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Review article:

IMMUNOMODULATION AND ANTICANCER POTENTIALS OF YOGURT PROBIOTIC

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ABSTRACT

Probiotics are defined as live microbial food ingredients that produce several beneficial effects to human health. Probiotic bacteria have been mostly investigated in the prevention and treatment of different gastrointestinal diseases and allergies. Probiotic products, however, are usually consumed by the general, healthy population but not much is known on their immunomodulatory effects in healthy adults. It is not fully clear how probiotics exert their beneficial effects on health, but one of the most probable mechanisms of action is the modulation of immune responses via the mucosal immune system of the gut. Yogurt is one of the products that produce several beneficial effects on human health. The potentials of yogurt in various ways like improving immune system balancing gut micro flora, enhance immunity. The purpose of the present study was to review the immunomodulatory properties of yogurt containing probiotic strains. Role of yogurt as probiotic in improvement of immunity, production of cytokines and on immune function has been evaluated. Taken together, all the beneficial immunological potentials of yogurt in probiotic immunotherapy could be of clinical significance. The mechanisms of specific host-probiotic interactions in the gut resulting in systemic and clinical effects warrants further investigations.

Keywords: probiotic; lactic acid bacteria; yogurt

INTRODUCTION

Probiotics are defined as “living micro-organisms” that confer a health benefit on the host (FAO/WHO, 2002) and they have been mostly studied in the prevention and treatment of gastrointestinal disorders (Adolfsson et al., 2004; Meydani and Ha, 2000). Probiotic bacteria are defined as "living micro-organisms", which upon ingestion in certain numbers, exert health benefits beyond inherent basic nutrition" (Guarner and Schaafsma, 1998). Literature survey reveals beneficial potentials of yogurt in various ways like lowering cholesterol levels, improving immune system, balancing gut micro flora and preventing constipation, diarrhea and bloating, preventing fugal infection and improving digestibility of food constituents and improves immune response and anticarcino-

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genic activity (Ganjam et al., 1997). The immunological potentials of *Lactobacillus acidophilus* (LAB) have raised a lot of interest in recent years due to their immune-stimulating properties. Several strains of LAB were reported to display stimulatory properties on cells of the innate immune system *in vitro*, including macrophages and NK cells (Weid et al., 2001). Probiotics comprise of approximately 65 % of the world functional food market (Agrawal, 2005). The growing popularity of yogurt over the years has largely been due to its perceived health benefits. However, the putative health benefits of yogurt consumption in humans have not been thoroughly investigated. The present study is aimed to review the capacity of yogurt in improvement of immune system and their anticarcinogenic potentials (Perdigón et al., 1995). Yoghurt contains viable cells of two species of lactic acid bacteria, *Lactobacillus delbrueckii ssp. Bulgaricus* and *Streptococcus thermophilus* in a concentration of 10^8 cells/ml. Yogurt has long been recognized as healthy milk product with higher nutritional value and significant health beneficial effects (Wood, 1992). Fermented milk product yogurt is one of the best-known foods that contain a huge amount of calcium, 40 % of the daily value and considered as staple food everywhere (Adolfsson et al., 2004). A typical commercial yogurt contains fat (0-3.5 %), milk solids, non fat (8.25-14 %), sugar (0-10 %) and stabilizer (0-2 %). Yogurt containing ingredient and their functions are 1. Dairy ingredients are milk cream, milk powder, condensed milk as a source of protein lactose and minerals 2. Sweeteners: are sucrose, fructose and aspartame for sweet taste 3. Stabilizers such as gelatin, modified food, starch, pectin, whey protein concentrates for control water and texture 4. Functional ingredients are tri calcium phosphate, citric acid, potassium sulfate for buffering and mold inhibition (Parvez et al., 2006; Baroja et al., 2007)**.** Yogurt results from the fermentation of milk in presence of live *Lactobacillus bulgaricus*, *Streptococcus thermophilus* and *L. acidophilus* (Jayamanne and Adams, 2004). Scientific evidence suggests that probiotic bacteria consumed at a level of 10^9-10^{11} cfu/day can decrease the incidence and severity of some intestinal illnesses (Zubillaga et al., 2001). Conventional and commercially available yogurt, both contain *Lactobacillus bulgaricus* and *Streptococcus thermophilus* with additional *Lactobacillus casei* (Meyer et al., 2007). Furthermore, *Lactobacillus plantarum* demonstrated beneficial immunomodulatory activity by increasing IL-10 synthesis and secretion in macrophages and T-cells derived from the inflamed colon of human (Pathmakanthan et al., 2004). Some of the health benefits which have been claimed for probiotics include the following: improvement of the normal microflora, prevention of infectious diseases and food allergies, reduction of serum cholesterol, anticarcinogenic activity, stabilization of the gut mucosal barrier, immune adjuvant properties, alleviation of intestinal bowel disease symptoms and improvement in the digestion of lactose in intolerant hosts (Galdeano et al., 2007).

Probiotic bacteria interact with three components of the gastrointestinal tract including intestinal epithelial cells, luminal flora, and the mucosal immune cells. Yogurt containing LAB plays critical role on the immune system and the ability to fight off an infection (Conge et al., 1980; DeSimone et al., 1993; Halpern et al., 1991; Perdigon et al., 1988). The present investigation was to explore the immunomodulatory and anticarcinogenic activity exerted by yogurt. However, the mechanisms by which intestinal bacteria modulate the immunity are complex and incompletely understood.

Role in immunity improvement

Yogurt containing *Lactobacillus spp. Lactobacillus (acidophilus, casei, plantarum, delbrueckii, gasseri)* and *Bifidobacterium (longum, bifidum, adolescentis, infantis)* produce certain bioactive peptides, which stimulate the proliferation and maturation of T lymphocytes and improve immunity by increasing the number of IgA

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through producing plasma cells (Malin et al., 1996; Schiffrin et al., 1995; Gill et al., 2000). Moreover, muramyl dipeptide, a low molecular weight product of the peptidoglycans, which stimulates production of pro and anti inflammatory cytokine by macrophages, monocytes and lymphocytes (Isolauri et al., 2001). Yogurt, induce adjuvant activity at the mucosal surface and improve phagocytosis by increasing the proportion of lymphocytes and natural killer cells (Mc-Cracken and Gaskins, 1999). Moreover, monocytes play critical roles in the induction of cytokines following the augmentation of NK cell activity during the stimulation of human peripheral blood mononuclear cells with *L. casei* strain Shirota (Shida et al., 2006). Yogurt, stimulate the production of teichoic acid, which reduces IgE-mediated disorders and liberates low molecular weight peptides in gastro intestinal tract, that trigger the immune system and produce conjugated linoleic Acid, which has immunomodulatory and anticarcinogenic activity (Isolauri et al., 2001; Perdigón et al., 1995). Yogurt, produce conjugated linoleic acid, which has immunomodulatory activity (McCracken and Gaskins, 1999). Furthermore, yogurts possess properties that potentiate the release of interferon-γ (IFN-γ) by immunocompetent cells (DeSimone et al., 1986). The immunomodulatory effects of LABs were also shown in the cytoplasmic fraction of *Lactobacillus acidophilus, Lactobacillus casei and Bifidobacterium longum*. Enhanced number of total T cells, NK cells and MHC class II+ cells and CD4-CD8+ T cells were also demonstrated (Lee et al., 2004). The immunoregulatory functions of *L. casei*, a well-known probiotic strain, have been extensively studied using in vitro and in vivo murine models. *L. casei* stimulates murine macrophages to secrete IL-12, which induces T cells to produce IFN-γ and *also* promotes the differentiation of naïve CD4+ T cells. Administration of *L. casei* to mice enhance the production of IL-12, TNF-α, and IFN-γ and augmented NK cell activity, leading to the prevention of influenza virus infection and cancer (Shida et al., 2006).

Prevention of infections

Relation between fermented milk and immune responses has been demonstrated by various research groups, either in mice or in human (Meydani and Ha, 2000). However, yogurt mediated stimulation of immune response has been recently explored (Meyer et al., 2007). Breakthrough comes after induction of cytokines in presence of foods also (Adolfsson et al., 2004). Significant impairments of several aspects of immunity, including phagocytosis, cell-proliferation response to mitogens, T lymphocyte number, and cytokine production have been described in nutritional deficiencies (Meydani and Ha, 2000). Yogurt has several beneficial effects on human health such as enhancement of immunity against intestinal infections as well as production of certain compounds which stimulate the immune system, enhance specific and non-specific immune response. Many recent studies have focused on the possible effects of LAB on the immune system and the ability to fight off infections (Conge et al., 1980; DeSimone et al., 1988; Halpern et al., 1991; Perdigon et al., 1988). Yogurt containing LAB activates both a systemic and local immune response by increasing the percenttage of B-lymphocytes and lipopolysaccharide induced proliferative responses of peyer's patches in the intestine (DeSimone et al., 1987). In addition to potentiate effects of the organism itself, the peptide products of the microorganism may possess immunomodulating activity, produce a systemic effect. Identified as hexapeptide that exert an anti-infectious immunostimulatory response on alveolar macrophages in mice and there was a significant increase in the resistance to pneumonia infection (Parker et al., 1984; Matar et al., 1996)**.** Thus use of probiotic needs to be considered as a supportive therapy for immunocompetent patients.

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Production of cytokines

Cytokines induced by LAB are considered to play key roles in immunoregulation. Several studies have revealed that some specific strains of *lactobacilli* can induce proinflammatory cytokines such as interleukin-1 (IL-1), IL-6, IL-12, tumor necrosis factor alpha (TNF-α), and gamma interferon (IFN-γ) as well as anti-inflammatory cytokines such as IL-10 and transforming growth factor β (Christensen et al., 2002; Niers et al., 2005; Weid et al., 2001). In these cytokines, IFN-γ and IL-12 potently augment the functions of macrophages and NK cells, which may be a possible mechanism of their anticarcinogenic and anti-infectious activity (Biron et al., 1999; Trinchieri, 2003). On the other hand, induction of IL-10 and transforming growth factor β by *lactobacilli* is assumed to participate in the down-regulation of inflammation, since these cytokines can inhibit the functions of macrophages and T cells and promote the development of regulatory T cells (Levings et al., 2002).

Cytokines, which are protein mediators produced by immune cells, are involved in the regulation of cell activation, growth and differentiation, inflammation, and immunity. Induction of proinflammatory cytokines, such as interleukin- 12 and tumor necrosis factor alpha has been well documented. Stimulation of innate immune functions has been explored in human fed with fermented milk products containing probiotics (Weid et al., 2001). On the other hand yogurt fed mice shown an increase in B lymphocytes IgA^+, induction of IFN-γ and TNF-α release. Production of cytokines *in vitro* model as blood mononuclear cells cultured in the presence of yogurt bacteria, produced interleukin l-β, tumor necrosis factor, and interferon α and γ both in human and mice (Pereyra et al., 1997). According to Bloksma et al. (1979) in germ-free animal ingesting yogurt, shows nonspecific increase of immunoglobulin (Ig) 3G1, IgG2, IgG2a, IgG2b, and IgM antibodies. Yan and Polk (2002) proposed that many probiotic effects are modulated through immune regulation of pro and anti-inflammatory cytokines.

Studies suggest 63 % and 24 % increased production proinflammatory cytokines TNF-α in 100-200 g of probiotic and conventional yogurt treated women, respectively in two weeks. On the other hand 40 % and 108 % significant stimulation of IL-1B and IFN-gamma in conventional yogurt treated women. Furthermore, 129 % increased production of IO-10 in conventional yogurt fed women was shown. Therefore it was concluded both conventional and probiotic yogurt enhanced the stimulated production of pro inflammatory cytokines (Meyer et al., 2007).

Improvement of immune function

It has been shown that some strains of probiotic lactobacilli are effective in reducing the incidence of cancer and infectious diseases, ameliorating inflammatory bowel diseases, and preventing allergies in experimental animal models and in humans ((Kalliomäki and Isolauri, 2004; Rafter, 2002; Sartor, 2004). LAB protects against pathogen by means of competitive inhibition. Animal models and human studies provide a baseline understanding of the degree and type of probiotic-induced immune response. Probiotic bacteria are able to enhance both non-specific and specific immune responses by activating macrophages; viable probiotic cells, dead cells. L-cysteine acts as precursor in the biosynthesis of the tri-peptide glutathione and glutathione has antioxidant activity and is involved in the detoxification of many xenobiotics, including carcinogens. Hydroxymethyl glutarate, which may inhibit hydroxy-methyl-glutarate co A reductase activity (Ganjam et al., 1997). During milk fermentation of yogurt in presence of LAB various biologically active metabolites or compounds released in the medium. These products can inhibit enzyme activities and prevent cancer for example β-glucuronidase and nitroreductase (de Moreno de leBlanc and Perdigón, 2005). The end products and the highly reactive intermediates derived from

these reactions such as reactive nitroso and N-hydroxyintermediate and aromatic amines are mutagenic and carcinogenic (Gillette et al., 1968). The reduction of aromatic nitro- and azo-compounds result from the activity of the intestinal flora (Zachariah and Juchau, 1974; Peppercorn and Goldman, 1972).

Immunomodulatory and anticancer effects of yogurt as probiotic on human

Role of yogurt as probiotic in immunity improvement potentials has been well documented. Reports reveals fermented food or yogurt enhance phagocytic activity in presence of *Streptococcus thermophilus* with *Lactobacillus johnsonii* and prevent infections, in a required dose of 10^9/d (Donnet et al., 1999). Yogurt containing *Streptococcus thermophilus* with *Lactobacillus delbrueckii* subsp. *bulgaricus* increase 2'-5' A synthetase activity (Pereyra et al., 1997). On the other hand *Lactobacillus brevis* subsp. *Coagulans* increases a-IFN (Kishi et al., 1996). In contrast, Yogurt doesn`t improve immune function in premenopausal women and in breast cancer (Campbell et al., 2000). Furthermore, it has also been shown that yogurt containing *Lactobacillus* GG or *Bifidobacterium lactis* increase IgA secreting cells in human model in a required dose ($2x10^{10\text{-}11}$ CFU/day) (Malin et al., 1996; Fukushima et al., 1998; Kaila et al., 1992). *Lactobacillus* GG is found to increase IgM secreting cells (Isolauri et al., 1995). Yogurt containing *Streptococcus thermophilus* with *Lactobacillus delbrueckii* subsp. *bulgaricus*; is demonstrated to increase 2'-5' A synthetase activity as well as increase blood serum IFN-γ, B lymphocytes and NK cell activity (DeSimone et al., 1993; Pereyra and Lemonnier, 1993). Furthermore, fermented milk with *L. johnsonii* or *Bifidobacterium bifidum i*ncrease phagocytosis of *Escherichia coli* as well increased serum IgA response to *Salmonella typhi* (Schiffrin et al., 1995; Amster et al., 1994). Moreover, random clinical trials revealed that oral ingestion of *L. casei* prevent bladder cancer, colorectal tumors, restores NK cell activity. Therefore, suggested that orally ingested *L. casei* enhance innate immunity and suppress the occurrence of cancer (Shida et al., 2006).

CONCLUSION

In this review we are presenting the beneficial potentials of yogurt in context with immune response. Studies documenting probiotic effects of yogurt in humans are limited. Probiotic immunotherapy using yogurt could be an emerging field of disease management through the diet. However, molecular mechanisms leading to yogurt-induced immunomodulation are poorly understood. Thus, we strongly recommend that yogurt could be further developed as a possible potential universal antineoplastic agent for multitargeted therapy, which is not only cost effective but also easily available and clinically safe for human trials. Thus, application of yogurt may provide a mechanism through which probiotic bacteria ameliorate inappropriate inflammation and induce tolerance.

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