either turn a tumor cell suppressive or oncogenic.

Colorectal, gastric, and esophageal cancers are the most common cancers that comes under gastrointestinal tract (GI) cancers.

Table1: Types of cell line along probiotics strains

S. No	CELL LINE	PROBIOTIC STRAIN	EFFECT	REFERENCES
1	Caco-2	*Bifidobacterium adolescentis SPM0212* *Enterococcus faecium RM11* *Lactobacillus fermentum RM28*	Decrease in cell proliferation	Kim et al., 2008 Thirabunyanon et al., 2008
		Lactobacillus rhamnousus GG *Bifidobacterium lactis Bb12*	Induction of apoptosis	Altonsy et al., 2010
		Bacillus polyfermenticus *Pediococcus pentosaceus FP3* *Lactobacillus salivarius FP25/FP35* *Enterococcus faecium FP51* *Lactobacillus planetarium A7* *Lactobacillus rhamnous GG* *Clostridium butyricum ATCC* *Bacillus subtilis ATCC 9398* *Lactobacillus pentouse B281* *Lactobacillus plantarum B282*	Decrease in cell proliferation	Ma EL et al., 2010 Thirabunyanon & Hongwittayakorn et al 2013 Sadeghi et al., 2014 Chen et al., 2015 Saxami et al., 2016
2	HT-29	*Bifidobacterium adolescentis SPM0212* *Bacilius polyfermenticus* *Lactobacillus plantarum A7* *Lactobacillus rhamnosus GG* *Bacillus polyfermenticus KU3* *Lactococcus lactis NK34*	Decrease in cell proliferation	Kim et al., 2008 Ma EL et al., 2010 Sadeghi et al., 2014 Lee et al., 2015 Han et al., 2015
		Lactobacillus casei ATCC 393	Induction of apoptosis	Tiptiri et al., 2016
		Lactobacillus pentosus B281 *Lactobacillus plantarum B282*	Decrease in cell proliferation	Saxami et al., 2016
3	SW480	*Bifidobacterium adolescent SPM0212*	Decrease in cell proliferation	Kim et al., 2008
4	DLD-1	*Bacillus polyfermenticus* *Lactobacillus paracasei* *Lactobacillus rhamnosus GG*	Decrease in cell proliferation	Ma EL et al., 2010 Orlando et al., 2012
5	NMC460	*Bacillus polyfermenticus*	Cell colony formation in cancer cells	Ma EL et al., 2010
6	HCT116	*Clostridium butyricum ATCC* *Bacillus subtilis ATCC 9398*	Decrease in cell proliferation	Chen et al., 2015
7	SW1116	*Clostridium butyricum ATCC* *Bacillus subtilis ATCC 9398*	Decrease in cell proliferation	Chen et al., 2015
8	LoVo	*Bacillus polyfermenticus KU3* *Lactococcus lactis NK34*	Decrease in cell proliferation	Lee et al., 2015 Han et al., 2015
9	AGS	*Bacillus polyfermenticus KU3* *Lactococcus lactis NK34*	Decrease in cell proliferation	Lee et al., 2015 Han et al., 2015
10	CT26	*Lactobacillus casei ATCC 393*	Induction of apoptosis	Tiptiri et al., 2016

Considerable research has verified that probiotics retains anti-proliferative or pro-apoptotic activities in GI cancers. A study done by Zhang et al 2018 also demonstrates that combination of brown rice and probiotics *L. acidophilus* and/or *B. animalis subsp. lactis* may suppress colonic preneoplastic lesions via regulating antioxidation and apoptosis in rats. A dysbiotic gut microbiota profoundly influences cancer pathogenesis thereby modulating both host's immune response and inflammation pathways. Earlier reports state that probiotic organism such as *Bifidobacterium adolescentis* SPM0212 and *Lactobacillus rhamnosus* strain GG (LGG) showed a substantial upsurge in proapoptotic characterisitics and inhibit human gastric cancer cells and three colonic cancer cells lines including HT-29, Caco-2 and SW 480.

Yet another study revealed the presence of Lactobacillus kefiri in kefir exibited apoptotic impact on myeloid leukaemia cell lines. In addition to it, the cell lines HT-29, MCF-7, AGS and Caco2 displayed decreased viability against Enterococcus lactic IW5 which was obtained from human gut [4]. Till date, there has been studies on established mechanisms in cancer prevention and treatment by probiotics which may include (i) variation of gut microbiota, (ii) enrichment of gut barrier functions, (iii) degradation of potential carcinogens (iv) protection effect of DNA damage of intestinal epithelium, and (v) improvement of immune and inflammatory system in the body. Irrespective of the observed advantages, larger

and controlled clinical trials are further needed to truly validate both the efficacy and the safety of dispensing selected species of probiotics during or following anti-cancer treatment.

PREBIOTICS IN HEALTH AND NUTRITION

There is a recent hype towards the concept of, an alternative approach for the consumption of food ingredients. Prebiotics are dietary fiber that is utilized by gut microbiota, especially probiotics. Albeit the presence of endogenous factors like mucin secretions can affect the microbial balance, the main source of energy comes from the host diet. Human diet is the chief source of energy for their growth. These non-digestible dietary substances are fermented by the beneficial intestinal microbes thereby acquiring the energy to persist in the environment from degrading indigestible binds of prebiotics. Besides that, the gut microbiota which is now working under the catalytic effect of prebiotic influences intestinal functions, such as breaking down of molecules for energy and retaining integrity of the intestine. In addition to it, they also restrain pathogens from colonizing in healthy individuals. This is mainly achieved through induction of some immunomodulatory molecules combined with antagonistic effects against pathogens by lactic acid that is produced by Bifidobacterium and Lactobacillus genera. The most conventional prebiotics that has been tested for the prebiotic function Galacto-oligosaccharides (GOS), Fructo-oligosaccharides (FOS), and Trans-galacto-oligosaccharides (TOS) are the most common prebiotics that has been tested for the prebiotic function.The outcome of fermentation of prebiotics produces short-chain fatty acids (SCFAs), including lactic acid, butyric acid, and propionic acid.

DISCUSSION

The key components produced by SCFAs are acetate, butyrate, propionate, metabolites and gases. Each of these fatty acids metabolizes in different organs, acetate in muscle, kidneys, heart, and brain, while propionate undertakes metabolism in the liver and is a neoglucogenic substrate that may prevent cholesterol synthesis and normalize lipogenesis in adipose tissue. On the other hand, butyrate is mainly metabolized by the colonic commensal bacteria act as substrate to perform different mechanisms like regulating cell growth and differentiatio. Other than these energy sources, SCFAs also presents many vital physiological functions, including, inhibiting the growth of pathogens, influencing the bowel motility, maintaining the luminal pH and reducing colon cancer by stimulating cancer cells apoptosis. Furthermore, SCFAs also aid in rising the population of regulatory T (Treg) cells and reducing production of proinflammatory cytokines in the large intestine, through G-protein coupled receptors (GPCRs). Altogether these entities result in an enhanced integrity of the intestine and maintain optimal intestinal immunity. Although the role of relative probiotic numbers is essential to maintain the optimal immunity balance. Evidence concerning the two most studied prebiotics, FOS and inulin, assists in resisting digestion by gastric juice and pancreatic enzymes in vivo. However, this negative effect is retrieved by selective effects on bifidobacteria and lactobacilli by impacting various aspects of bowel function through fermentation. There have been studies relating to commercial combinations of prebiotics and probiotics in the aspect of diarrhea. In which, a mixture of probiotic bacteria and prebiotic component were fed and checked for the colony forming unit wherein the results looked less impressive. These stark contrasts in results may be due to changes in gene expression and metabolism based on the composition and activity of gut microbiota after the administration of nutrients with prebiotics or probiotics. Furthermore, the health claims have to be substantiated with probable clinical trials.

CONCLUSION

The ability to focus on specific organisms in the large intestine for well-defined, health-promoting purposes would be of great significance. Diverse probiotic species have disclosed to prevent many degenerative diseases, including obesity, diabetes, cancer, cardiovascular disease, malignancy, liver diseases, and intestinal bowel disease. Though diets and different nutrients have reported to have an effect on gut microbiota communities' supplementary omics studies productively and markedly should be performed to elucidate the genetic makeup and the products obtained from the transcription. Efforts to utilize multiple omics platforms (metagenomis, met proteomics and metabolomics) would yield more light on how this complex framework functions. Furthermore, the identification of new probiotics and isolation from the microbiome and mixture of probiotic species would be a prime pathway for future studies to promote host health. This may also lead to establishment of enhanced functional foods to maintain synergism between the host and microbial niche.

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