Review Article **Asian J Agri Biol, 2015, 3(2): 83-92.**

MODULATION OF IMMUNE SYSTEM BY TAKING PROBIOTIC BACTERIA: ESPECIALLY FOCUS ON LACTIC ACID BACTERIA

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ABSTRACT

The lactic acid bacteria are gaining more attention as probiotics, because they are generally recognized as safe for consumption. The lactic acid bacteria are commercially very important group of bacteria and have a lot of positive impact on the health of host. The literature studies showed that the lactic acid bacteria exert positive impact on the health to modulate the immune response and protect the host against enteric pathogenic microbes. The lactic acid bacteria enhanced the secretion of IgA and improved the activity of macrophages and T cells. These, also, enhanced the production of interferon's expression. In short, the consumption of lactic acid bacteria in food modulates the immune system by the secretion of IgA, prevents enteric infectious microbes, and improves the activity of interferon and interleukins.
Keywords: - Immune system, lactic acid bacteria, probiotic, mucosal immunity

INTRODUCTION

There is a strong correlation between the intestinal microflora and immune system. It is a common observation that the germs free organisms are more susceptible to diseases, meaning that the germ free organisms have poor or underdeveloped immune system. The germ free organisms have less immunoglobulin, IgA and less developed immune cells as compared to other organisms. However, when the normal microflora was given to the germ free organisms, they showed the normal development of immune system and also developed the resistance against various diseases. This study showed that the stimulation of microflora enhanced the development of immune system of host and the functional immune system was very important for the host as it protected the host against various diseases (Gill, 1998).

The immune system of an organism consists of various cell types and organs. The organs of immune system are lymph nodes, spleen, thymus and bone marrow. The cells of immune system are white blood cells (WBC). WBCs are further divided into phagocytes which provide nonspecific immunity and lymphocytes for specific immunity. The antigens interact with these cells and induce cellular immune response and humoral immune response mediated by the activated cells and antibodies. Various adhesion molecules enhance the interaction between immune cells and antigens. These activated cells discharge various kinds of cytokines inducing different immune responses. These immune responses can be evaluated by considering the number and level of various cytokines, antibody level, immune cells such as B cell or T cell and the study of various phagocytic activities. The lactic acid bacteria can be used to prevent the malnutrition, cancer and enteric infections. The results of various studies showed that the *Lactobacillus casei* can prevent the malnutrition, cancer and enteric infections by the secretion of IgA. The yogurt contains the lactic acid bacteria which inhibit the growth of carcinoma by enhancing the activity of IgA (Perdigon et al., 1995).

The lactic acid bacteria generally include the species of genera *Lactobacillus*, *Lactococcus* and *Bifidobacterium*. The lactic acid bacteria are generally considered nonpathogenic microbes and are beneficial to the human health. One of the major probiotic potentials of lactic acid bacteria is the enhancement of immune system by inducing the proliferation of immune cells and the synthesis of various antibodies by pathogenic microorganisms. The lactic acid bacteria are nonpathogenic and safe for human consumption that is why lactic acid bacteria are used in various dairy products.

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These bacteria are also used as the vector for the delivery of local vaccines. Various kinds of lipopolysaccharides secreted by these bacteria enhance the production of interleukin 6 (IL-6), IL-10 and cytokines tumor necrosis factors alpha (TNF-α). These lipopolysaccharides contribute in the defense mechanism of host (Mercenier et al., 1996; Lidbeck and Nord, 1993; Miettinen et al., 1996).

The lactic acid bacteria in food have the ability to colonize with intestinal cells. This ability is very important for enhancing the immune system of host. In vitro, the *Lactobacillus acidophilus* stick to the enterocytes that why it is the hypothesis that the lactic acid bacteria can interact with the immune cells in vivo and enhance the immune system of host. However the *Bifidobacterium bifidum* is another most important immunomodulator strain of lactic acid bacteria. The host was divided into two groups and supplied the *L. acidophilus* and *B. bifidum* in food to study the lymphocyte and phagocyte activity in blood of the host. There existed no change in the lymphocyte but the phagocytic activities changed in the blood of both host groups (Schiffrin et al., 1997). The induction of immune response is not easy mechanism, due to the oral tolerance development but under certain condition lactic acid bacteria can be used to induce the immune response. The some lactic acid bacteria induce the specific immunity and other lactic acid bacteria can induce the inflammatory immune response (Perdigon et al., 1999).

Now-a-days, the vaccines and healthy nutrition are used to prevent the infectious diseases. The causes of death from the infectious disease can be reduced by the improvement of nutrition. However, lactic acid bacteria showed strong relationship among the disease, nutrition and the immune system, and the massive use of vaccines reduced the risk of spreading various infectious diseases all around the world. The lactic acid bacteria can be used to improve the nutrition as well as for the development of vaccines. The lactic acid bacteria can be used as the probiotic food which has the ability to stimulate the immune system of host. The consumption of probiotic food increases the resistance against the various infectious diseases (Alvarez et al., 2007; Alvarez et al., 2009b).

However, the scientific study on molecular biology is unable to develop genetically modified strains of lactic acid bacteria expressing the antigens from various pathogenic microbes. The recombinant lactic acid bacteria strains can be used to induce the immunity of host against different pathogenic microbes. This review deals with the scientific literature regarding the use of recombinant or naturally occurring lactic acid bacterial strains to develop the immunity.

Improvement of immune system by lactic acid bacteria

Various studies show that the consumption of lactic acid bacterial strains having probiotic potential and exert beneficial effect on the health of host by using the immunomodulator action (Alvarez et al., 2009a). Although, most of the lactic acid bacteria strains develop immune response against various GIT tract pathogens. However some lactic acid bacteria strains have immunobiotic effect and develop mucosal immunity against wide range of pathogens. The probiotic lactic acid bacteria induce the immunity either by the activation of lymphoid cells and sending the signal through the innate cell surface recognition receptor and by using these two mechanisms the lactic acid bacteria enhance the systemic or local immune response. However the probiotic lactic acid bacteria strains can be used as immunotherapy for cancer, allergy and various other infectious diseases (Cross, 2002). The table 1.1 summarize the immunomodulation effect of various probiotic lactic acid bacteria strains.

Table 1.1: Supplementation of food containing lactic acid bacteria strains and their effect on immune system

Route	Lactic acid bacteria Strains	Effect on Immune system	References
Oral	*Lactobacillus casei* & *acidophilus*	Decrease pathogen translocation and increase the serum antibody level against Salmonella	(Perdigon et al., 1990b; Macías et al., 1992)
Oral	*Lactobacillus rahmnosus* & *Bifidobacterium lactis*	Decrease pathogen translocation, increase survival, enhance phagocytic activity	(Gill et al., 2001; Shu et al., 2000)
Oral	*Lactobacillus casei*	Enhances the phagocytic activity and serum IgA level, increases survival, decreases pathogen translocation	(Paubert-Braquet et al., 1995; Perdigon et al., 1990a)
Oral	*Lactobacillus casei*	Lower the burden of pathogen in GIT tract, enhances the pathogen-host specific response	(De Waard et al., 2002)
Oral	*Bifidobacterium bifidum* & *Bifidobacterium infantis*	Reduce diarrhoea, enhance IgA level	(Qiao et al., 2002)
Oral	*Bifidobacterium lactis*	Enhances the phagocytic activity, high efficiency of food conversion, low morbidity index	(Shu et al., 2001)
Oral	*Bifidobacterium lactis*	Enhances the phagocytic activity, low morbidity index, enhance IgA level , low pathogen load in somatic tissue	(Shu and Gill, 2001)
Oral	*Lactobacillus casei*	Reduce diarrhea, Lows the burden of pathogen in GIT tract, enhance IgA level	(Ogawa et al., 2001)
Oral	*Lactococcus lactis*	Enhance IgA & IgG level, enhances interleukin level, high phagocytic activity	(Villena et al., 2008)

The immunomodulator characteristics of probiotic lactic acid bacteria are strains dependent and dose of the specific strain. The mice were treated with the Lactobacillus casei for various time periods. After treatment the mice were infected with the *Streptococcus pneumoniae* and the immune response was determined after fifteen days of infection. The mice group feeding with *Lactobacillus casei* showed low number of pneumococci within the lung and also developed fast response against the *S. pneumonia* as compared to the control group. The mice feeding with *L. casei* showed enhancement in the phagocytic activity due to the nitro blue tetrazolium and myeloperoxidases activity within the lung of mice. Also the mice feeding with the *L. casei* showed higher level of IgG and IgA as compared to control group of mice. Furthermore this group of mice normalized the balance between the interleukin-10 and tumor necrosis factor. The conclusion of this study is that the mice group feeding with the Lactobacillus casei induced very strong immune response and inflammatory response against various infections (Racedo et al., 2006).

Taking in to the *L. lactis* induced the innate and specific immunity against wide range of pathogen that causing damage to the lung of host. The host feeding with the *L. lactis* showed the regulation of tumor necrosis factors increased the level of neutrophils level within alveolar space and higher phagocytic activities as compared to the control group of host. The *L. lactis* enhanced the production of interleukin-4, interleukin-10, higher level of IgG and IgA during the infections. The conclusion of this study is that the orally supplementation of *L. lactis* improves the resistance against various lungs infections (Villena et al., 2008).

Yogurt was prepared containing *L. bulgaricus* and *L. thermophilus* strains with immunomodulation activity. The mice feeding with *L. bulgaricus* and *L. thermophilus* improved the resistance against various pathogens and developed innate and specific immunity as compared to control group of mice. The result of his studies shows that the consumption of yoghurt enhanced the respiratory immunity against wide range of pathogens. However, the *L. bulgaricus* and *L. thermophilus* also enhanced the IgG and IgA serum level as compared to the control group of mice (Racedo et al., 2009).

Mostly the treatment of lactic acid bacteria enhanced the both kinds of immune response in respiratory tract (Figure 1.1).

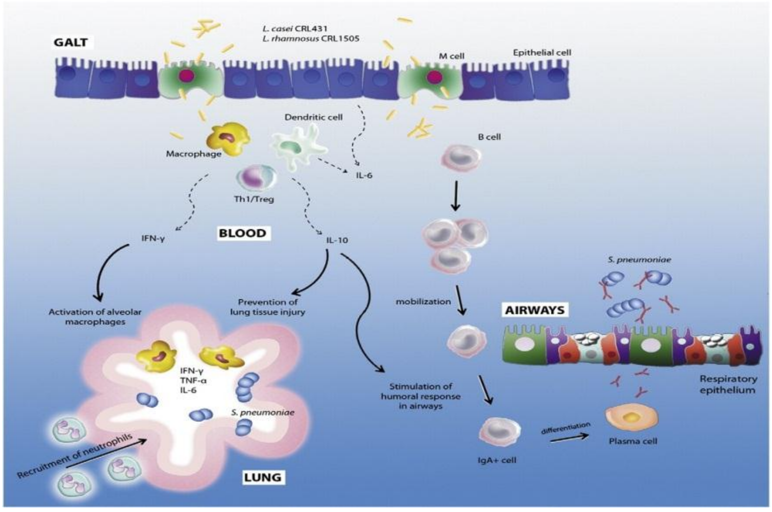

Figure1.1:- Enhancement of Immune response by lactic acid bacteria strains (Racedo *et al.*, 2009). After the intake, the lactic acid bacteria strains interact with the cells of gut associated lymphoid tissue. The dendritic cell and epithelial cells received and transport bacteria. After the contact of lactic acid bacteria strains with dendritic cell a signal is produced which enhances the production of cytokines. These cytokines improve the function of T and B cells of immune system.

Table 1.2:- Immune system overview

Categories of immune system	Defense barrier	Barrier component	Function of the components
Innate immune system	Physical barrier	Skin	Protect against the pathogen entry
		Mucous membrane	Prevent the antigen entry in to systemic circulation
	Cell mediated barrier	NK cells	Abolish the infected cell
		Phagocytic cell	Engulf foreign particles
		Inflammatory cells	Discharge inflammatory mediators
	Some other factor	Cytokine	Activate the immune cells
		Complements	Boost phagocytosis
		Acute phase proteins	Repair the damage tissue
Acquired immune system	B- Lymphocyte	Plasma cells	Secrete antibody
	T-Lymphocyte	$CD4^+$ cells	Lymphocyte activation
		Th1 cells	Induce cell mediated response
		Th2 cells	Induce humoral immunity
		$CD8^+$ cells	Destroy infected cells
		Cytotoxic cells	Destroy infected cells
		Suppressor cells	Suppress the lymphocyte activity

Lactic acid bacteria and innate immunity

The macrophages are very important component of immune system and it maintains the immunological host defense and homoeostasis. Also the alveolar macrophages are the major population in the lungs of host. The macrophages play very important role in defense system of host against infectious pathogens. The macrophages are heterogeneous cells having antigen processing, immunomodulation and phagocytic activity. These macrophages play very important role in inducing the innate and acquired immunity against infectious pathogens (Gordon and Read, 2002).

After the interaction of alveolar macrophages with lactic acid bacteria, macrophages activated and produced cytokines. These activated macrophages enhance the microbial killing and phagocytosis activates (Wissinger et al., 2009). However, as the load of invading pathogens increases the macrophages generate the some intermediary's molecules such as IL-6 , MIP-1ß, IL-8 , IL-1ß, MIP-1 and TNF-a and these intermediate recruit neutrophils in to the alveolar space. These neutrophils play very important rule to cleaning the invading pathogens by enhancing the phagocytic activity (Zhang et al., 2000; Kyd et al., 2001).

The lactic acid bacteria can be use for the development of various fermented milk products. Recent study indicates that the lactic acid bacteria strains have some health promoting effect by modulating the immune system of host. The natural killer cells play very important rule in the development of host immune system. The intake of fermented milk product containing Lactobacillus casei enhance the natural killer cells activity against wide range of pathogens (Nagao et al., 2000). The patient that intake probiotic lactic acid bacteria have high level of IgA antibody and enhancement in immune response as compared to the control group (De Roos and Katan, 2000).

The probiotic lactic acid bacteria strains have the ability to modulate the immune response. Dental administration of Lactobacillus casei strain has been found to boost innate immunity by stimulating the activity of splenic NK cells. Oral feeding with killed Lactobacillus casei surely could stimulate the production of particular Th1 cytokines, resultant in inhibited creation of IgE antibodies in contrast to Ovalbumin during trial mice (Figure 1.2) (Matsuzaki and Chin, 2000).

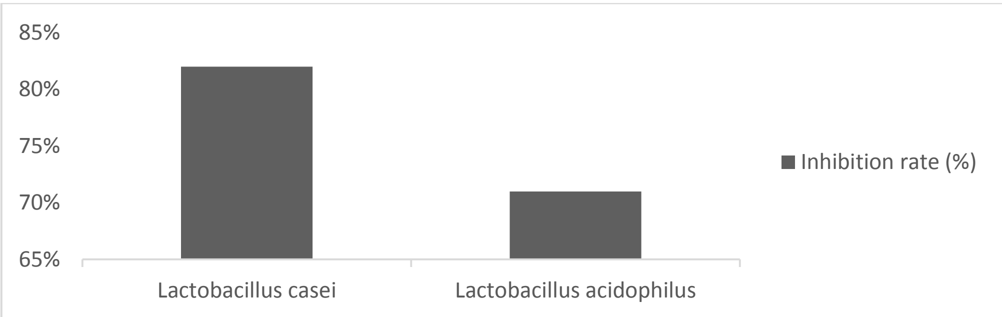

Figure 1.2:- NK cells activity by the dental administration of Lactobacillus case

Lactic acid bacteria and humoral immunity

There are total thirty adult volunteers were divided in to three different treatment groups which were feeding the *Lactobacillus* GG and *L. lactis* for seven days. Attenuated vaccine having the Salmonella typhi Ty21a were given to all three treatment groups to minimize the pathogenic infections. All the treatment groups shows very good response to the vaccine. However there no difference in the number of IgA, IgM and IgG secreting cells among the three treatment groups. The group receiving the vaccine with *Lactobacillus* GG had higher number of IgA and the group receiving the vaccine having *L. lactis* had higher number of CR 3 receptor which are specific for the expression of neutrophils. The result of this study indicate the probiotic lactic acid bacteria strains had the immunomodulator effect (Fang et al., 2000).

Various study show that the lactic acid bacteria have the protective effect against the wide range of infection and tumor. The *L. casei* and *L. plantarum* interact with the peyer patch cells and this interaction enhance the IgA, $CD4^+$ cells. The consumption of lactobacillus lactis and lactobacillus bulgaricus enhance the level of IgA but not $CD4^+$ cells. For the humoral immunity it is important to maintain the balance of $CD4^+$ and $CD8^+$ cells. If the population of $CD8^+$ cells increase induce the inflammatory response by the cytotoxicity mechanism of $CD8^+$ cells and if the population of $CD4^+$ increase it can enhance the HLA class

III by the cytokine pathway (Herich and Levkut, 2002).

The chronic fatigue syndrome is a complex disease. Research data show that the patient having chronic fatigue syndrome have low number of lactic acid bacteria, increase oxidative stress, low level of essential fatty acid and also lack certain nutrients. Allergy is also develop in this condition and the helper T cell types is increase under this condition. The lactic acid bacteria have the ability to enhance the immune system by increasing the cellular immunity. The lactic acid bacteria also have the ability to enhance the status essential fatty acid and strong antioxidant (Logan et al., 2003).

Table 1.3:- Lactic acid bacteria strains for the therapeutic application

Lactic acid bacteria strains	Molecules	Action	References
Lactobacillus lactis	Proteinase	Antigen delivery system	(Bernasconi et al., 2002)
Lactobacillus lactis	Nuclease	Antigen delivery system	(Langella and Le Loir, 1999)
Lactobacillus lactis	Protein A	Antigen delivery system	(Steidler et al., 1998b)
Streptococcus godonii	M6 protein	Antigen delivery system	(Medaglini et al., 1995)
Streptococcus godonii	Type III polysaccharide of streptococci	Passive protection of neonatal pups from group B streptococci disease	(Beninati et al., 2001)
Streptococcus godonii	Antibody H6	*C. albicans* vaginitis	(Beninati et al., 2000)
Lactobacillus lactis	Lipase	Pancreatic insufficiency compensation	(Drouault et al., 2000)
Lactobacillus lactis	Bovine beta lactoglobulin	Food allergy	(Chatel et al., 2001)
Lactobacillus lactis	IL-2 and IL-6	Enhance the immunity	(Steidler et al., 1998a)
Lactobacillus lactis	IL-10	Treatment of bowel disease	(Steidler, 2001)
Lactobacillus lactis	L7 and L12 riosomal proteins	Vaccine against brucellosis	(Ribeiro et al., 2002)
Lactobacillus lactis	Nonstructural protein 4	Protection for diarrhea	(Enouf et al., 2001)
Lactobacillus lactis	Pneumococcal type 3 capsular polysaccharide	Immunization for pneumoniae	(Gilbert et al., 2000)
Lactobacillus plantarum	Cholera toxin B	Protection from cholera B toxin	(Slos et al., 1998)
Streptococcus godonii & *Lactobacillus casei*	V3 domain of gp120	HIV immunization	(Oggioni et al., 1999)
Lactobacillus lactis	Fragment C of tetanus toxin	Effect of epitope location	(Reveneau *et al.*, 2002)
Lactobacillus lactis	Fragment C of tetanus toxin	Protection against tetanus toxin	(Grangette *et al.*, 2001)

Lactic acid bacteria and cancer

Yoghurt having lactic acid bacteria can be widely used to prevent the cancer by producing some anti-carcinogens molecules (Burns and Rowland, 2000). During the life some incident occurred that increase the chances for infectious diseases and suppressed the protection by the beneficial microflora. The probiotic lactic acid bacterial strains can be used to control the negative metabolic activities (Sanders, 2000).

The probiotic lactic acid bacteria prevent the tumor by change of clonal motility, change of pH to suppressed the activity of microbes, enhance the immune system of host and also by the inhibition of bacteria that change the procarcinogen in to carcinogen (McIntosh, 1996). Experimental study show that the fermented products containing the probiotic lactic acid bacteria prevent the cancer formation and proliferation. The experimental data show that the mice feeding on yoghurt can reduced the formation of cancer cells as compared to control group of mice (McIntosh, 1996). The Bifidobacterium longum are very useful for the prevention of liver cancer. The Lactobacillus casei is very useful strains for the prevention of cancer. The consumption of lactic acid bacteria strains produced the polysaccharides having antitumor activity at cellular level (McIntosh, 1996; Morotomi, 1996).

Professional medical studies proposed the consumption of fermented foods, for example yogurt, could alleviate a number of the signs involving atopy in addition to could also slow up the development involving allergic reaction and cancer, possibly with regulations immune response. The various control study shows that the consumption of fermented foods containing the lactic acid bacteria improve the production of type I and II interferons. In model animal study, the consumption of lactic acid bacteria reduce the allergy by enhancing the IL-4 and IL-6. Some recent study also indicate that the lactic acid bacteria also enhance the production of IL-12 and IL18 (Cross et al., 2001).

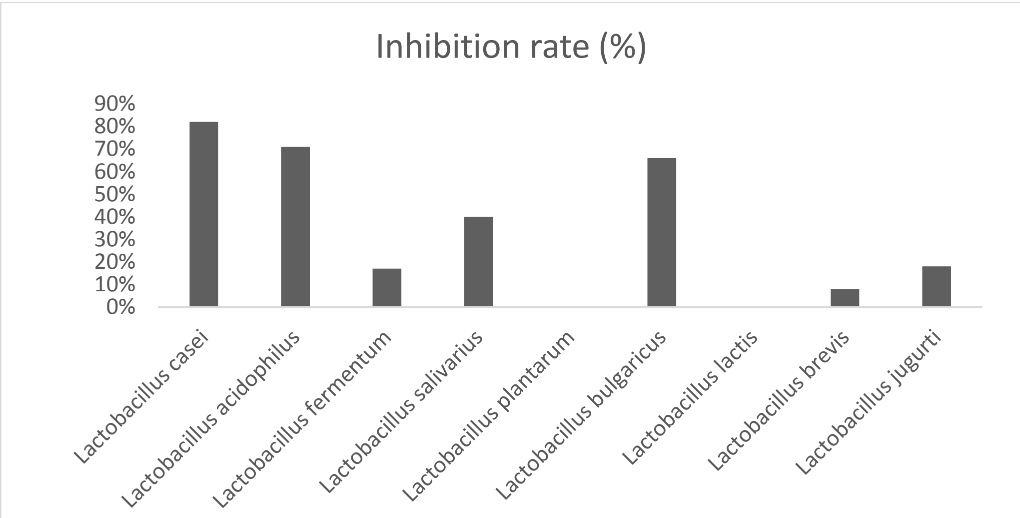

Figure 1.3 Antitumor activities of *Lactobacillus* lactic acid bacteria strains

CONCLUSION

The retaining of health is very serious problem and difficult now a day and it depends upon the equilibrium balance of microbiota in body of host. The normal indigenous microbiota confirm various benefit to the health of host and when this balance is disturb than pathogen start multiply.

Therefore probiotic bacteria consumption enhances the immune system of host by establishing the balance between the pathogen and beneficial microbes.

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