The Mechanisms of Immune System Regulation by Probiotics in Immune-Related Diseases

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Abstract: Probiotics are live microorganisms which when administered in adequate amounts, may confer a health benefit on the host. Stimulation and regulation of immune system is among well documented benefits claimed for probiotics. Both innate and adaptive immune system can be regulated by these microorganisms. Effects of probiotics on immune system are significantly dependent on the strain, dosage and the investigated condition. In this article the mechanisms through which probiotics may regulate immune system were reviewed. These mechanisms are consist of blockage of adhesion sites for pathogenic bacteria, competition for nutrients, production of inhibitory compounds, degradation of the toxin receptors in the mucosa membrane, activation of phagocytic and natural killer cells as well as regulation of cellular and humoral immunity. Also the immune-related diseases including immune deficiency (Acquired immunodeficiency syndrome) and hypersensitivity (allergy, inflammatory bowel disease, diabetes mellitus type 1 and rheumatoid arthritis) were discussed.

Keywords: Probiotic, immune, regulation, mechanism, Food, disease.

1. INTRODUCTION

The word "probiotics" was first used by Elie Metchnikoff in the beginning of the 20th century. It was proposed that adult human body has 10 times more bacterial cells in his gastrointestinal tract than eukaryotic cells in his body [1, 2]. Probiotics are "Live microorganisms which when administered in adequate amounts confer a health benefit on the host" [3, 4]. Lactic acid bacteria (LAB) and bifidobacteria are the most widespread types of microbes used as probiotics; but certain yeasts and bacilli may also be categorized as probiotics [2, 5].

The immune system includes a complex array of cells and molecules, which interact to provide protection from challenge by eradicating all elements perceived as foreign. The immune system consists of innate and acquired components. The innate immune responses constitute the first line of host defense and comprise a set of resistance mechanisms that are non-specific to a given pathogen; it plays its role exclusively by phagocytosis. Unlike the innate immune system, the adaptive immunity demonstrates a high level of specificity and memory. Cellular and humoral immunity are the major components of the adaptive immune system [6]. The innate and adaptive immune systems are highly integrated and interdependent. In addition to being a pre-requisite for adaptive immunity, the innate immune response is responsible for the detection and elimination of pathogens [7].

Microbiota of the gastrointestinal tract has an important impact on the anatomical, physiological and immunological development of the host. It stimulates the immune system to react quickly to infection with pathogens and by bacterial antagonism it inhibits the colonization of the gut by harmful or pathogenic

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bacteria [5, 8]. Several immunological studies have been performed in the probiotic field using different strains in various models. Recently great attention has been paid to the possibility of using probiotics to enhance immune system function in immunity-related diseases and many clinical trials have been conducted in this regard. The aim of the present article is to review the literature for the immunological potential of probiotics and to highlight the immune-related disorders for the prevention and control of which, probiotics have been applied.

2. EFFECT OF PROBIOTICS ON IMMUNE-RELATED DISEASES

All the diseases human is affected by are closely implicated with immune system; they are most likely either involved in pathogenesis of the disease or the consequence of the ailment. Immune deficiency and immune hypersensitivity are the two extremities of the spectrum of immune related diseases, which have been widely studied in connection with probiotics.

2.1. Deficiency of Immune Function

Acquired immunodeficiency syndrome (AIDS) is a human immune system disorder caused by the human immunodeficiency virus (HIV) [9]. Transmission of HIV virus generally occurs by introduction of body fluids from an infected person into the body of an uninfected person. A period of rapid viral replication follows, leading to an abundance of virus in the peripheral blood. During primary infection, several million HIV virus particles may exist per milliliter of blood [10]. This response causes a marked drop in the numbers of circulating CD_4^+ T-cells. This acute viremia is associated in almost all patients with the activation of CD_8^+ T-cells, which kill HIV-infected cells, and consequently with antibody production, orsero-conversion. The CD_8^+ T-cell response is thought to be vital in controlling virus levels, which peak and then reduce, as the CD_4^+ T-cells increase to normal. A proper CD_8^+ T-cell response has been associated with slower disease progression and a better prognosis, though it does not eradicate the virus [11].

When CD_4^+ T-cell numbers decline below 200 cells per µL, cell-mediated immunity is lost and infections with a variety of opportunistic microbes develop. The first symptoms often include moderate and unexplained weight loss, recurring respiratory tract infections (such as sinusitis, bronchitis, otitis media, pharyngitis), prostatitis, skin rashes and oral ulcerations [11]. Diarrhea is a common complication in AIDS patients as well. Probiotics due to their capability of hindering pathogenic bacteria have been tried in easing some symptoms of the affected people and enhancing the quality of their lives. Clinical trials in this regard which are so scarce, are presented in Table **1**.

2.2. Over-Sensitivity of Immune System

The adaptive immune response provides specific resistance against infection with bacteria, viruses, parasites, and fungi. Particularly, it is able to present rapid protection against a constant challenge with the same or a similar foreign organism or toxin. Some immune responses, however, give rise to an extreme or inappropriate reaction; this is usually referred to as hypersensitivity. There are four major types of hypersensitivity; in type (I), allergic reactions are produced through release of particular mediators. In type (II), a cytotoxic action is induced as an antibody is directed against antigen on an individual's own cells (target cell) or foreign antigen. In type (III), immune complexes are deposited in the tissue causing local tissue damage and inflammation; autoimmune disorders are the result of this type of hypersensitivity. In type (IV), antigen-sensitized T-cells secrete lymphokines when encountering the same antigen for the second time which ends in inflammatory reactions [42]. Due to their greater prevalence, this review focuses on autoimmune diseases and allergies and the impact probiotics may have on patients suffering from these disorders.

2.2.1. Autoimmune Diseases

The immune system has remarkable diversity and because the repertoire of specificities expressed by the B and T-cell populations is generated randomly, it is bound to include many that are specific for self-components. Thus, the body must establish self and non-self determinants to prevent auto-reactivity. Like all mechanisms self-recognition mechanisms have a risk of dysfunction and several diseases have been identified in which there is autoimmunity due to bountiful production of auto-antibodies and auto-reactive T-cells. Autoimmune disorders can be classified into two main subtypes; the target organs in organ-specific diseases commonly include the thyroid, adrenal, stomach, and pancreas; the non-organ-specific disorders, often referred to as systemic autoimmune diseases, which include the rheurnatological diseases, characteristically involve the skin, kidney, joints, and muscle. Probiotics have been reported to be beneficial in alleviating the symptoms of a number of autoimmune disorders. Inflammatory

Table 1: Effects of Probiotic Supplementation on Immune Related Diseases

immune-related diseases	Type	Carrier	Strain	Dose	Duration	Healthy effect	Ref.
Deficiency	AIDS	Formula	*B. bifidum & S. thermophilus*	2.5×10^{10} CFU	8 weeks	CD4 ↑	(Trois, *et al.*, 2007) [12]
	AIDS	Not mentioned	*L. plantarum*	Not mentioned	2 weeks	Shortened acute diarrhea	(Cunningham-Rundles, *et al.*, 2000) [13]
	AIDS	yogurt	*L. rhamnosus*	10^{10} CFU	30 days	GI symptoms were alleviated and tolerance to antiretroviral treatment was improved	(Irvine, *et al.*, 2011) [14]
	AIDS	yogurt	*L. rhamnosus & L. reuteri*	2.5×10^{12} CFU	15-30 days	CD4 ↑	(Anukam, *et al.*, 2008) [15]
Over-sensitivity	Pouchitis	Packet	VSL3	3×10^{12} CFU	9 months	Less relapses in the probiotic group	(Gionchetti, *et al.*, 2000) [16]
	CD	Capsule	*Saccharomyces Boulardii*	1 gr	6 months	The disease was remained in the remission	(Guslandi, *et al.*, 2000) [17]
	CD	Bag	*Lactobacillus. GG*	1.2×10^{10} CFU	12 months	endoscopic recurrence at one year was not prevented and severity of recurrent lesions was not reduced	(Prantera, *et al.*, 2002) [18]
	Pouchitis	Packet	VSL3	9×10^{11} CFU	1 year after colitis surgery	The onset of acute pouchitis was prevented probiotic group	(Gionchetti, *et al.*, 2003) [19]
	Pouchitis	Capsule	*Lactobacillus. GG*	$1\text{-}2\times10^{10}$ CFU	3 months	Clinical or endoscopic response was not improved	(Kuisma, *et al.*, 2003) [20]
	UC	Fermented milk (Vifit)	*Lactobacillus. GG*	1.4×10^{10} CFU	1 years	The onset on pouchitis was delayed	(Gosselink, *et al.*, 2004) [21]
	UC	Packet	VSL3	4.5×10^{11} CFU	8 weeks	Remission occurred at 8 weeks	(Tursi, *et al.*, 2004) [22]
	Pouchitis	Sachet	VSL3	6×10^{11} CFU	1 year or until relapse	Antibiotic introduced remission was maintained	(Mimura, *et al.*, 2004) [23]
	UC	Capsule	*E. coli.Nissle*	$5\text{-}50\times10^{9}$ CFU	1 year	Efficacy of remission maintenance was equivalent to gold standard	(Kruis, *et al.*, 2004) [24]
	CD	Capsule	*Lactobacillus. GG*	2×10^{9} CFU	6 months	Mmedically induced remissionwas not maintained or induced	(Schultz, *et al.*, 2004) [25]
	CD	Capsule	*Lactobacillus.* GG	10^{10} CFU	24 months	Treatment didn't prolong time to relapse	(Bousvaros, *et al.*, 2005) [26]
	UC	Tablet	*Lactobacillus. GG*	1.8×10^{10} CFU	1 year	Remission was maintained and relapse was prevented	(Zocco, *et al.*, 2006) [27]
	CD	Packet	*L. johnsonii*	4×10^{9} CFU	6 months	Endoscopic recurrence of CD was not prevented	(Marteau, *et al.*, 2006) [28]
	CD	Sachet	*L. Johnsonii*	10^{10} CFU	3 months	Early endoscopic recurrence was not prevented	(Van Gossum, *et al.*, 2007) [29]
	UC	Packet	VSL3	Weight-based	1 year	Remission was maintained in the supplemented children	(Miele, *et al.*, 2009) [30]
	UC	Packet	VSL3	7.2×10^{12} CFU	12 weeks	Supplementation was safe and effective in achieving clinical responses and remissions	(Sood, *et al.*, 2009) [31]

(Table 1). Continued.

immune-related diseases	Type	Carrier	Strain	Dose	Duration	Healthy effect	Ref.
	UC	Sachet	VSL3	3.6×10^{12} CFU	8 weeks	Rectal bleeding was improved and remission was reinduced in relapsing UC patients	(Tursi, *et al.*, 2010) [32]
	UC	Enema	*E. coli.Nissle*	$1\text{-}4\times10^{9}$ CFU	8 weeks	A dose-dependent efficacy of rectal EcN compared to placebo was observed	(Matthes, *et al.*, 2010) [33]
	UC	Enema solution	*L. reuteri*	10^{10} CFU	8 weeks	Mocusal inflammation improved and mucosal IL-10 expression significantly increased whereas IL-1β, TNFα and IL-8 significantly decreased	(Oliva, *et al.*, 2012) [34]
	RA	Capsule	*Lactobacillus. GG*	10^{10} CFU	1 year	ILs were not decreased, but subjective well-being increased	(Hatakka, *et al.*, 2003) [35]
	RA	Caplet	*Bacillus coagulans*	2×10^{9} CFU	2 months	patient global assessment and self-assessed disability improved and CRP decreased	(Mandel, *et al.*, 2010) [36]
	RA	Capsule	*L. rhamnosus and L. reuteri*	4×10^{9} CFU	3 months	No clinical improvement were observed but there was functional improvement	(Pineda, *et al.*, 2011) [37]
	AD	sachet	*L. acidophilus*	3×10^{9} CFU	6 months	did not reduce the risk of AD in high-risk infants	(Taylor, *et al.*, 2007) [38]
	AD	powder	*L. rhamnosus & L. reuteri*	0.5×10^{10} CFU	6 weeks	significant changes in the production of the cytokines IL-2, IL-4, IL-10, or IFN-γ in conclusion they have was beneficial in the management of AD	(Rosenfeldt, *et al.*, 2003) [39]
	Allergy	yogurt	*L. gasseri & L. coryniformis*	2×10^{8} CFU	3 months	CD4/CD25 ↑	(Martínez-Cañavate, *et al.*, 2009) [40]
	Allergy	capsules	*L. rhamnosus GG*	5×10^{9} CFU	4 weeks	IFN-γ ↑	(Pohjavuori, *et al.*, 2004) [41]

bowel disease (IBD), type (I) diabetes mellitus and rheumatoid arthritis are amongst disorders most studied in this regard [43].

2.2.1.1. Probiotics and IBD

Inflammatory bowel disease (IBD) includes two distinct diseases; Crohn's disease (CD) and ulcerative colitis (UC), both of which are among chronic disorders but have fairly different pathogeneses, underlying inflammatory profile, symptoms and treatment approaches. UC is basically restricted to the colon and/or rectum and is characterized by inflammation and superficial ulceration of the colonic mucosa. On the other hand, CD occurs as skip lesions in any section of the intestinal tract and is characterized by transmural granulomatous inflammation. Pouchitis is another disorder which results from complex ileal pouch-anal anastmosis (IPAA) surgery for UC. It is crucial to note that UC is a Th2 immune response while CD is chiefly a Th1 driven immune response. The precise etiology of IBD is unidentified. Based on current evidence it is proposed to be a result of dysregulated immune response to particular enteric microbiota in genetically susceptible persons. Although a variety of microorganisms and their products have been identified in inflamed tissues of IBD patients, no specific microbe has been proven to cause IBD. However, there is tremendous evidence that the initiation and

perpetuation of the disease is strongly affected by the intestinal microbiota. This lately attained knowledge has encouraged researchers to explore the effects of manipulating intestinal microbiota and restoring immune system homeostasis on IBD progress. Several studies have examined the possibly of probiotic supplementation in the prevention and/or treatment of diverse inflammatory bowel disorders [6, 44]. The available clinical evidence for the use of probiotics in the treatment of IBD is summarized in Table **1**.

2.2.1.2. Probiotics and Type (I) Diabetes Mellitus

Diabetes mellitus (DM) is a main cause of morbidity and mortality in the world. Type (I) diabetes which accounts for 1-10% of cases is the consequence of autoimmune destruction of pancreatic B-cells. The suggested mechanism for this is over-production of pro-inflammatory cytokines (such as IL-1β, TNFα and IFNγ). Up-regulation of IL-10 has been shown to protect B-cells against this destruction [45]. To date, only a small number of studies have investigated the anti-diabetic effects of probiotics [46]. To the best of our knowledge, no clinical trials have been performed in this regard, thus far.

2.2.1.3. Probiotics and Rheumatoid Arthritis

Rheumatoid arthritis (RA) is characterized by chronic synovitis and causes stiffness, pain, loss of mobility and progressive erosion of the joints. It usually involves multiple joints symmetrically. Hand and wrists are the most commonly affected joints, but the elbows, neck, shoulders, hips, knee, and feet may also be influenced. Extra-articular symptoms of RA can include development of nodules under the skin (especially at the elbows), lymphadenopathy, vasculitis and even peripheral neuropathy. Although the etiology of RA is not fully understood yet, increasing evidence suggests that CD_4^+ T-cells, which display a principally Th1 pattern of cytokine expression, have an important role in the pathogenesis of the disease [6]. Blockade of IL-12 and/or TNF-α has been revealed to reduce progression of collagen induced arthritis in mice [47] and results in significant clinical improvement in RA patients [48]. In Table **1**, clinical trials performed on the effects of probiotics on rheumatoid arthritis are summarized.

2.2.2. Allergic Diseases

Allergy is a hypersensitivity disorder of the immune system. Allergic reactions occur when a person's immune system reacts to normally benign substances in the environment. These reactions are acquired, predictable, and fast. Allergic reactions are characteristic because of excessive activation of mast cells and basophile by immunoglobulin E [49]. This reaction results in an inflammatory response which can range from uncomfortable to hazardous [50]. The balance between Th1 and Th2 cytokine production can determine the direction and outcome of an immune response; allergic reactions are the result of abnormal response of Th2 type [51].

The usual treatment of this disease consists of removing the incriminated antigen of the food source (elimination diets), which may prove very inconvenient when put into practice. In addition, immunotherapy and manipulation of the gut microbiota and mucosa can be attempted [52]. Probiotic bacteria have been shown to efficiently down-regulate inflammation associated with hypersensitivity reactions in patients with atopic eczema and food allergy [53, 54]. Probiotics may enhance endogenous barrier mechanisms of the gut and alleviate intestinal inflammation, providing a helpful tool for treating food allergy [53]. The most recent clinical trials in which allergic patients were supplemented with probiotics are summarized in Table **1**.

3. CONCLUSION

Gut microbiota plays a major role in regulation and stimulation of immune system. Imbalances in the context of these microbes can either be the cause or the consequence of a wide range of diseases. Probiotics, due to their capability of increasing the beneficial bacteria ratio in the intestines, have been tried in several immune related disorders, particularly deficiency (AIDS) and oversensitivity (autoimmune disease and allergy) the immune responses, in attempt to prevent the disease or alleviate the symptoms of the existing ailment. The results from the studies performed in this regard, indicate that probiotics can be most effective in subjects whose immune responses are less than normal at baseline. Besides, the strain administered and its dosage can affect the results of the investigations as well. An interesting point to take into account is that a particular strain may exert different effects on the subjects' immune function in different populations which emphasizes the importance of the physiologic status of the consumers on the benefits they may draw from the probiotic intervention; this is the reason probiotics are claimed to be good regulators of immune system.

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