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Short Communication

Role of Probiotics in Immune Regulation

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In the present era, the research has been more focused on the natural mechanisms for managing, treating and curing the human diseases due to the several side effects of the chemotherapeutic agents and synthetic drugs. One of such natural mechanisms has come up with the use of beneficial microbes called as 'Probiotics'. These microorganisms normally prevent infection and have a positive effect on nutrition. According to 'WHO' probiotics are the live microorganisms, which when administered in adequate amounts, confer a health benefit on the host [1]. Evidence has accumulated that certain probiotic microorganisms offer considerable health benefits for humans (Figure 1). However, one of the most important characteristics of probiotics is regulation of host immune response by which they are able to manipulate the host immune response towards the infectious microbes and can be useful in treatment of infectious diarrhea and day care related illness, antibiotic associated diarrhea caused by *Clostridium difficile*, inflammatory bowel disease, traveler's diarrhea, allergy, irritable Bowel Syndrome etc.

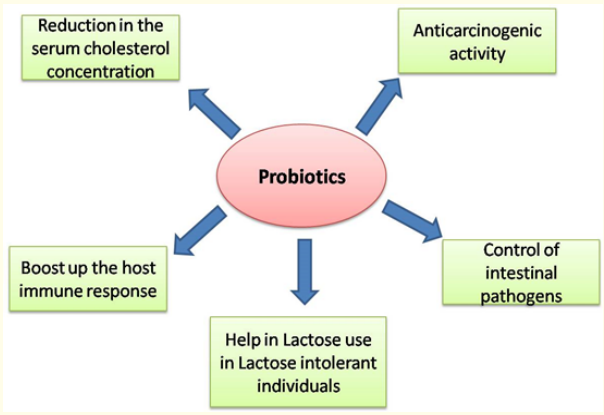

Figure 1: Health benefits provided by probiotics.

Probiotics are usually isolated from the commensal microflora that inhabits the skin and mucosas [2]. Probiotic stays in gastrointestinal tract (GIT) and the quantity and composition of microbial species vary in the entire GIT; however, species level diversity of microbes varies individual to individual [3].

Metchnikoff [4] first suggested that the consumption of lactic acid bacteria may benefit the human host's immune system. In addition to the major probiotic group of lactic acid bacteria, probiotic activity has been found to be associated with *Lactobacilli* (*LGG, gasseri, salivarius*), *Lactococci, Bifidobacteria* (*bifidum, longum, infantis*), *Streptococcus* (*thermophilus, cremoris, faecium, infantis*), *Enterococcus* (*faecium*), non-pathogenic *E. coli* (Nissle 1917), B*acillus coagulans* and *Saccharomyces* strains (*boulardii* and *cerevisiae*) [4,5].

One of the facts is that approximately 70% of our body's immune system is located in the GIT [6]. New born child have immature intestinal immune system and its development start when it come in contact with microbial antigens and diets [7]. Important effects of these microorganisms and their products have been demonstrated in immune system [8,9]. Probiotics in GIT do several physiological functions inside the body system, mainly metabolic, trophic, and immunologic functions [10]. GIT are loaded with millions and trillions of microbes where they degrade undigested carbohydrates to produce important immunoregulatory molecules such as short-chain fatty acids (SCFAs) and synthesizes essential vitamins [11,12]. Short-chain fatty acids affect immune responses and epithelial integrity via G protein–coupled receptors and epigenetic mechanisms [13]. Moreover, studies with germ-free (GF) animals suggested that the microbiota is necessary for the development and regulation of immunity in the gut where it prevents the development of inappropriate inflammation [14-16]. The administration of the probiotics (a mixture of *Bifidobacteria*, *Lactobacilli* and *Streptococcus salivarius*) was shown to have effect on suppressing intestinal inflammation in several experimental colitis models [17,18].

Lactobacillus casei have been shown to augment total and pathogen-specific secretory IgA levels upon infection in mice by stimulating B cell class switching to IgA [19]. However, specific antibodies against *L. casei* were not produced, indicating the non-responsiveness of the gut immune system to this beneficial bacterium. Moreover, in infant rabbits pretreated with *L. casei*, morbidity of subsequent EHEC (Entero-Hemorrhagic *E. coli*) infection was reduced due to increased mucosal levels of anti-EHEC and anti-Shiga toxin IgA antibodies compared with controls [20]. Further, *L. casei* down-regulated the transcription of a number of genes encoding pro-inflammatory effectors such as cytokines and chemokines and adherence molecules induced by invasive *S. flexneri.* This resulted in an anti-inflammatory effect that appeared mediated by the inhibition of the NF-κB pathway, particularly through stabilization of I-κBα [21].

In addition, several studies have reported that modifications in the proportions of microorganisms in the gut (qualitatively or quantitatively) and, consequently, in the concentrations of the compounds produced and released by them in the lumen, play a role in the development of pathological conditions including inflammatory bowel disease (IBD), colon cancer, and type 1 and 2 diabetes mellitus [8,9,22]. Probiotics exert different immunomodulatory effects on various immune components (Figure 2). Some of the compounds that have been implicated in the effects of microbiota on host cells are microbial-derived ligands of toll like receptors (TLRs) such as LPS and flagellin, which activate, respectively, TLR-4 and -5 and modulate distinct aspects of host metabolism and immune responses [16]. Moreover, long term association of commensal microbes within the GIT make them recognized by the innate immune system as harmless. Commensal microbes induce an unusual pattern of maturation of dendritic cells (DC) such that these retain the ability to drive Treg. Moreover, it is likely that immunoregulatory disorders commonly occur first in those individuals whose innate immune systems are least efficient at driving Treg. The increased regulatory dendritic cells (DCreg) and Treg induced by 'Microbes reside in gut' lead to two immunoregulatory mechanisms mediated in part by release of IL-10 and TGF-β. Recently, Min and Rhee [23] have reviewed the influences of microbiota on the development of the gut mucosal immune system which include gut-associated lymphoid tissues (GALT), mucosal Barrier, Th17 cells, Tregs, DCs, innate lymphoid cells, IgA-producing B Cells, and plasma Cells. In addition, the role of gut microbiota in immune homeostasis and autoimmunity has extensively been reviewed by Wu and Wu [24].

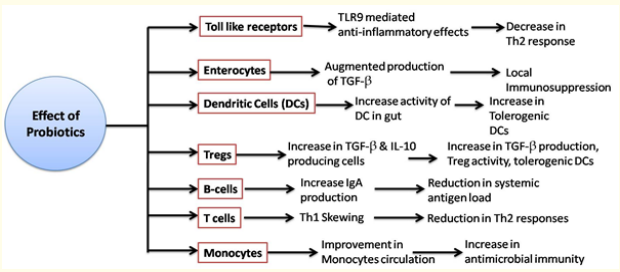

Figure 2: Immunomodulatory effects of probiotics.

Although microorganisms surprise us in so many ways yet it is very difficult to understand their role in manipulating the immunological mechanisms. Since, they take part in immune activation as well as immune suppression by triggering various kinds of cytokines and chemokines, their use in boosting immunity and suppressing the hyper-immune response is now taking a lead in managing several human diseases including autoimmune disorders [25]. However, their thorough knowledge for *in vivo* use, biosafety aspects and dose dependent effect in immunocompromized persons and new born babies still leave few questions on their commercial use. Hence, extensive investigations including basic biological studies, molecular and translational studies are warranted to understand the interaction between microbiota and its effect on host immune system by various mechanisms.

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