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Overview on the Role of Probiotics as Immunomodulator s in Farm Animals

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ABSTRACT

Probiotics are beneficial microorganisms that improve the microbial balance of a host animal in all species. Immunomodulators are substances that keep tuning the immune system, so that probiotics are considered as immunomodulators that can stimulate the immune system of the host. Probiotics have many different bacterial species, *Lactobacillus, Bifidobacterium*, *Bacillus* and *Enterococcus*. They used to ameliorate certain physiological functions, safeguard of disease and mitigation of risk factors. Immunomodulation is a complex phenomenon that needs careful consideration, understanding of mechanisms of probiotic activities and immune functionality along either systematic or locally in GIT.

Probiotics able to modulate the immune response via regulating the mediators secreted by intestinal immune system cells and T helper cell as well as regulatory cell stimulation. The interactions between probiotics and immune cells (enterocytes) are complex that is not achieved by a single mechanism. Probiotics are not immune specific, but they have been shown different mechanisms like production of mucin, reduction of permeability of GIT, increasing phagocytic capacity and activation of macrophage and natural killer (NK) cell. On the other hand, cytokines and other regulatory substances are increasing as well as antibodies production (IgA, IgM, and IgG). This review has discussed the probiotics immunological mechanisms in the farm animals.

Keywords: Probiotics- immune-modulation- farm animals.

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Introduction

The term probiotic is meaning ‘in support of life’ or in another recent meaning, defined as “a source of viable, naturally occurring microorganisms” [1].

Probiotics are nonpathogenic beneficial microorganisms, which are found to have immunological impacts besides the known microbiological and metabolic properties. Recent research has revealed the importance of probiotics in many aspects of immune-mediated mechanisms. They are focusing not only on the probiotic’s composition and diversity but also on the immune modulation [2].

Probiotics can also provide benefits to boost the immune system by modulating the immune functions via various mechanisms such as; soluble substances from these microbes that alter epithelial permeability, their cell wall components, other stimulating molecules or mediate activation and maturation of dendritic cells, B and T-cells [3]. There are proteinaceous, exopolysaccharides, other cell wall components and microbial metabolites

(short-chain fatty acids and compounds derived from protein degradation) which have been produced from probiotics and have an immunomodulatory effect [4].

The immune system involves groups of immune cells and signaling molecules which interact with microorganisms and antigens. The innate immunity compresses certain responses; production of mucin and phagocytic cells activities (neutrophils, macrophages, natural killer cells). On the other side, the adaptive immune system shares an important role; firstly antigen-presenting cells begin to activate, then specific B and T cells are mobilized, specific signaling molecules (cytokines) are released, which regulate both the innate and adaptive immune responses. B cells differentiated to plasma cells which secrete antibodies (humoral immunity), whereas T cells are subdivided into T helper (Th) cells ($CD4^+$) and T cytotoxic (Tc) cells ($CD8^+$) (cell-mediated immunity) [5].

The innate immune cells needed to identify 'self' versus 'non-self', using specific surface markers. Briefly, most of pathogens or microorganism commonly concerned molecular patterns, which their recognition receptors (PRRs) or Toll-like receptors present at the nucleus or surface of immune cells respectively; table (1) [6, 7].

Table (1): Bacterial and fungal antigens with their respective immune receptors [8].

PAMPs or MAMPs in bacteria	**TLR/PRR**	**Species**
Lipopolysaccharide	TLR4	Gram-negative bacteria
Lipoteichoic acid	TLR2	Gram-positive bacteria
Peptidoglycan	TLR2-NOD1 (or NOD2)	most bacteria
Triacyl lipopeptides	TLR1 or TLR2	most bacteria
Diacyl lipopeptides	TLR2 or TLR6	*Mycoplasma* spp.
Glycan ligands (surface layers)	DC-SIGN	many bacteria
Porins	TLR2	*Neisseria*
Flagellin	TLR5	*Salmonella typhimurium*
Fimbriae (Mannose glycoproteins)	TLR4	*Escherichia coli*
CpGDNA	TLR9	all bacteria
PAMPs or MAMPs in fungi		
Zymosan	TLR2 or TLR6	*Saccharomyces cerevisiae*
Phospholipomannan	TLR2	*Candida albicans*
Mannan	TLR4	*C. albicans*
O-linked mannosyl residues	TLR4	*C. albicans*
β-Glucans	TLR2	*C. albicans*

PAMPs = Pathogen-associated molecular patterns; MAMPs = microorganism-associated molecular patterns; TLR = Toll-like receptor; PRR = pathogen recognition receptors.

How do probiotics modulate immune modulation?

Immune modulation is considered the most important action mechanism of probiotics. Probiotics maintained the proper balance of beneficial populations of bacteria in the intestine. They are important for the improvement and stimulation of the immune system and pathogens control [9]. The mechanisms of some probiotics and immune-boosting effects are shown in figure (1).

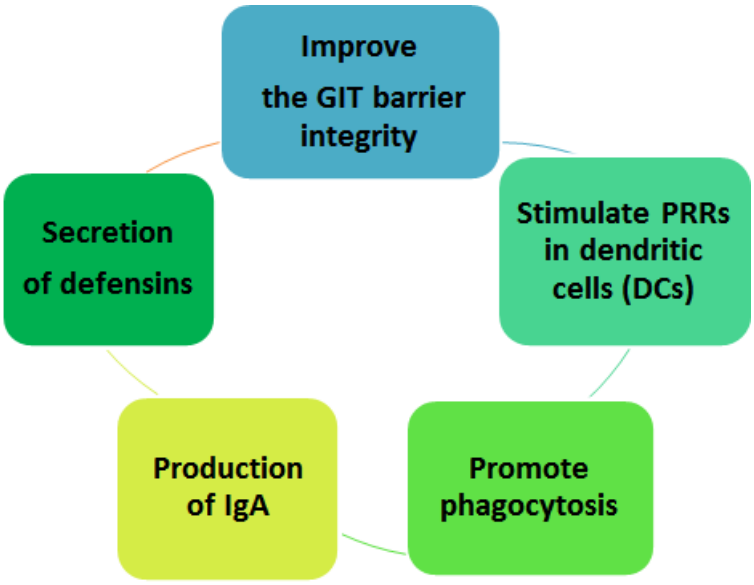

Figure (1): the immune boosting effects and common mechanisms of probiotics [9].

Probiotics can stimulate PRRs in dendritic cells (DCs) or in intestinal epithelial cells resulting in the production of cytokines that will allow the polarization of naive T cells towards the differentiation to regulatory T cells (Tregs) [10]. notably $CD4^{+}CD25^{+}FoxP3^{+}$ Tregs or Th1 effector cells that produce proinflammatory interleukins like interleukin-2 (IL-2) and IL-12, tumor necrosis factor-α (TNF-α) and interferon-γ (IFN-γ) [11- 14].

Probiotics can modulate Th1 by their metabolites as short-chain fatty acids (SCFAs), the Th1 modulation results in stimulation of phagocytes that fight pathogens through phagocytosis process [15].

Probiotics enhance the release of certain immunoglobulins (e.g. IgA), via boosting the secretion of IL-10 and TGF-β which regulate "with the assistance of $CD4^{+}$ T cells" the differentiation of B cells into plasma cells (IgA antibody-secreting cells) [16]. This differentiation enhances the IgAs release from the enterocytes into the intestine, where they controlled antigens and pathogens [17, 18]. Production of IgA plays an important role in prevention of the attachment and penetration of pathogenic microorganism in the epithelial cell lines. Moreover, it guards epithelial tissues in cases of deficient release of mucus so

prevents inflammation and damage of tissue [19]. Also, IgA up-regulates the expression of pIgR “an Fc receptor protein” [20].

Intestinal homeostasis is essential to prevent inflammation of intestine and provides the balance between immune activation and regulation [21, 22]. Non-inflammatory protection through immunomodulation is dependent on using the probiotic bacteria which improve the GIT barrier integrity by reducing the release of pro-inflammatory cytokines as IL-17 and chemokines “which implemented in neutrophils attraction” in the intestinal mucosa [23-25].

The epithelium cell line of the intestine can be protected by defensins and mucous that produced from specialized epithelial cells and goblet cells [26-29]. The antimicrobial peptides, defensins, are a major family of antimicrobial substances that sharing in the protective surface of the mucosa by binding to the cell membrane of microorganism where pore-like structures are formed that caused bacterial membrane defects. Probiotics can induce the expression of β-defensin-2 and β-defensin-3 that link to the different arms of the defense system of the host [30].

Conclusion

Novel studies have revealed that probiotics play a very essential role in the activation of host immune responses. The gathered data declared that probiotics can modulate the development and maintenance of the immune system. Because of the continuous interaction of the immune system with the variable microbiota located in the intestinal environment, A ‘balanced immune system’ probably exist; probiotics have the potential to aid in this process via various mechanisms.

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