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REVIEW ARTICLE

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Probiotics importance and their immunomodulatory properties

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Abstract

Mammalian intestine contains a large diversity of commensal microbiota, which is far more than the number of host cells. Probiotics play an insecure and protective role against the colonization of intestinal pathogenic microbes and increase mucosal integrity by stimulating epithelial cells. Probiotics have innate capabilities in many ways, including receptor antagonism, receptor expression, binding and expression of adapter proteins, expression of negative regulatory signal molecules, induction of microRNAs, endotoxin tolerance, and ultimately secretion of immunomodulatory proteins, lipids, and metabolites to modulate the immune system. Probiotic bacteria can affect homeostasis, inflammation, and immunopathology through direct or indirect effects on signaling pathways as immunosuppressant or activators. Probiotics suppress inflammation by inhibiting various signaling pathways such as the nuclear factor-κB (NF-κβ) pathway, possibly related to alterations in mitogen-activated protein kinases and pattern recognition receptors pathways. Probiotics can also inhibit the binding of lipopolysaccharides to the CD14 receptor, thereby reducing the overall activation of NF-κβ and producing proinflammatory cytokines. Some effects of modulation by probiotics include cytokine production by epithelial cells, increased mucin secretion, increased activity of phagocytosis, and activation of T and natural killer T cells, stimulation of immunoglobulin A production and decreased T cell proliferation. Intestinal microbiota has a major impact on the systemic immune system. Specific microbiota controls the differentiation of cells in lamina propria, in which Th17 cells secrete interleukin 17. The presence of Th17 and Treg cells in the small intestine is associated with intestinal microbiota, with the preferential Treg differentiation and the absence of Th17 cells, possibly reflecting alterations in the lamina propria cytokines and the intestinal gut microbiota.

KEYWORDS
immunomodulation, microbiota, probiotics

1 | CONTEXT

Increasingly, alterations in the microbial composition of the gut are becoming a theory to increase the prevalence of inflammatory diseases in the Western society. Many environmental factors, as well as genetic factors, affect the host microbial colonization. It is clear that intestinal microbiota can affect the digestive system and immune system responses (Fuller, 2012). The intestine is colonized by intestinal

microbiota, which consists of hundreds of bacterial species that play an important role in the health of the host. The microbiota has mostly protective function and activates metabolic and trophic processes (Parvez, Malik, Ah Kang, & Kim, 2006). They protect the host from microbial pathogens by producing bacteriocins, as well as competition for nutrients and attachment to the microbiota. In addition, intestinal bacteria are capable of fermenting nondigestible carbohydrates into short-chain fatty acids (SCFA) and also play a role in the synthesis of vitamins and iron absorption (McFarland, 2006).

The mucosa-associated lymphoid tissue (MALT) is a very extensive and complex part of the small intestine and colon immune system organized in sites such as lymphoid follicles and Peyer's patches (PPs), in which antigens from the lumen received by antigen-presenting cells (APCs) and stimulates immunoglobulin A (IgA) synthesis (Hill et al., 2014).

SCFA also has a trophic effect, which increases the proliferation and cellular differentiation of intestinal epithelial cells. In addition, they are possible inhibitors of neoplastic cell proliferation. The bacteria in the lumen of the intestine react to the immune system through pattern recognition receptors such as a toll-like receptor (TLR) and recognize pathogens via PAMPs (Lebeer, Vanderleyden, & De Keersmaecker, 2010). Host–microbes interaction has a special importance in early life. Challenges with antigens are essential for intestinal and MALT maturation. The intestinal immune system has the ability to tolerate harmless diets, common bacteria, and antigens, but fights pathogenic antigens to maintain intestinal homeostasis and prevents immune impairs (Castillo, Perdigón, & De Moreno de Leblanc, 2011; Mattila-Sandholm et al., 2002; Van Immerseel et al., 2010). Therefore, microbiota interaction with intestinal epithelial and immune dams is involved in the development of oral tolerance and modulates acquired and innate, topical and systemic immune systems (De Kivit, Tobin, Forsyth, Keshavarzian, & Landay, 2014).

2 | PROBIOTICS

Until today, several bacteria and fungi species have been used for human health. Several bacterial species and their role as a positive probiotic agent have been evaluated such as *Lactobacillus* and *Bifidobacterium* species. Accordingly, *Lactobacillus*, *Bifidobacterium*, and *Saccharomyces boulardii* are the most common bacterial and fungal species participating as probiotics (Mattila-Sandholm et al., 2002).

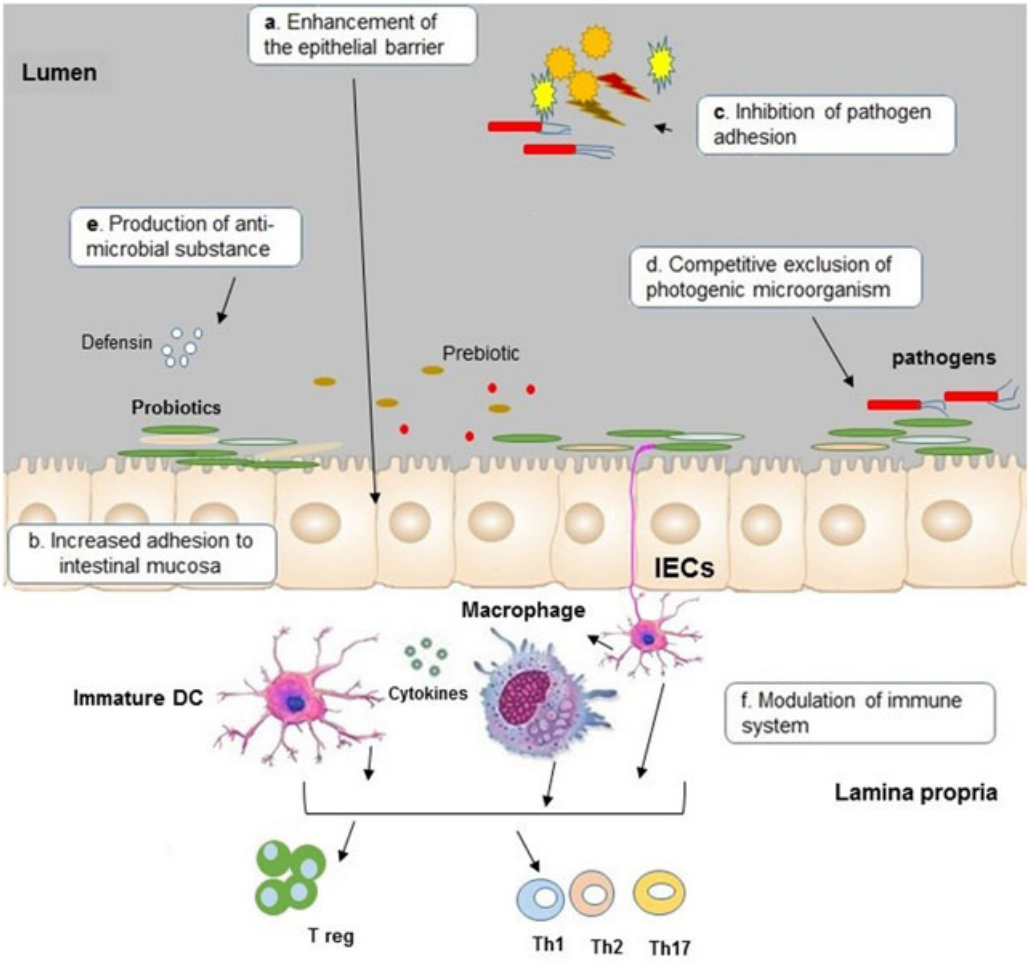

FIGURE 1 Major mechanisms action of probiotics. DC: denditic cells, IEC: intestinal epithelial cells [Color figure can be viewed at wileyonlinelibrary.com]

These micro-organisms when consumed in sufficient amounts, act in the interest of host health and are able to withstand the prevailing physiochemical conditions in the gastrointestinal tract (GIT; Castillo et al., 2011). Its beneficial effects have been demonstrated in some of the disorders, such as diarrhea, allergies, inflammatory bowel disease (IBD), lactose malabsorption, and necrotizing enterocolitis in preterm infants (Van Immerseel et al., 2010).

Despite the importance of symbiosis agents produced by intestinal bacteria, the absence of common organisms in germ-free (GF) mice can have a positive effect on some AD. Clinical symptoms have been attenuated in several models of autoimmune patients in the GF mouse, which sometimes leads to the perception that intestinal bacteria themselves are a threat to the immune system (Shen, Zuo, & Mao, 2013; Veerappan, Betteridge, & Young, 2012). However, this is likely to occur only in cases where the normal flora of the gut is destabilized and the harmful bacteria species increase too much.

These probiotics have numerous effects on the GIT and Gut-associated lymphoid tissue (GALT), which modulate intestinal function and immune responses by enhancing activation and adjustment or tolerance (Hidalgo-Cantabrana et al., 2014). These effects include the competitive elimination of pathogens in intestinal dams. The major probiotic mechanisms of action include increased integrity and enhancement of the epithelial barrier, increased adhesion to intestinal mucosa, and concomitant inhibition of pathogen adhesion, competitive elimination of pathogens in intestinal dams, production of antimicro-organism substances and modulation of dendritic cells (DC), the effect on T cell polarity and modulation of the immune system, and inflammation (the results of this function shown in Figure 1).

3 | PREBIOTICS

Various molecules can act as prebiotics such as SCFA, peptidoglycans, and polysaccharide A. Their main effect is related to microbial metabolism. In fact, if no dietary fiber is present in the colon, the anaerobic bacteria receive energy from protein fermentation (Hill et al., 2014). This metabolism results in the production of toxic and potent carcinogenic compounds (such as ammonium or phenolic compounds). In contrast, carbohydrate fermentation (such as dietary fiber) produces SCFAs such as acetate, propionate, or butyrate,

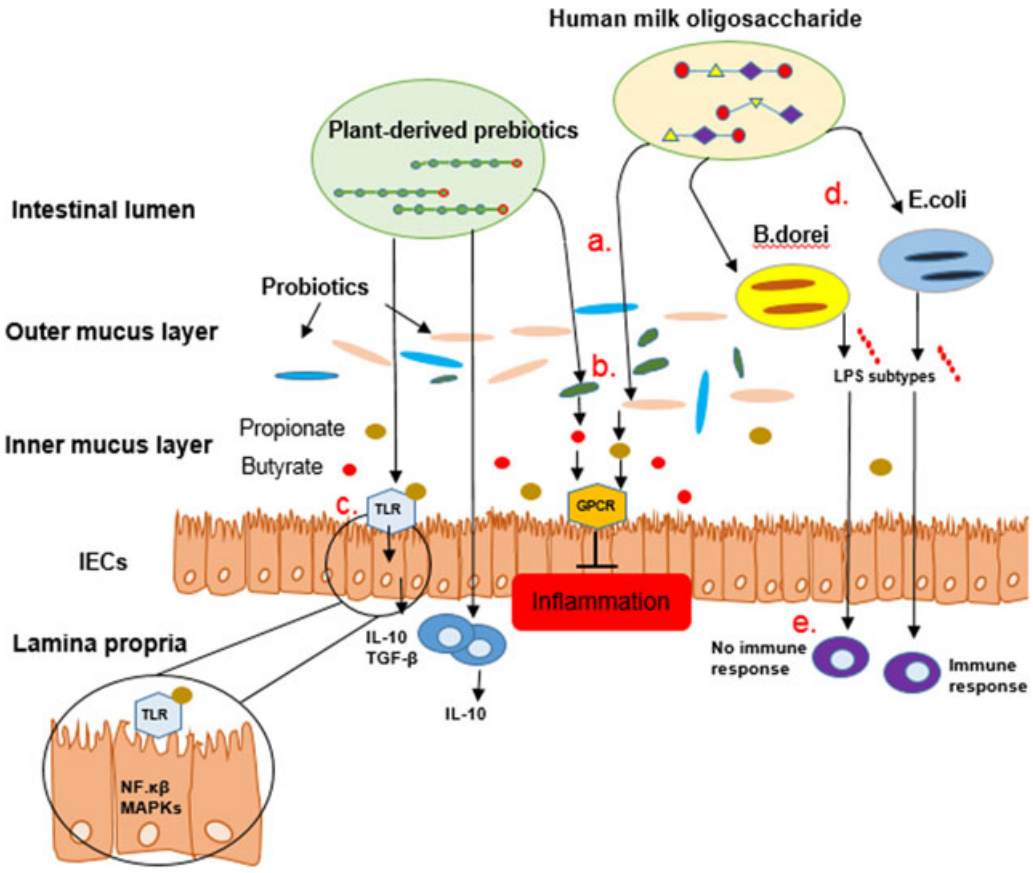

FIGURE 2 Mechanisms of action for prebiotic-mediated immune regulation. (a) Both plant- and human-derived oligosaccharides are metabolized by gut microbiota communities to (b) produce bacterial metabolites including SCFAs such as propionate and butyrate. SCFAs and other bacterial metabolites effects on APCs and IECs via Toll-like receptors and GPCRs. (c) Directly activate Toll-like receptors expressed on IECs and host immune cells by intact prebiotics may also induce the anti-inflammatory cytokines IL-10 and TGF-β. (d) Bacterial communities (*Bacteroides* dorei versus *Escherichia coli*) invert HMOs to produce LPS subtypes and products with different immunogenicity on the host (e). APC: antigen-presenting cells; GPCR: G protein-coupled receptor; HMO: human milk oligosaccharides; IEC: intestinal epithelial cells; IL-10: interleukin 10; LPS: lipopolysaccharides; NF-κβ: nuclear factor-κB; SCFA: short-chain fatty acids; TLR: toll-like receptor [Color figure can be viewed at wileyonlinelibrary.com]

which are not toxic to the host (Slavin, 2013) and generates potential fuel for epithelial cells. Several oligosaccharides are considered as prebiotic, which include inulin, Galacto-oligosaccharides (GOS), fructo-oligosaccharides, soybean oligosaccharides and xylo-oligosaccharides (Kondepudi, Ambalam, Nilsson, Wadström, & Ljungh, 2012).

Prebiotics are indigestible and resistant to absorption and digestion, so they are mainly transmitted to the colon and distal colon. Prebiotics are described as "selective" fermented compounds that allow for specific alterations in both the compositions (and activity of commensal microbes) conferring benefits to the host health (Fritzen-Freire et al., 2012). The most complex GOS and short-chain trisaccharides (such as sialyllactose or fucosyllactose) in human milk oligosaccharides (HMO) are usually the first prebiotics used by humans and used as the basis for the growth and activity of *Bifidobacterium* spp and lactic acid bacteria in infants (Geurts, Neyrinck, Delzenne, Knauf, & Cani, 2013). Apart from the structural features, the regulation of immune function through prebiotics is affected by the intestinal microbiota. Regulatory mechanism of the immune system is affected by prebiotics of both plant and human oligosaccharides are selected by a population of intestinal microbiota producing metabolites such as SCFAs. SCFAs and other bacterial metabolites can activate the G protein-coupled receptor (GPCR) expressions on the intestinal epithelial cells (IEC) to reduce host inflammatory responses. Intact prebiotics may also directly stimulate Toll-like receptors on IECs and host immune cells and induce expression of interleukin 10 (IL-10) and transforming growth factor β (TGF-β) anti-inflammatory cytokines. The bacterial population (*Bacteroides dorei* vs. *Escherichia coli*) metabolizes the HMOs and produces subtypes of lipopolysaccharides (LPS) with different immunogenicity in the host (Foolad, Brezinski, Chase, & Armstrong, 2013; Peshev & Van den Ende, 2014; Figure 2).

Apart from immune regulation through microbial interactions, growing evidence also indicates the direct potential of regulatory effects of oligosaccharides on the immune system. For example, laboratory studies have demonstrated that exposure to prebiotics directly results in the release of cytokines and chemokines in the intestinal epithelial cells, monocytes, and DC (Hill et al., 2014, Lehmann et al., 2015) which is shown in Figure 2.

4 | PROBIOTIC EFFECTS ON DIGESTIVE SYSTEM IMMUNE FUNCTION

Antigenic elements of probiotics (e.g., cell wall compounds) are able to pass the intestinal dam through intestinal epithelial and M cells on the surface of the Peyer's patches. Subsequently, these cells process and

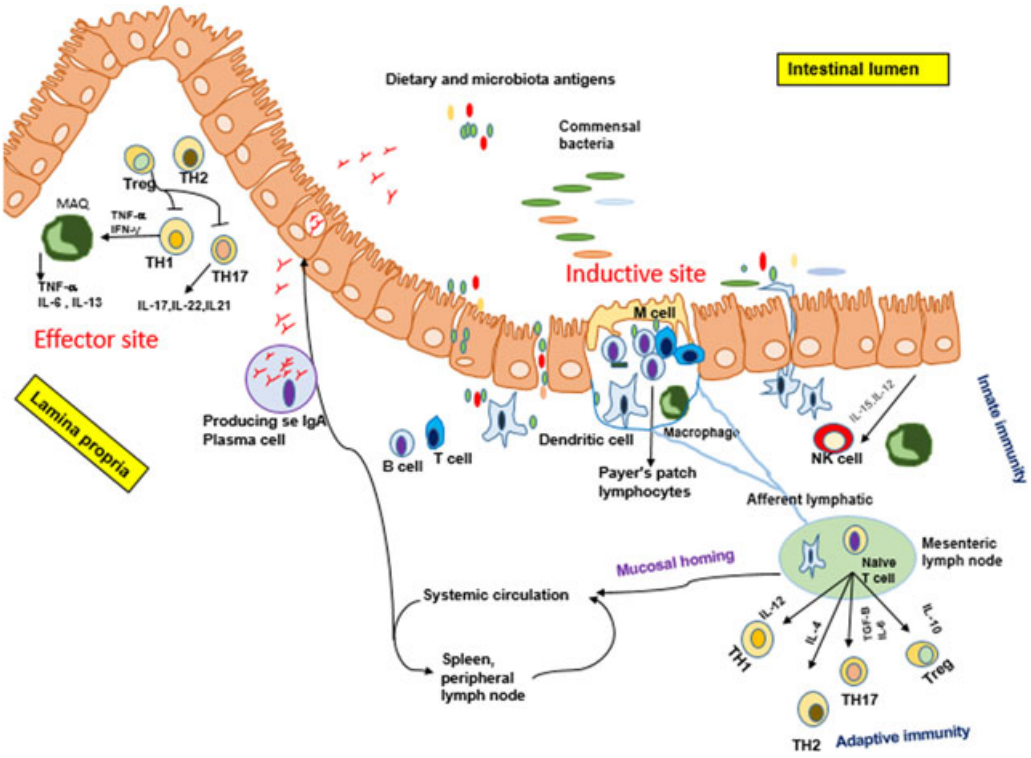

FIGURE 3 Modulation and development of innate and systemic immune responses by microbiota. The bacterial cells and soluble factors may then regulate and activate the APCs such as DCs and macrophages. The M cells may deliver the probiotic bacterial cells and their soluble factors by transepithelial transport from the intestinal lumen to lymphoid tissues within the mucosa. In addition, probiotics and/or their soluble factors may be captured by DCs. The postulated mechanism of action of probiotics on the regulation of systemic immune responses through the activated mucosal APCs. Antigen-primed mature APCs migrate to mesenteric lymph node to differentiate naive $CD4^+$ Th0 cells into various Th subpopulations (Th1, Th2, Treg, and Th17) depending on the cytokine secretion pattern. Cytokines and T cells will be drained into the blood system and migrate to liver and spleen ultimately to regulate the systemic immune responses there. APC: antigen-presenting cells; DC: dendritic cells; IgA: immunoglobulin A; NK: natural killer [Color figure can be viewed at wileyonlinelibrary.com]

present them to the immune system, which includes the innate and acquired immune responses.

Inductive sites of the immune response in the intestine are related to the GALT follicles organized at the PP's surface. The M cells present in the PP have the ability to transport and absorb macromolecules, micro-organisms, and particles directly from the lumen to lymphatic tissue via endocytosis. The absorption of antigens, macromolecules, and micro-organisms can also occur through active transport by vesicles between epithelial cells in enterocyte cells and M cells. Eventually, DC may expand its dendrites through tight epithelial attachments and thus directly absorb lumen antigens. When antigenic molecules are passed across the intestinal tract, they can stimulate innate and flexible immune systems (Madej & Bednarczyk, 2016; Sławińska et al., 2014).

5 | THE INTERACTION OF PROBIOTICS WITH THE IMMUNE SYSTEM

Probiotics present in the temporary form, and colonize only during their regular consumption period in the intestines of children and elder matures, and disappear as soon as their intake is stopped, likely through the competitive control of normal commensal flora. Although probiotics seem to make and mediate efficient functions without affecting the overall composition of the fecal microbiota, this may not be very surprising, since there is evidence simply describing the number of bacteria in the microbial community that cannot predict functional and biological outcomes (Kim et al., 2013; Walker, 2013).

The direct interaction of bacteria and their products with IECs is a potential route for the interaction of host micro-organisms at intestinal mucosal surfaces and GALT. IECs and APCs are participants in the innate immune system. Additionally, APC interactions with T cells are necessary to succeed in the acquired immune responses. Commensal and probiotic bacteria modulate the activity of IEC cells, which in turn allows IEC to confer effects on key immune cells including DCs, macrophages, and intraperitoneal lymphocytes (Fong, Shah, Kirjavainen, & El-Nezami, 2016; Villena & Kitazawa, 2014; Figure 3).

Inhibition of NF-κβ activation in IECs by commensal colon bacteria was first detected in case of *Salmonella* spp (PhoPc *S. typhimurium* and *S. pullorum*) that was able to inhibit the nuclear transfer of DNA-binding NF-κβ protein, by inhibiting Ikβ-α ubiquitination (Kemgang, Kapila, Shanmugam, & Kapila, 2014; Villena et al., 2014). This mechanism is reported to reduce the expression of inflammatory cytokines and their mediators, such as IL-8 (Yadav et al., 2016). Therefore, IECs assumed able to counteract the high burden of commensal bacteria present in the distal area of the human intestine.

6 | PROBIOTICS AND INNATE IMMUNE CELLS

Innate immune cells act as the first line of defense against pathogens, but their ability to recognize antigens is not specific. The phagocytic cells, such as neutrophils, monocytes, macrophages, and natural killer (NK) cells are key cells of the innate immune system. DCs, macrophages, and monocytes are the interface between innate and acquired immune systems because they act as APCs operating professionally.

Probiotics have antiviral properties, while also increasing the cytotoxic potential of NK cells and the macrophage phagocytosis capacity. In fact, cell wall components, such as lipoteichoic acid (LTA), of Gram-positive bacteria (*Bifidobacterium* spp or *Lactobacilli*) can stimulate NO synthase (as a mechanism of cell death infected with the virus) by macrophages (via the secretion of tumor necrosis factor α [TNF-α]) induces an increase in the configuration of important phagocytosis receptors such as FcγRIII and TLRs (Dongarrà et al., 2013; Sommer & Bäckhed, 2013). The role of these cells is very important for the initiation of acquired immune responses, as the primary T cells respond to antigens provided by APCs and the cytokines produced and secreted in the acquired immunity, differentiating the specific $CD4^+$ T helper subtypes (Th1, Th2, or Th17) cells (Kim et al., 2014; Walker, 2013; Figure 3).

7 | MODULATION OF INTESTINAL EPITHELIAL CELLS

In the aspect of homeostasis in the intestine, there is a good balance between the proliferation of epithelial cells, differentiation, and apoptosis, which allows an active and dynamic cell dam to constantly replace itself and protect from infectious pathogens. The IECs represent a physical barrier that protects the separation of luminal microbes, digestion, and the mucosal immune system. Probiotics and commensal species can interact with IECs in a variety of ways, including indirect effects on biofilms and direct impact by enhancing dam function by increasing tight junction and production of mucin, induction of antimicrobial peptides and the production of heat shock proteins; modulating the proinflammatory, immunomodulatory cytokines, and interfering with pathogenesis (Chen, Xie, Yu, & Zhou, 2008).

Some of the effects include modulating cytokine production by epithelial cells, increasing mucin secretion, increasing the activity of phagocytosis and NK cells, activating T and natural killer T (NKT) cells, stimulating IgA production, and reducing T cell proliferation (Qiu, Zhang, Yang, Hong, & Yu, 2013). Given that each effect is strain specific, an action is specific to certain bacterial strain. Probiotics can regulate the responses of T cells and release cytokines through a specific species. For example, *L. rhamnosus* induces immune cells towards Th1 in children suffering from allergies to cow milk, and in atopic children, relieves inflammation by stimulating IL-10 production. Probiotics and their secreted factors may stimulate DCs, macrophage and monocyte cells with their TLR receptors, and then stimulate the specific T cells responses.

Evidence of how microbiota forms the body's immune system is based on the studies of GF mice, which completely lack microbiota. Such mice demonstrate a deep immunodeficiency: not only the

hypoplastic cellular parts of the B and T cells is impaired in the PPs and lamina propria, but the spleen and lymph nodes also have areas with weak B and T cells. As a result, serum IgG and IgA levels in the GF mice are reduced (Dong, Rowland, & Yaqoob, 2012). In addition, cytokine production is greatly influenced, and thus the response of T cells changes to the Th2-type responses. Typically, immune cells are isolated from intestinal microbiota by a single-cell epithelial layer. Hence, immune responses against microbiota are rare and only occur when infiltrated into the epithelial layer. Such a reaction seems to be limited to the mucosal layer, because DCs that are irritated by these bacteria remain in the PPs or mesenteric lymph nodes (MLN), and therefore it is assumed that the systemic immune system ignores bacteria in the intestines. In fact, the effect of intestinal bacteria on the intestinal immune system, especially in the innate immune system, such as neutrophils and macrophages, is significant. These cells recognize microbial products via pattern recognition receptor (PRR) reactions to microbiota are rare and only happen when they penetrate the epithelial layer (Bron, Van Baarlen, & Kleerebezem, 2012).

The use of probiotics as a preventive and therapeutic strategy for various diseases from allergies to autoimmune diseases (AD) has recently been reported. Three interacting factors, including intestinal microbiota, an intestinal leaky mucous membrane, and intestinal immunity, are responsible for making a complete environment for the development of AD. The regulation of intestinal microflora by probiotics can influence the development of mucosal/systemic immunity along with AD. In addition, by using various probiotic strains, the development or stimulation of Th2-mediated immune responses is described which exacerbates atopic disease. Similarly, some probiotics are known to stimulate Th1 responses, which is one of the mechanisms that can suppress the Th2-mediated allergic diseases. As a result, excessive immunosuppression may be expected to exacerbate or stimulate Th1-mediated immune responses and to cause diseases such as type-1 diabetes and multiple sclerosis. Probiotics are used in allergic diseases, which are sometimes useful such as in patients with atopic dermatitis and allergic rhinitis (Fuller, 2012). Based on the health hypothesis, alterations in human intestinal microflora in developed societies appear to increase the prevalence of AD compared with allergies. The regulation of gastrointestinal microbial compounds by probiotics may affect the development of mucosal/systemic immunity as well as AD (Parvez et al., 2006).

8 | PROINFLAMMATORY CYTOKINES MODULATION

Probiotics can suppress inflammation by inhibiting various signaling pathways such as the NF-κβ pathway, which may be related to alterations in mitogen-activated protein kinases (MAPK) and PRR pathways. Various probiotics can inhibit Ikb-βα or ubiquitination phosphorylation and NF-κβ inhibitor degradation and reduce the nuclear translocation of p65, which reduces the binding of NF-κβ to the DNA. Selected probiotics can also inhibit the binding of the LPS to the CD14 receptor, thereby reducing the overall activation of NF-κβ and, as a result, the production of proinflammatory cytokines (Mykhal'chyshyn, Bodnar, & Kobyliak, 2013). Some probiotics can also control the MAPK pathway checkpoints, which indicate that both NF-κβ and MAPKs play a role in the production of proinflammatory cytokines, thus the use of probiotics may target these pathways, which have a proper anti-inflammatory effect. For example, lipoteichoic acid (a TLR2 ligand) isolated from *L. plantarum* (pLTA) inhibits the production of TNF-α induced by LPS (TLR) by reducing the degradation of Ikb-α and Ikb-β, which results in suppression of NF-κβ activation (Carey & Kostrzynska, 2012; Lebeer, Claes, & Vanderleyden, 2012). Additionally, pLTA pretreatment inhibits the phosphorylation of ERK, JNK, and P38 MAPKs in monocytic THP-1 cells, indicating a modulation of signaling pathways by endotoxin tolerance. Upstream of the NF-κβ and MAPK pathways detect microbes by PRRs, and these components are also affected by pLTA. The expression of LPS caused by TLR4, NOD1, and NOD2 by pLTA is suppressed, but the interleukin-1 receptor-associated kinase 3 is induced, which is a negative TLR signaling regulator (Carey & Kostrzynska, 2012). This indicates that pLTA can tolerate LPS (ET) because these PRRs are involved in the LPS recognition. However, the expression of LPS, CD14 coreceptor intolerable cells with pLTA is increased suggesting that CD14 also participates in the interaction between TLR2 and LTA, which may reduce the interaction between CD14 and LPS and reduce inflammation. These results indicate that pLTA is effective in preventing and treating LPS-induced septic shock. Additionally, pure pLTA inhibits LTA (aLTA) production by *Staphylococcus aureus* induced by TNF-α in THP-1 cells, thus indicating a TLR2 mediated homo-tolerance level (Rodes et al., 2013). The effects of pLTA on NOD signaling have also been studied. The proinflammatory response induced by *Shigella flexneri* GN (flexPGN) on THP-1 cells was reduced after pretreatment with pLTA, resulting in a significant reduction in the production of TNF-α and IL-1, which was associated with a decrease in NOD2 expression regulation. This finding demonstrated that pLTA could modulate the flexPGN-associated inflammation. Additionally, pLTA-resistant THP-1 cells reduce ERK, JNK, and P38 MAPK phosphorylation and also decrease NF-κβ activity. These results indicated that pLTA could induce interactions between TLR2 and NOD2 signaling against a NOD2 agonist such as flexPGN (Robertson & Girardin, 2013, van Baarlen, Wells, & Kleerebezem, 2013).

In addition to modulating the NF-κβ pathways, probiotics can inhibit the activator protein-1 (AP-1) transcription factor (Fos/Jun hydrodynamic factor) by inhibiting C-Jun regulated by MAPK. A special strain of *L. reuteri*, ATCC PTA 6475 suppresses TNF-α transcription by inhibiting the activation of c-Jun and then AP-1. The levels of proinflammatory cytokines can also be modulated by activating the cytokine-signaling proteins (SOCS) family (Plaza-Diaz, Gomez-Llorente, Fontana, & Gil, 2014). SOCS protein is a negative regulator of cytokine-signaling pathways characterized by activation/phosphorylation dependent on the JAK transcription factors of the SMART STAT; a combination of the JAK/STAT/SOCS isoforms that

detect immune expression profiles (Habil, 2015; Russo, Linsalata, & Orlando, 2014). In general, STAT1 is associated with signaling interferon (IFN) and IL-12, while STAT3 is associated with anti-inflammatory signals IL-10 and IL-6. SOCS3 is induced by IL-10 and IL-6, which can suppress the expression of the gene for proinflammatory cytokines and also inhibit negative signaling of IL-10 and IL-6. *Bifidobacterium* spp can reduce the levels of LPS-induced messenger RNA (mRNA), IL-1, and TNF-α in RAW264.7 macrophage cells, which are related to inhibiting Ikβ phosphorylation and increasing the level of SOCS1 and SOCS3 mRNA (Yeşilova, Çalka, Akdeniz, & Berktaş, 2012). A similar study demonstrated that *B. breve*, *L. rhamnosus GG* (LGG), and *L. helveticus* induce SOCS3 macrophage expression. These studies suggest that different inflammatory pathways can be induced by the use of different probiotics to produce anti-inflammatory effects. Such anti-inflammatory effects are not limited solely to the direct effects of probiotic-dependent SOCS suppression of inflammatory cytokines in macrophage cells; LABs have induced the expression of SOCS2 in *L. plantarum* and SOCS3 in *L. acidophilus*, which indicates activation/phosphorylation of STAT1 and STAT3, and JAK2 inactivation. Such effects in JAK2 have a profound and discriminatory effect on the polarization of macrophages and subsequent specific responses that JAK2 is necessary for GM-CSF and IFN signaling, but not for IL-6 and IFN-α/β signaling (Vaghef-Mehrabany et al., 2014).

In addition to IL-10, granulocyte colony-stimulating factor (G-CSF) has anti-inflammatory effects. It has been demonstrated that *L. rhamnosus* GG and GR-1 release G-CSF from macrophages and G-CSF has a paracrine effect on neighboring macrophages and can suppress inflammatory responses. G-CSF suppresses TNF-α production by activating STAT3 and inhibiting C-Jun. In addition, GR-1 strain increased the production of G-CSF in human intestinal lamina propria cells. However, the reduction of G-CSF production was observed in cells from the tissue of patients with IBD. GR-1 can regulate immune responses through G-CSF release, and G-CSF produces proinflammatory cytokines through crosstalk between macrophages and DC. Overall, these results indicate that the production of *L. rhamnosus* G-CSF may have anti-inflammatory effects on the key immune cells in the intestine and is important for the maintenance of immunological normal homeostasis in the intestine.

Although the probiotics modulation characteristic of the macrophage signaling pathways is progressing at high speeds, the different effects of probiotics are different in the subgroups of macrophage. In general, macrophages exist in two subsets: M1 macrophages with proinflammatory and M2 macrophages with anti-inflammatory/regulatory effects. The M2 macrophage is associated with mucosal homeostasis and tolerance, which is activated by anti-inflammatory/regulatory cytokines such as IL-10, TGF, and IL-1Rα. On the other hand, M1 macrophages are associated with immunogenic activation and proinflammatory responses derived from TNF, IL-1, IL-6, IL-8, and IL-12 produced by this subset (Abdelouhab et al., 2012). The desired effect can be the use of probiotics to regulate the selectivity of the macrophages subtypes, thus M1 macrophages are inhibited in inflammatory pathologies and M2 macrophages is inhibited in suppressor pathologies such as mucosal cancers (Rodes et al., 2013). To this end, a group of probiotic species such as *L. casei Shirota*, *L. fermentum*, *L. plantarum*, *L. salivarius*, and *B. breve* has been described to selectively modulate the production of IL-6, TNF-α, and LPS-induced activation of NF-κβ from M1 and M2 macrophages; all of which also depend on the CD14-dependent TLR2/TLR4 coreceptor expression. The potential of probiotics to regulate the inflammatory subset of M1 macrophages through their effects on TNF-α secretion and the fact that cytokines often exhibit excessive levels, necessitate further studies to control signaling events and secretion of proinflammatory cytokines overlapping TNF-α. Two of these related cytokines including IL-1 and IL-18, indicate TNF-α functional impairment. Both of these are produced as precytokines and have different processing pathways before the discharge.

9 | ACQUIRED IMMUNE RESPONSE MODULATION THROUGH PROBIOTICS

Many probiotic species are able to stimulate the production of secretory IgA by B cells that bind to antigens, thus limiting their access to the epithelium. Probiotics such as LGG have been demonstrated to stimulate specific anti-IgA antibodies against rotavirus in children infected with rotavirus viral gastroenteritis, which is theoretically significant in preventing recurrent infection. Therefore, they can reduce the frequency and duration of diarrhea (Habil, 2015).

Currently, it has been proven that our diet affects colonizing bacteria and intestinal microbiota by making a pattern between useful and unuseful bacterial species. When fermented, fiber produces microbiota metabolite or SCFA, which can have its own beneficial effects on health and preserve homeostasis and metabolism function, as well as profound anti-inflammatory effects through adjusting development and preparation performance. Strong anti-inflammatory effects by SCFA may act via GPCRs (Jeon et al., 2012), or through inhibition of histone deacetylase; these metabolites contribute to the development of coliform epithelium homeostasis, the improvement of tightly controlled areas between intestinal glands and host (Van Immerseel et al., 2010; Veerappan et al., 2012). Similarly, these metabolites can also affect immune cells located near the lymph nodes of the intestine, as well as by systemic circulation, can affect environmental tissues. An overview of the effect of the diet on the microbiota of the gut and the way microbial metabolites can be produced alternate the outcome of inflammation and autoimmunity (Kwon et al., 2013; Plaza-Diaz et al., 2014; van Baarlen et al., 2013). Modulation of the immune system is shown in Figure 3.

10 | PROBIOTICS ARE ABLE TO REGULATE THE SYSTEMIC RESPONSES BY MUCOSAL APCS

The APCs including DCs, macrophage, and monocyte cells are essential for maintaining homeostasis in the gastrointestinal tract. These cells can process antigens, and along with class-1 and class-2

major histocompatibility complex (MHC) molecules, present them on their surface in the process of maturation. Furthermore, adhesive molecules and stimulants are expressed on the mature APCs, which convert the early T cells into T cells. The APCs produce cytokines and chemokines required for the replication, differentiation, and response of T cells (Basso et al., 2014). For example, Interleukin 12 stimulates these cells toward Th1. The APCs play a critical role in the initiation of a specific immunological response or immunological tolerance induction (Hempel et al., 2012).

The gastrointestinal tract provides various antigens such as food antigens and various microbes and potentially pathogenic microbes. Antigens and colonized bacteria are associated with gastrointestinal mucosa with epithelial cells and underlying immune cells, such as APCs (Fong, Kirjavainen, Wong, & El-Nezami, 2015, Villena & Kitazawa, 2014). Probiotics are prescribed orally and microbial components are detected by receptors for PRR patterns such as TLRs on APCs and epithelial cells; then the regulatory effect of the immune system is placed in the intestine (Villena et al., 2012).

After binding of TLR to PAMP and antigen insertion, APCs mature with the expression of stimulant molecules such as CD80 and CD86, and IL-12 associated with Th cells (Jenkins & Moon, 2012). Additionally, microbial antigens associated with MHC class II are presented on mature APC for presenting to immature T cells to activate acquired immune response (Marchuk, 2013). Since MyD88 deficient DCs are defective in IFN-γ production, the innate immune response is dependent on MyD88. The mature APCs migrate to MLN to differentiate the $CD4^+$ Th0 cells into various Th subtypes, according to the cytokine pattern (Liu & Uzonna, 2012; Figure 3). In this case, IL-12 and IFN-γ cause differentiation of Th1; IL-4 and IL-2 contribute to the Th2 differentiation; TGF-β and IL-6 differentiate Th17, and TGF-β and IL-12 promote the Treg differentiation. Cytotoxic T lymphocytes are also activated and enhance the cellular immune response and cause phagocytosis with Th1 cells. The cytokines and T cells are transmitted to the bloodstream and eventually transferred to the liver and spleen to regulate the immune system (Riella, Paterson, Sharpe, & Chandraker, 2012).

11 | THE SHAPING OF T CELL SUBSETS BY MICROBIOTA

Recent findings suggest that intestinal microbiota has a major impact on the systemic immune system. Specific microbiota controls the differentiation of cells in lamina propria, in which the $CD4^+$ T cells (Th17 cells) expressing IL-17 are particularly abundant. Th17 cells produce a majority of the proinflammatory cytokines such as IL-17, IL-21, and IL-22, and thus play an important role in AD, such as arthritis and experimental autoimmune encephalomyelitis (Jeon et al., 2012). The presence of Th17 cells in the small intestine is associated with intestinal microbiota and their number significantly decreases in GF lamina propria, in spite of the increase in the number of regulatory cells $Foxp3^+$ T (Treg) cells. Both Th17 and Treg cells need TGF-β, while the differentiation of Th17 cells also requires IL-6 (Kwon et al., 2013). The Treg preferred differentiation and the absence of Th17 cells probably reflect alterations in the lamina propria medium cytokines in the small intestine of GF mice. In the large intestine, a CD70 high CD11c low subset in lamina propria, producing cytokines to differentiate Th17 activated with ATP derived from commensal bacteria can lead to the preferential differentiation of Th17 cells. In an effort to determine whether all of the intestinal microbiota in general or just a specific subset of bacteria, was responsible for the development of Th17 cells, Ivanov treated rats with antibiotics and selected them to kill a variety of bacteria. They found that vancomycin-susceptible bacteria are capable of causing and differentiating Th17 cells in small intestinal lamina propria. Later, they identified the same group of segmented filamentous bacteria (SFB) responsible for the induction of Th17 cells (Ivanov et al., 2009). The same mice prepared from two different sources differed in the number of Th17 lamina propria cells, and microbiota analysis indicated that the SFB colonization was different between the two populations. The importance of SFB in launching T cell responses in the intestines in other groups was confirmed by evaluating the cytokine profile of the gut in GF mice with SFB. It is interesting to note that engineered mice with the expression of the alpha-defensin2 gene (DEFA2; encoding a protective antimicrobial peptide) lacked SFB and the number of Th17 cells in their lamina propria was decreased, while in negative transgenic mice, SFBs were present (Anukam & Reid, 2007; Ashraf & Shah, 2014) (Figure 3).

12 | IN VIVO IMMUNOREGULATORY EFFECTS OF PROBIOTICS

In ApoE*3Leiden mice fed with a high-fat diet, the *Propionibacterium freudenreichii* ssp. shermanii JS has been demonstrated to reduce the TNF-α immune response in the intestine, while LGG leads to an increase in IL-10 level (Oksaharju et al., 2013). After treatment with *L. casei Shirota* in concanavalin A-induced spinal cord stem cells in nonobese diabetic mice, it was demonstrated that a low level of IFN-γ was produced by them, but higher levels of IL-2, IL-4, IL-6, and IL-10 were produced resulting in the reduction of T-$CD8^+$ cells that contribute to the decrease in B cells (Cagliero, Marini, Cena, Veglia, & Guardamagna, 2014).

B. breve seems to eliminate food allergy because of a reduction in the Th2 response in allergic rats and increases the number of Treg and IL-10 and recover the activity of the intestinal epithelial duct. *B. longum* CECT 7347 increased the expression of NF-κβ and IL-10 in the intestinal mucosal tissue of enterocolitis and reduced the production of TNF-α (Jeon et al., 2012). *B. pseudocatenulatum* JCM 7041 reduced production of IFN-γ and IL-6 in PPs of OVA23-3 transgenic mice (Fong et al., 2016).

Escherichia coli Nissle 1917 (EcN), along with minocycline, improves the damage to the intestine and prevents colitis occurrence (Alvarez, Badia, Bosch, Giménez, & Baldomà, 2016). EcN with

minocycline has been reported to have a more beneficial effect on the mouse model induced by dextran sodium sulfate, or the activating colitis because they decrease the expression of TNF-α, IL-1β, IL-2, MIP-2, MCP-1, ICAM-1, and iNOS, and MMP-9 and increases the production of MUC-3 and ZO-1 (Plaza-Diaz et al., 2014). It has been demonstrated that EcN reduces IL-4 and IFN-γ with an increase in IL-10 production and a tendency to increase the secretion of TGF-β in the spleen of mice with allergen associated dermatitis.

The combination of *L. acidophilus* NCC 2628, *L. acidophilus* NCC 2766 and *L. johnsonii* NCC2767 increased the expression of intestinal IL-10 but decreased the ratio of TNF-α/IL-10, IFN-γ/IL-10, and IL-12p40/IL-10 and thus a combination of probiotics may reduce bowel inflammation in dogs with chronic enteropathy (Fong et al., 2016).

13 | EPIGENETIC AND POSTTRANSCRIPTIONAL EFFECTS OF PROBIOTICS ON GENE EXPRESSION

Recently, probiotic functions in IEC and other cells have been recently identified, including epigenetic and posttranslational alterations that lead to alterations in the expression of genes involved in immune responses. One of these mechanisms involves a different induction of microRNAs (miRNAs; Veltman, Hummel, Cichon, Sonnenborn, & Schmidt, 2012). Recently, *L. paracasei* NCC 2461 has been demonstrated to increase anti-inflammatory effects in peripheral blood mononuclear cells (PBMCs) by regulating miRNA. This effect is related to the reduction of the level of miR-27a, which plays a role in regulating the expression of IL-10. It is also clear that the interaction between the host immune system and the commensal micro-organisms is bidirectional. For example, a recent study has demonstrated that host mRNA secreted by intestinal epithelial cells through exosomes in feces contributes to the redistribution of the composition, and structure of microbiota. The researchers also found that miRNA feces could enter living bacteria, bind to bacterial DNA, and regulate gene transcription to enhance the growth and multiplication of bacteria. A recent study suggests that miRNA is induced by probiotics soluble intermediates (Viladomiu, Hontecillas, Yuan, Lu, & Bassaganya-Riera, 2013).

Each species of bacteria has its own substrate. Most strains belonging to *Bifidobacterium* and *Lactobacillus* spp preferentially use fructan instead of glucose as a substrate (Fong et al., 2016; Villena & Kitazawa, 2014). However, other bacteria such as *Clostridia* and *Bacteroides* are also able to grow with fructan (Ghouri et al., 2014; Villena et al., 2014). However, their growth from *Bifidobacterium* is less effective due to less absorption from the media (especially in the case of oligofructose). Therefore, prebiotics are useful to ensure the selective stimulation of bacterial strains (Kim et al., 2014). In fact, in humans, prebiotics, in particular, increase *Bifidobacterium* spp populations in fecal specimens (Kayama, Jeon, & Takeda, 2014; Kemgang et al., 2014; Yadav et al., 2016), while the population of *Lactobacilli* is significantly increased in rodents (mice and rats; Basso et al., 2014; Hempel et al., 2012).

14 | CONCLUSION

Probiotics suppress the inflammation by inhibiting various signaling pathways and reduce the overall activation of NF-κβ and the production of proinflammatory cytokines. Some modulatory effects of probiotics include cytokine production by epithelial cells, increased mucin secretion, and activity of phagocytosis and NK cells, activation of T and NKT cells, stimulation of IgA production, and a decrease in T cell proliferation. Intestinal microbiota has a major impact on the systemic immune system. Specific microbiota controls the differentiation of cells in lamina propria, in which $CD4^+$ T cells (Th17 cells) secrete IL-17. The presence of Th17 and Treg cells in the small intestine is associated with intestinal microbiota, with the preferential Treg differentiation and the absence of Th17 cells, possibly reflecting alterations in the lamina propria cytokine dependent on the intestinal gut microbiota.

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