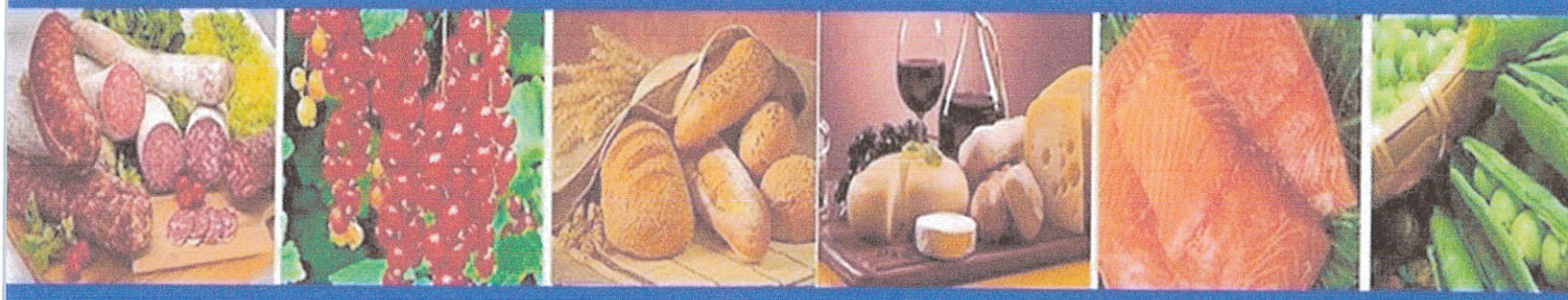

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CONTENT

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RESPONSES OF DENDRITIC AND NK CELLS AFTER MULTISPECIES PROBIOTIC ADMINISTRATION IN BALB/C MICE

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ABSTRACT

Dendritic and Natural killer (NK) cells play important roles in the innate immune response. The administration of probiotics is known to affect the immune response. The study aims to assess the effects of multiple probiotic species on the activities of dendritic and NK cells after gastrointestinal damage induced by bacterial lipopolysaccharide (LPS). Male Balb/c mice (n=24) were randomized into four groups: the K-I group (LPS and probiotics), K-II group (LPS only), K-III group (probiotics only), or K-IV group (no intervention). LPS was produced by *Escherichia coli* O5:B55 cells, while the probiotics were a combination of *Lactobacillus acidophilus* PXN 35, *L. casei* subsp. *casei* PXN 37, L. rhamnosus PXN 54, L. bulgaricusPXN 39, Bifidobacterium breve PXN 25, B. infantis PXN 27, and *Streptococcus thermophilus* PXN 66. LPS was administered on day 15, while probiotics were administered for 21 consecutive days. After 21 days, the mice were sacrificed and the numbers of dendritic and NK cells were determined by immunohistochemical staining of the ileum. Comparisons with the independent samples *t*-test showed that as compared to the control group, probiotic administration had significantly increased the numbers of dendritic cells, but not NK cells. Meanwhile, in the presence of LPS, there was a significant difference in the number of dendritic cells between the probiotic-LPS and the LPS only groups, but not NK cells. Multiple probiotic species can regulate the innate immunity response through dendritic cells, but not NK cells, in Balb/c mice.

1.Introduction

Pathogenic bacteria, including those that cause diarrhea, induce the release of various cytokines (Sheil *et al.*, 2006; Kuo, Merhige and Hagey, 2013)2), which will lead to an imbalance in the immune response (Saavedra, 2007). Macrophages are the first line of defense against microbial invasion. Secreted cytokines can recruit polymorphonuclear cells to the area of inflammation in the lamina propria. In the immature phase, dendritic cells are also phagocytes that can process both soluble and particulate antigens. The most significant functions of dendritic cells are the processing and presentation of antigens, especially naive T cells (Mannon, 2005; Shi *et al.*, 2017). Dendritic cells can recognize antigens by monitoring extracellular areas of the lamina propria, by phagocytosis of apoptotic epithelial cells, or hand interdigitation through tight junctions (to prevent damaging to junction

integrity) in order to directly recognize antigens in the lumen (Mannon, 2005; Delcenserie *et al.*, 2008).

Natural killer (NK) cells also participate in the innate immune response in the intestinal mucosa and play important roles against bacterial infections. Despite being derived from T cells as precursors, NK cells do not react to adaptive antigens. Nevertheless, NK cells recognize class I major histocompatibility complex (MHC) molecules through the binding of the surface receptors, which then inhibits the release of perforin and ganzyme proteins. Cells that do not express MHC class I molecules, such as virus-infected or tumor cells, are subjected to the activities of NK cells (Mannon, 2005).

Probiotics are combinations of microorganisms that have demonstrated or thought to have some beneficial effect when consumed (Kearney and Gibbons, 2018), such as reducing the pH of the intestinal lumen, secretion of antimicrobial peptides, inhibition of bacterial adhesion and invasion of epithelial cells, improving barrier function by increasing mucus production, increasing barrier integrity, and improving immunomodulation of epithelial cells, dendritic cells, monocytes/macrophages, and lymphocytes (B lymphocytes, NK cells, T cells) (Floch and Montrose, 2005; Ng *et al.*, 2009). Studies of mice and humans have confirmed that probiotics can induce an immune response and accelerate the healing of various gastrointestinal disorders both acute and chronic (Isolauri *et al.*, 2001; Marteau *et al.*, 2001; Guarino, Vecchio and Canani, 2009; Ritchie and Romanuk, 2012).

These findings of previous studies present an opportunity to explain the mechanisms of probiotics in the prevention of diarrhea through the role of dendritic and NK cells. The mechanism are further explained through experiments that are designed to analyze the relationship between innate immunity activation, especially dendritic and NK cells, in healthy versus pathogen-exposed mice.

2. Materials and methods

2.1. Animals

Male Balb/c mice (n = 24; age, 10–12 weeks; body weight, 30–40 g) were obtained from the Farma Veterinary Center (Surabaya, Indonesia) and acclimated for 1 week prior to experimentation. The study protocol was approved by the Animal Care and Use Committee of the Veterinary Medicine School of Universitas Airlangga (Surabaya, Indonesia). The mice were fed standard feed with free access to water at all times. After acclimation, the mice were randomly allocated to one of four groups: the K-I group, which received probiotics and lipopolysaccharide (LPS), the K-II group, which received LPS only, the K-III group, which received probiotics only, or the K-IV group, which received no intervention. LPS was administered only once on day 15, while probiotics were administered for 21 consecutive days. Each experimental group consisted of six mice. All mice were examined daily for morbidity and other symptoms of illness, such as reduced activity level, abnormal evacuation, and decreased body weight. At the end of the experiment, the ileum was dissected for analysis.

2.2. Probiotics and LPS

The probiotics used in this study contained 1×10^9 colony-forming units of a combination of bacteria *Lactobacillus acidophilus* PXN 35, *L. casei* subsp. *casei* PXN 37, *L. rhamnosus* PXN 54, *L. bulgaricus* PXN 39, *Bifidobacterium breve* PXN 25, *B. infantis* PXN 27, and *Streptococcus thermophilus* PXN 66. The probiotics in powder form were dissolving in 1.5 mL of sterile water and administered to mice in groups K-I and K-III via a gastric tube once daily for 21 consecutive days.

LPS, as a representative bacterial endotoxin, was produced by Escherichia coli O55:B5 cells (L2880; Sigma-Aldrich Corporation, St. Louis, MO, USA). LPS was dissolved in 0.9% non-pyrogenic sterile NaCl (10:1 ratio) and administered orally through a gastric tube on day 15 at dose of 250 μg/kg

body weight. LPS was orally administered via a gastric tube on day 15 of the study to the mice in both groups.

2.3. Histological analysis and detection of immunoglobulin-producing cells

On day 22 (at the end of the experiment), the abdomens of Balb/c mice in all groups were opened under ether anesthesia. After cleaning, 10% formalin buffer solution was used to fix the ileum sections. This process was followed by dehydration, clearing, and embedding. Tissue sections were probed with mouse monoclonal antibodies against follicular dendritic cells (F3803; Sigma-Aldrich Corporation) and NK cells (MA1-70100; Thermo Fisher Scientific, Waltham, MA, USA). The samples were observed under a light microscope (CX21; Olympus, Tokyo, Japan) and photographed with an ILCE6000 camera (Sony, Tokyo, Japan). The number of immunopositive cells was determined by counting the mean number of cells in 20 random fields at 450× magnification. The results are expressed as the number of cells in fields of vision.

2.4. Statistical analysis

Differences between groups were analyzed with the independent sample *t*-test for normally distributed data or the Mann–Whitney test for abnormally distributed data. A probability (p) value of < 0.05 was considered statistically significant

3.Results and discussions

The aim of this study was to analyze ability of probiotics to modulate the mouse immune responses, as represented by dendritic and NK cells, in response to exposure to LPS. The mean values of dendritic and NK cell counts for each group are presented in Figure 1 and the baseline characteristic has shown on table 1.

Table 1. Baseline characteristic

GROUP	WEIGHT(G)	AGE(W)
	N=6 Mean ±6SD	N=6 Mean ±6SD
1 (probiotic + LPS)	31,61±1,59	11,50±0,83
2 (LPS)	33,92±3,27	10,66±0,81
3(Probiotic)	31,61±1,59	11,00±082
4 (none)	32,73±2,75	10,83±0,75
Total	32,46±2,18	10,99±0,80

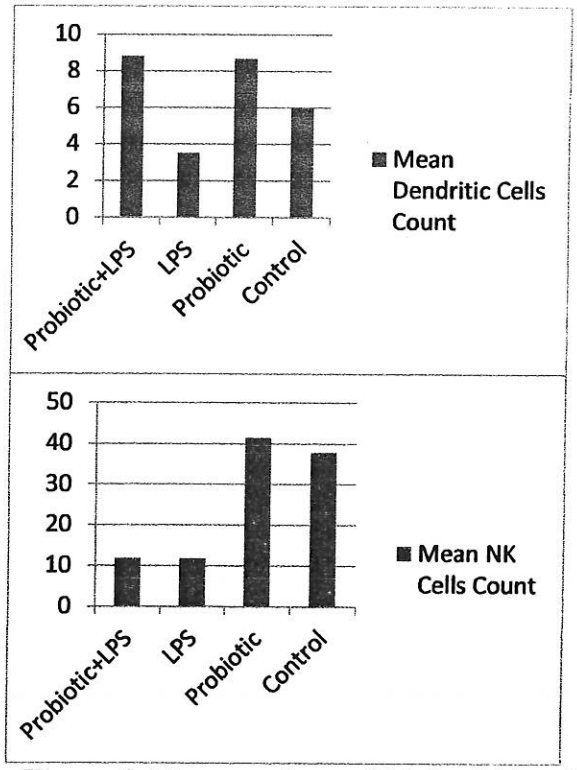

Figure 1. Mean numbers of (a) dendritic cells and (b) NK cells.

The numbers of both dendritic and NK cells were normally distributed; therefore, the independent sample t-test was performed to compare cell counts between the probiotic and control (no treatment) groups. The results revealed significant differences in the numbers of dendritic cell, but not NK cells, between the groups

Table 2. Comparisons of dendritic and NK cell counts in the probiotic and control groups

Variables	Probiotic		Control		*P*
	n	Mean (SD)	n	Mean (SD)	
Dendritic cells	6	8.67 (2.07)	6	6 (1.41)	0.026
NK cells	6	41.5 (13.23)	6	37.83 (20.87)	0.724

The results of the independent sample t-test between the probiotic-LPS (probiotics for 21 consecutive days and LPS on day 15) and LPS groups revealed significant differences in the numbers of dendritic cells, but not NK cells.

Table 3. Comparison between dendritic and NK cell counts of the probiotic+LPS and LPS groups

Variables	Probiotic-LPS		LPS		*P*
	n	Mean (SD)	n	Mean (SD)	
Dendritic	6	8.83 (1.72)	6	3.5 (1.05)	0.000
NK cell	6	11.83 (3.82)	6	11.83 (9.67)	1.000

3.1. Effects of Probiotics on Innate Immunity

Defense of the intestinal mucosa involves a combination of immunological and non-immunological processes, both of which can strengthen resistance of the intestinal mucosa (Blum and Schiffrin, 2003). Probiotic-induced enhancement of the immune system has been confirmed by evidence-based studies (Saavedra, 2007; Shi *et al.*, 2017). Various studies of probiotics mention the benefits of modulating the immune system both in vitro and in vivo (Cross *et al.*, 2004).

3.2. Effects of Probiotics on Dendritic Cells

The innate immune status of the probiotic group, as determined by the number of dendritic cells, was significantly increased, as compared to that of the control group, demonstrating that the administration of probiotics improves the innate immune response. Therefore, it can be concluded that defense mechanisms and the immune response were improved in the probiotic-treated intestinal mucosa, as compared to non-treated controls. This finding is consistent with the theory that synbiotics stimulate both the innate and adaptive immune responses in the mucosa (Saavedra, 2007). Communication occurs between probiotic bacteria as normal flora and the host's immune system (Corthésy, Gaskins and Mercenier, 2007; Barzegari *et al.*, 2014). Probiotics are potential immunomodulators that increase the amount and intensify the maturation of dendritic cells in the form of antigen-presenting cells (Mohamadzadeh *et al.*, 2005), which can recognize pathogen-associated molecular patterns through toll-like receptors (TLRs) (Corthésy, Gaskins and Mercenier, 2007). Therefore, dendritic cells have the capacity to "drive" a T cell subset based on intestinal microflora composition (Christensen, Frøkiær and Pestka, 2002) of both normal and pathogenic microflora (Foligne, 2007).

In this study, there were significantly increased numbers of dendritic cells in the probiotic-LPS group, as compared to the LPS-only group. Past studies have reported that the increased immunological resistance of the host fights against diarrhea-causing pathogens. This concept is considered more reasonable, considering that the main target is to improve the immune response in the mucosa. Also, several randomized controlled studies and meta-analysis have found that the administration of probiotics can effectively prevent gastroenteritis (Guarino, Vecchio and Canani, 2009).

LPS administration will induce an inflammatory response in healthy mice, as demonstrated by the upregulated responses of factors of the innate and adaptive immune systems. Since probiotic exposure, which can increase activation and the number of dendritic cells through TLR-2 expression, was absent

(Dogi, Galdeano and Perdigón, 2008) in the LPS-only group, a lower number of dendritic cells was obtained. In this group, there was also a decrease in TLR-4 expression caused by CD14 deficiency, so that the immunological process was leaning toward TH2 cells and there was a disruption of stimulation of TLR-4 expression, which inhibited dendritic cell activation (Mohamadzadeh *et al.*, 2005; Dogi, Galdeano and Perdigón, 2008). In contrast, mice that were first administered probiotics had statistically significant higher numbers of dendritic cells, as compared to the LPS-only group, which further reinforces the theory that probiotics have anti-inflammatory activities. The most marked anti-inflammatory effect was shown by bifidobacterial species, which upregulated interleukin (IL)-10 production by dendritic cells and decreased expression of the costimulatory molecules CD80 and CD40. These effects of probiotic bacteria on dendritic cells may underlie their anti-inflammatory activities.

Effects of Probiotics on NK Cells

No previous study has used NK cells to evaluate the status of innate immunity. NK cells are natural defensive components against viral infections and tumor cells (Delves *et al.*, 2006). Increased NK cell activity is thought to be part of the capability of the immune response to inhibit malignancy. Upon activation, NK cells respond to bacterial infection in two ways: first, by removing perforin and granzyme enzymes, which induce the apoptosis of infected cells, and, second, by producing interferon (IFN)-γ, which activates macrophages and increases the ability to kill and devour bacteria. Macrophages release IL-12, a potent cytokine that re-activates NK cells (Abbas, Lichtman and Pillai, 2012; Baratawidjaja and Rengganis, 2009).

Many studies have revealed that the administration of probiotic bacteria will affect the overall nonspecific immune response by increasing pathogen phagocytosis through increased macrophage activation and subsequent cytokine production (Erickson and Hubbard, 2000). Another study of 50 adults found that the addition of the probiotic B. lactis HN019 to milk could increase the activities of polymorphonuclear cells and NK cells, as compared to the control group (Chiang *et al.*, 2000). Similarly, another study found that the administration of Lactobacillus casei ssp. with dextran significantly increased the activities of NK cells in the spleen of Balb/c mice (Ogawa *et al.*, 2005). Also, the addition of the probiotics L. gasseri and L. coryniformis to yogurt had significantly increased the number of NK cells in the blood of healthy adults by 21% (Olivares *et al.*, 2006). This is in line with the results of a present study of an increase in the number of NK cells, although this increase was not significant. However, another study of 20 healthy young female subjects reported that the consumption of L. casei Shirota fermented milk for 4 weeks had no influence NK cell activity (Spanhaak, Havenaar and Schaafsma, 1998). Therefore, further studies are needed to determine the most effective strains and doses of probiotics for the stimulation of NK cells.

The results of the in vivo study showed that the number of NK cells in the innate cell immune was decreased after the administration of LPS. Different results were obtained in another study that found that LPS can stimulate NK cell proliferation, secrete IFN-γ, and increase toxicity of NK cells to in vitro target cells in human blood (Nedvetzki *et al.*, 2007). This difference can explained by the differences in observation methods (in vivo vs. in vitro). The decrease in NK cell number and activities in the in vivo studies can occur due to natural microbiota in the intestine that act as probiotics.

Probiotic administration increases the activity and production of NK cells, which are cytotoxic lymphocytes, the main component of the innate immune system, are increased in number along with increased production of IL-12. This finding is in line with the results of previous studies, which stated that administration of probiotics could increase the numbers of cells expressing IL-1, IL-2, and IL-12. IL-12 and IL-18 are produced by Th1 and

NK cells and act as synergistic stimulators of IFN-γ and enforce the probiotic response toward mononuclear cells. LPS will increase the activities of NK cells through mechanisms that involve IFN-γ. Hence, NK cells become more efficient and toxic (Salata *et al.*, 1984). However, in our in vivo study, the number of NK cells had continued to decrease after LPS exposure, even though probiotics were administered beforehand. The NK cell count did not significantly differ between the probiotic-LPS and LPS-only groups.

4. Conclusions

The results of this study showed that multiple probiotic species can regulate the innate immune response through dendritic cells, but not NK cells, in Balb/c mice.

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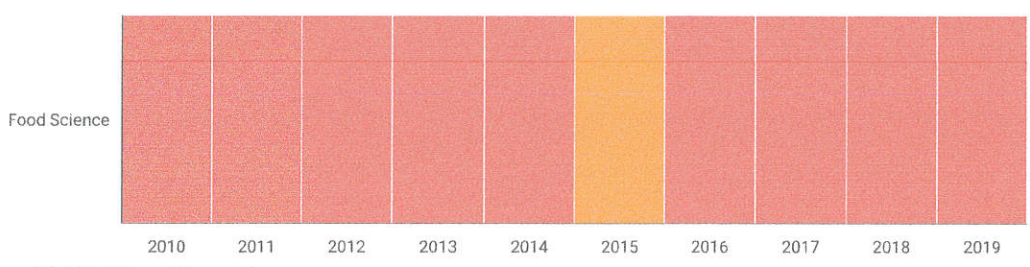

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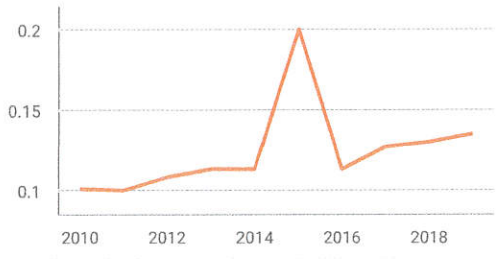

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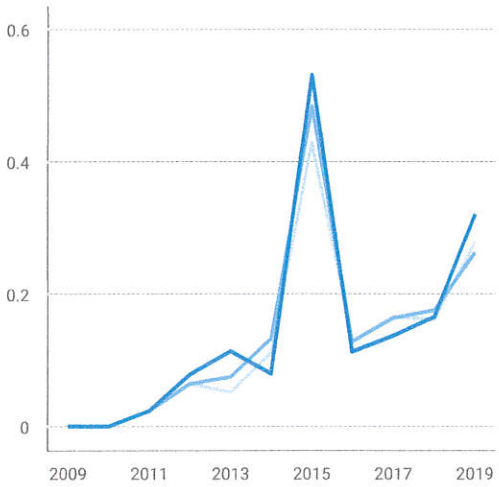

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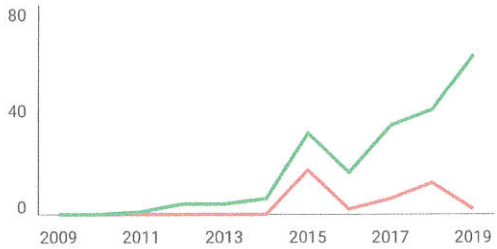

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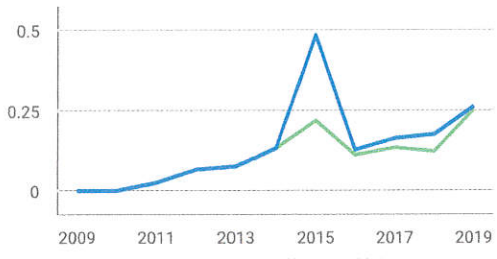

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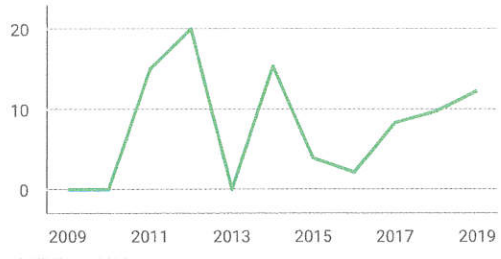

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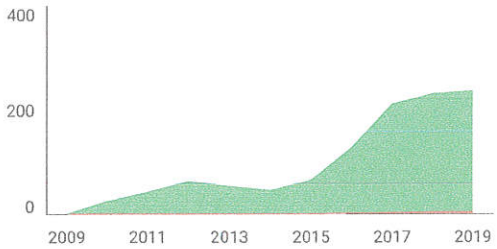

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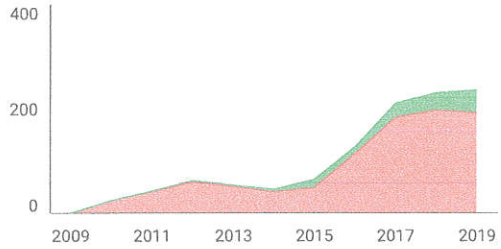

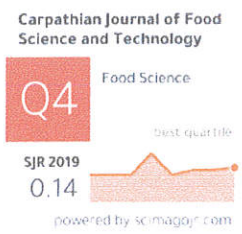

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