Scientific Papers. Series D. Animal Science. Vol. LXVI, No. 1, 2023
ISSN 2285-5750; ISSN CD-ROM 2285-5769; ISSN Online 2393-2260; ISSN-L 2285-5750

EFFECT OF USING *Lactobacillus plantarum*, *Bifidobacterium* AND ITS CONSORTIUM PROBIOTIC YOGURT IN PREVENTING THE GROWTH OF *Klebsiella pneumoniae* THAT CAUSES PNEUMONIA

Lovita ADRIANI[1], Tuti WIDJASTUTI[2], Tissiana Irca NABILA[2]

[1]Departement of Physiology and Biochemistry, Faculty of Animal Science, Universitas Padjadjaran, Indonesia
[2]Depart. of Animal Nutrition and Feed Technology, Faculty of Animal Science, Universitas Padjadjaran, Indonesia

Corresponding author email: lovita@unpad.ac.id

Abstract

Klebsiella pneumoniae has been linked with dysbiosis in the intestinal microbiota. This has led to the idea of improving respiratory defense by regulating the intestinal microbiota with the supplementation of beneficial strains, such as yogurt probiotics. To develop probiotics in yogurt, the addition of lactic acid bacteria (LAB) in it such as Lactobacillus plantarum and Bifidobacterium is needed. Yogurt is expected to improve human health, specifically in gastrointestinal and respiratory health. This study aims to study the effect of probiotic yogurt with a specific consortium based on Lactobacillus plantarum and Bifidobacterium to inhibit the growth of Klebsiella pneumoniae which causes pneumonia. The literature research method used Google Scholar and PubMed from 2000 to 2022 which obtained 60 journals. Based on observations, it was shown that Lactobacillus plantarum and Bifidobacterium were able to inhibit the growth of Klebsiella pneumoniae due to the decrease of pulmonary inflammation response after giving Lactobacillus plantarum, and the increase of IL-10 production by Bifidobacterium bacteria. Therefore, yogurt probiotics consortium could be used to prevent Klebsiella pneumoniae which causes pneumonia and lung damage.

***Key words**: Bifidobacterium, consortium microbiota, Lactobacillus plantarum, Klebsiella pneumoniae, yoghurt probiotic.*

INTRODUCTION

Klebsiella pneumoniae (KP) belongs to a group of Gram-negative bacteria that are rod-shaped. KP is able to ferment lactose, and this bacterium is facultative anaerobic, causes pneumonia, and causes high morbidity and mortality (Mizgerd, 2006). When it develops into pneumonia, the immune system responds more severely, producing more pro-inflammatory cytokines, infiltrating neutrophils and macrophages, and causing massive lung damage (Soares et al., 2006; Zhang et al., 2000). Although localized inflammation is known to be protective against pathogen infection, as it prevents pathogen spread, unresolved hyperinflammation is associated with long-term inflammatory disorders and death (Medzhitov, 2008). Klebsiella infection is acknowledged as a major health concern due to increasing antibiotic resistance. Strategies to strengthen the immune response and develop pulmonary defenses are needed to overcome pulmonary infections. In this case, probiotics have been the leading candidate in this context. Probiotics are populations of live non-pathogenic microorganisms that are able to favorably impact the host if administered in sufficient and appropriate amounts. This group of beneficial bacteria is able to buffer host immunity against pathogenic bacteria in the gut and prevent risks (Reid et al., 2003; Adriani et al., 2021). Previous studies have shown that probiotics are effective in stimulating the immune system and strengthening non-specific immunity (Adriani et al., 2022). Although previous studies have mostly reported probiotic research focusing on intestinal mucosal immunity, one of the most essential effects of probiotics is to increase the host's mucosal immunity (Vieira et al., 2013). Studies of microbial-based therapy strategies to treat lung infections continue to grow increasingly popular. Between the probiotic effects, the addition of probiotics has been linked to a reduced risk of pneumonia, shorten the period of common cold, and protect the respiratory from any pathogens, including viral infections (Kawase et al., 2010; Kawahara et al., 2015; Song et al., 2014).

Recently, the bacterium *Lactobacillus plantarum* and Bifidobacterium have been studied for their potential as a starter for making yogurt products. *Lactobacillus plantarum* bacteria is a gram-positive bacterium commonly used in dairy products, meat, and various fermented vegetables. Based on research by Li et al. (2017), states that several bacterial strains based in Sichuan and Mongolia show high coagulation abilities and proteolytic activity. These bacteria can survive well in fermented and post-fermented milk. This shows that milk media is a suitable medium for the growth of *Lactobacillus plantarum* bacteria.

Lactobacillus plantarum and *Bifidobacterium* are several lactic acid bacteria that also act as a probiotic, a live bacterium that can provide health effects to the host if consumed in sufficient quantities (FAO & WHO, 2006). Probiotics are included in functional foods because probiotics can maintain a balance in the intestinal microbiota, increase immunity, and other benefits for health (Quigley, 2019; Adriani et al., 2020). If this bacterium is used as a starter in the yogurt products, then the product is included in one of the functional food products. Therefore, research on the literature review of the potential of probiotic bacteria *Lactobacillus plantarum* as a starter in the production of functional yogurt needs to be carried out to provide an overview, information, and ideas from various previous studies. The results of this literature review are expected to be used as a reference for further research.

MATERIALS AND METHODS

The literature research used Google Scholar and PubMed from 2000 to 2022, which obtained 60 journals. Based on the observations, it was shown that *Lactobacillus plantarum* and *Bifidobacterium* were able to inhibit the growth of *Klebsiella pneumoniae* in the lungs. The probiotic works against the pathogenic bacteria were indicated by the decrease of pulmonary inflammation response after giving *Lactobacillus plantarum*, and the increase of IL-10 production by *Bifidobacterium* bacteria.

RESULTS AND DISCUSSIONS

Pneumonia is becoming a serious global health problem. Respiratory tract infections, especially pneumonia, have been a major cause of morbidity and mortality over the past 50 years; therefore, it continues to be a major concern in medical research (Armstrong et al., 1999).

The potential of probiotics for infectious diseases and pulmonary infections has been of great interest as awareness of the role of the immune system through gut mycoflora has increased (Forsythe, 2014).

The main mechanism of probiotics is to prevent microbial adhesion and exclusion competition of harmful microorganisms by increasing intestinal mucosal adhesion, synthesizing antimicrobial proteins, maintaining and strengthening epithelial barriers, and modulating the immune system (Bermudez-Brito et al., 2012; Adriani, Rifki & Widjastuti, 2020). The process can be seen in Figure 1.

Lactic acid is produced by LAB group microorganisms from various carbon sources, including simple carbohydrates (Carr et al., 2002). These beneficial microorganisms produce secondary bioactive metabolites, especially enzymes that are able to inhibit and stop the growth of microbes that are not beneficial to health, besides that they also produce exopolysaccharides and bacteriocin. These elements are connected to various probiotic effect mechanisms (Leroy & De Vuyst, 2004; de Melo Pereira et al., 2018; Lesmana et al., 2021). This mechanism for repairing the digestive tract is well known.

The interest in the application of these microbes to the prevention of lung infections is well demonstrated through the utilization of *Bifidobacterium* in cases of respiratory infections, such as asthma, allergies, and even influenza infections (Kawahara et al., 2015; Verheijden et al., 2015; Drago et al., 2015).

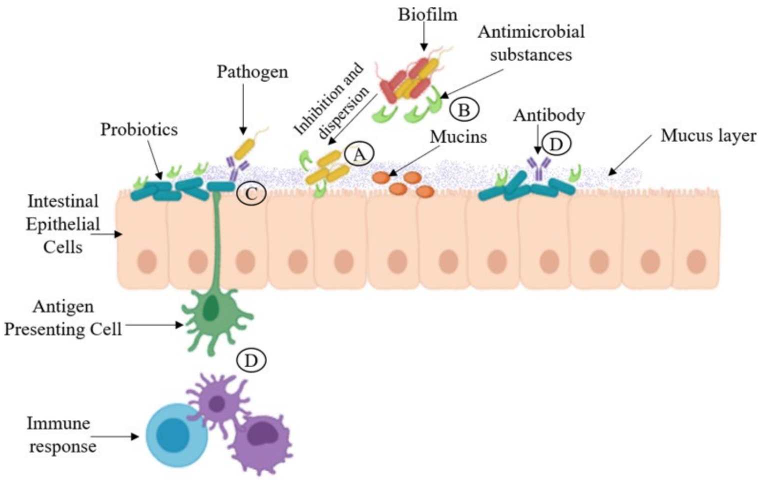

Figure 1. Mechanisms of how probiotics work: (A) Competitive exclusion of harmful bacteria. (B) Production of antimicrobial agents. (C) Enhanced adhesion to the intestinal mucosa and increased the epithelial barrier. (D) Stimulation of the immune system (Silva et al., 2020).

Therefore, maintaining immunity to the respiratory organs is important in reducing cases of pathogenic infections and also preventing them. Interestingly, the effects of diet or antibiotic treatment on the gut microbiota are associated with lung disease (Kim et al., 2014; Russell et al., 2012; Thornburn et al., 2014). Recent studies, as reported by Trompette et al. (2014) in mice, it appears that the metabolites produced by the fermentation of dietary fiber by intestinal microbes are able to protect the lungs from infection with pathogenic bacteria. *Bifidobacterium* bacteria are the largest short-chain fatty acid-producing bacteria in the fermentative commensal bacteria group (Fukuda et al., 2011). Several recent reports justify that the most abundant short chain fatty acid in the intestine is acetate. It was also shown that acetate is able to regulate inflammation prevention through various signaling pathways (Arpaira et al., 2013; Maslowski et al., 2009).

A study of the effects of the probiotic *Bifidobacterium* by mice which has been reported by Vieira et al. (2016) showed that the application of this probiotic was able to protect sample animals from *Klebsiella pneumonia*, indicated by a decrease in inflammation with increased production of IL-10, in addition to significant protection against the lungs, clearly indicated by a decrease in the population of pathogenic bacteria. One of the main reasons for this effectiveness is the increased activation of the TLRs Mal adapter protein. IL-10 can have various influence, depends on context and timing. In the setting of a lethal dose of *Klebsiella*, systemic inhibition of IL-10 enhanced bacterial clearance and reduced mortality (Lenz et al., 2007). IL-10 was also shown to prevent immunopathological consequences from infection caused by various pathogens (Wilson et al., 2005; Redford, Murray & O'Garra, 2011; Loebbermann et al., 2012). IL-10 is an important cytokine that plays a role to reduce inflammation (Serhan et al., 2007). Beside on this, the higher levels of IL-10 secreted by *Bifidobacterium* bacteria treatment in the lung to treat *Klebsiella* infection plays a role in the resolution of inflammation and restoring tissue homeostasis.

Lactobacillus spp. also has been largely recognized for having an anti-pathogen effect that is safe to consume (Ripamonti et al., 2011). However, the exact mechanisms of *Lactobacillus* spp. effect are not yet widely understood. A study by Yan et al. (2021) stated that *Lactobacillus plantarum* can improve mammals' digestive tract condition by increasing intestinal bacteria that utilize fatty acids such as Bacteroidetes and Blautia. To eliminate the strong *Klebsiella pneumoniae* and killing effect of Bacteroidetes and *Lactobacillus plantarum*, when *Lactobacillus* *plantarum* secretes a high amount of acetic acid, it can acidify the intracellular environment of *Klebsiella* and prevent its growth.

In addition, previous epidemiological studies showed that *Klebsiella pneumoniae* bacteria are liable for nosocomial infections that came from the gastrointestinal reservoir of the patients (Podschun & Ullmann, 1998). Hence, the administration of probiotics could be an alternative to prevent or even treat the respiratory infections caused by *Klebsiella pneumoniae*. These bacteria would not only prevent *Klebsiella pneumoniae* from proliferating in the intestine, but they would also control the inflammatory response and boost lung immunity.

Further research by Vareille-Delarbre et al. (2019) investigated the effect of *Lactobacillus plantarum* on the host immune response generated in lung tissue and cells by *Klebsiella pneumoniae*. Notably, *Klebsiella* did not affect the immune response in intestinal epithelial cell lines, in contrast to respiratory epithelial cells, possibly because the intestinal cells could handle the presence of *Klebsiella*. This is suitable with the fact that the human gastrointestinal tract is a reservoir for this pathogen and its colonization process does not lead to any harmful intestinal disorders (De Champs et al., 2004). *Lactobacillus plantarum* significantly decreased in the proinflammatory cytokine (KC, IL-6, and TNF-α) as the innate immune response from the pathogen. Although most studies have shown an impact of probiotics on the innate immune response (Giorgetti et al., 2015; Visozo et al., 2009; Boirivant & Strober, 2017), recent studies have speculated that these bacteria may also have an immunomodulatory effect at distal sites. (Vieira et al., 2016; Salva, Villena & Alvarez, 2010; Park et al., 2013; Racedo et al., 2006; Khailova et al., 2013).

Lactobacillus plantarum is also known to have the ability to secrete high amounts of IL-12. According to research by Vissers et al. (2010), all *Lactobacillus* strains were tested and stimulated by IL-10, TNF-α, and IFN-γ and IL-1β, the results of his research showed that *Lactobacillus* strains were able to act as strong inducers of the proinflammatory cytokine TNF-α (Timmerman et al., 2007; Maragkoudakis et al., 2006;) and also IL-12 (Haller et al., 2000; Shida et al., 2006), although other researchers reported different results that increased IL-12 production was not significant by lactic acid bacteria (Niers et al., 2005; Drouault-Holowacz et al., 2006). IL-12 production can be stimulated by all *Lactobacillus plantarum* strains, although Lactobacillus acidophilus cannot. The observed differences in IL-12 induction were due to differences in the cellular responses of these species and strains. These data indicate that *Lactobacillus plantarum* has a better ability to produce innate cytokines, such as IL-12 and TNF-α. *Lactobacillus plantarum* elicited higher production of IFN-γ, IL-12, and TNF-α, and therefore had a better capacity to enhance the response of the Th1 subset, compared to *Lactobacillus acidophilus*. In general, *Lactobacillus plantarum* strains are known to induce high amounts of IL-12, compared to *Lactobacillus acidophilus* (Vissers et al, 2010).

CONCLUSIONS

Klebsiella pneumoniae infection can be prevented by consuming probiotic yogurt containing *Lactobacillus plantarum* microbiota. Based on the trials conducted on mice, it can lessen the pulmonary inflammation, by decreasing numbers of lung innate immune cells (macrophages and neutrophils) as well as cytokines (keratinocyte-derived chemokine [KC], IL-6, and TNF-α) in the bronchoalveolar fluid, and generate an immunosuppressive Treg response in lungs.

While the consumption of *Bifidobacterium* leads to a faster resolution of inflammation associated with enhanced IL-10 production, and lessen the lung injury based on a result of a significant reduction of harmful bacteria that contributed to the mice mortality.

Therefore, based on the literature review, we can conclude that the combination of these two bacteria will greatly reduce and even maximize the prevention of *Klebsiella pneumoniae* infection.

ACKNOWLEDGEMENTS

We would like to thank the Ministry of Research and Technology and Academic

Leadership Grant (ALG) for the funding and facilities provided during the research.

REFERENCES

Adriani, L., Joni, I.M., Kumalasari, C., & Lesmana, R. (2020). The Application of Simple Technology for Making Yogurt Powder to Improve Biochemical Blood Profile of Broiler. *AIP Conference Proceedings*, 2219, 070009.

Adriani, L., Kumalasari, C., Rohandi, Joni, M., Latipudin, D. (2022). Effect of powder probiotic on the leukocyte, heterophil and lymphocyte level on laying hens. *Scientific Papers. Series D. Animal Science*, 65 (1), 115–122.

Adriani, L., Latipudin, D, Joni, I.M., Panatarani, C., Sania, G. (2021). Hematological status and egg production of laying hen with probiotic powder as feed supplements. *IOP Publishing*, 902, 012032.

Adriani, L., Rifki, M., Widjastuti, T. (2020). Blood Protein Profile Dynamics Due to Probiotic Yogurt Supplementation in Broiler Chickens. *Scientific Papers-Animal Science Series: Lucrări Ştiinţifice*, 74.

Armstrong, G.L., Conn, L.A., & Pinner, R.W. (1999). Trends in infectious disease mortality in the United States during the 20th century. *JAMA*, 281, 61–6.

Arpaia N, Campbell C, Fan X, Dikiy S, van der Veeken J, deRoos P. (2013). Metabolites produced by commensal bacteria promote peripheral regulatory T-cell generation. *Nature*, 504, 451–455.

Bermudez-Brito, M., Plaza-Díaz, J., Muñoz-Quezada, S., Gómez-Llorente, C., & Gil, A. (2012). Probiotic mechanisms of action. *Annals of Nutrition & Metabolism,* 61, 160–174.

Boirivant, M. & Strober, W. (2007). The mechanism of action of probiotics. *Curr. Opin. Gastroenterol.*, 23, 679–692.

Carr, F. J., Chill, D., & Maida, N. (2002). The lactic acid bacteria: A literature survey. *Critical Reviews in Microbiology,* 28, 281–370.

De Champs C, Rich C, Chandezon P, Chanal C, Sirot D, Forestier C. (2004). Factors associated with antimicrobial resistance among clinical isolates of Klebsiella pneumoniae: 1-year survey in a French university hospital. *Eur. J. Clin. Microbiol Infect Dis.*, 23, 456–462.

De Melo Pereira, G. V., de Oliveira Coelho, B., Magalhães Júnior, A. I., Thomaz-Soccol, V., & Soccol, C. R. (2018). How to select a probiotic? A review and update of methods and criteria. *Biotechnology Advances*, 36, 2060–2076.

Drago, L., De Vecchi, E., Gabrieli, A., De Grandi, R., & Toscano, M. (2015). Immunomodulatory effects of Lactobacillus salivarius LS01 and bifidobacterium breve BR03, alone and in combination, on peripheral blood mononuclear cells of allergic asthmatics. *Allergy Asthma Immunol. Res.*, 7, 409 – 413.

Drouault-Holowacz S, Foligne B, Dennin V, Goudercourt D, Terpend K, Burckel A & Pot B. (2006). Anti-inflammatory potential of the probiotic dietary supplement Lactibiane Tolerance: in vitro and in vivo considerations. *Clin. Nutr.*, 25, 994–1003.

Fagundes, C.T., Amaral, F.A., Vieira, A.T., Soares, A.C., Pinho, V., & Nicoli, J.R. (2012). Transient TLR activation restores inflammatory response and ability to control pulmonary bacterial infection in germfree mice. *J. Immunol.*, 188, 1411–1420.

FAO & WHO. (2006). *Probiotics in food: Health and nutritional properties and guidelines for evaluation*. Rome, I: World and Health Organization.

Forsythe, P. (2014). Probiotics and lung immune responses. *Ann. Am. Thorac. Soc.*, 11(Suppl. 1), S33 - 7.

Fukuda S, Toh H, Hase K, Oshima K, Nakanishi Y, Yoshimura K. (2011). Bifidobacteria can protect from enteropathogenic infection through production of acetate. *Nature*, 469, 543–547.

Giorgetti G, Brandimarte G, Fabiocchi F, Ricci S, Flamini P, Sandri G, Trotta MC, Elisei W, Penna A, Lecca PG, Picchio M, & Tursi A. (2015). Interactions between innate immunity, microbiota, and probiotics. *J Immunol Res,* 501361.

Haller D, Blum S, Bode C, Hammes WP & Schiffrin EJ. (2000). Activation of human peripheral blood mononuclear cells by nonpathogenic bacteria in vitro: evidence of NK cells as primary targets. *Infect. Immun.*, 68, 752–759.

Kawahara, T., Takahashi, T., Oishi, K., Tanaka, H., Masuda, M., & Takahashi, S. (2015). Consecutive oral administration of *Bifidobacterium longum* MM-2 improves the defense system against influenza virus infection by enhancing natural killer cell activity in a murine model. *Microbiol. Immunol.*, 59, 1–12.

Kawase, M., He, F., Kubota, A., Harata, G., & Hiramatsu, M. (2010). Oral administration of lactobacilli from human intestinal tract protects mice against influenza virus infection. *Lett. Appl. Microbiol.,* 51, 6–10.

Khailova L, Baird CH, Rush AA, McNamee EN, & Wischmeyer PE. (2013). *Lactobacillus rhamnosus* GG improves outcome in experimental *Pseudomonas aeruginosa* pneumonia: potential role of regulatory T cells. *Shock*, 40, 496–503.

Kim, Y.G., Udayanga, K.G., Totsuka, N., Weinberg, J.B., Nunez, G., & Shibuya, A. (2014). Gut dysbiosis promotes M2 macrophage polarization and allergic airway inflammation via fungi-induced PGE (2*). Cell Host Microbe,* 15, 95–102.

Lenz, A.M., Franklin, G.A., Fairweather, M., McClintock, M.L., Jala, V.R., & Peyton, J.C. (2007). Endogenous IL-10 leads to impaired bacterial clearance and reduced survival in a murine model of chronic peritonitis. *Cytokine*, 40, 207–215.

Leroy, F., & De Vuyst, L. (2004). Lactic acid bacteria as functional starter cultures for the food fermentation industry. *Trends in Food Science & Technology*, 15, 67–78.

Lesmana, R., Adriani, L., Haryawan, Z., Goenawan, H., Pratiwi, Y. S., Sylviana, N., & Supratman, U. (2021). Probiotic Composition of Fermented Cow Milk and Soy Milk Effect on Epidermal Growth Factor and Epidermal Thickness in Female Wistar Rats. *JAPS: Journal of Animal & Plant Sciences*, 31(4).

Li, C., Song, J., Kwok, L., Wang, J., Dong, Y., Yu, H., Hou, Q., Zhang, H., & Chen, Y. (2017). Influence of

Lactobacillus plantarum on yogurt fermentation properties and subsequent changes during postfermentation storage. *Journal of Dairy Science*, 100 (4), 2512–2525.

Loebbermann, J., Schnoeller, C., Thornton, H., Durant, L., Sweeney, N.P., & Schuijs, M. (2012). IL-10 regulates viral lung immunopathology during acute respiratory syncytial virus infection in mice. *PLoS One*, 7, 32371.

Maragkoudakis, P.A., Zoumpopoulou, G., Miaris, C., Kalantzopoulos, G., Pot, B., & Tsakalidou, E. (2006). Probiotic potential of *Lactobacillus* strains isolated from dairy products. *Int. Dairy Journal*, 16, 189–199.

Maslowski, K.M., Vieira, A.T., Ng, A., Kranich, J., Sierro, F., & Yu, D. (2009). Regulation of inflammatory responses by gut microbiota and chemoattractant receptor GPR43. *Nature*, 461, 1282.

Medzhitov, R. (2008). Origin and physiological roles of inflammation. *Nature,* 454, 428 – 435.

Mizgerd, J.P. (2006). Lung infectionea public health priority. *PLoS Med.*, 3, 76.

Niers, L.E., Timmerman, H.M., Rijkers, G.T., van Bleek, G.M., van Uden, N.O., Knol, E.F., Kapsenberg, M.L., Kimpen, J.L., & Hoekstra, M.O. (2005). Identification of strong interleukin-10 inducing lactic acid bacteria which down-regulate T helper type 2 cytokines. *Clin. Exp. Allergy,* 35, 1481–1489.

Park, M.K., Ngo, V., Kwon, Y.M., Lee, Y.T., Yoo, S., Cho, Y.H., Hong, S.M., Hwang, H.S., Ko, E.J., Jung, Y.J., Moon, D.W., Jeong, E.J., Kim, M.C., Lee, Y.N., Jang, J.H., Oh, J.S., Kim, C.H., & Kang, S.M. (2013). *Lactobacillus plantarum* DK119 as a probiotic confers protection against influenza virus by modulating innate immunity. *PLoS One,* 8, 75368.

Podschun, R., & Ullmann, U. (1998). Klebsiella spp. as nosocomial pathogens: epidemiology, taxonomy, typing methods, and pathogenicity factors. *Clin. Microbiol. Rev.*, 11, 589–603.

Quigley, E.M.M. (2019). Prebiotics and Probiotics in Digestive Health. *Clin. Gastroenterol. Hepatol.*, 17(2), 333–344.

Racedo S, Villena J, Medina M, Agüero G, Rodríguez V, & Alvarez S. (2006). *Lactobacillus casei* administration reduces lung injuries in a Streptococcus pneumoniae infection in mice. *Microbes Infect*, 8, 2359–2366.

Redford, P.S., Murray, P.J., & O'Garra, A. (2011). The role of IL-10 in immune regulation during M. tuberculosis infection. *Mucosal Immunol.*, 4, 261–270.

Reid, G., Jass, J., Sebulsky, M.T., & McCormick, J.K. (2003). Potential uses of probiotics in clinical practice. *Clin. Microbiol. Rev.,* 16, 658–672.

Russell, S.L., Gold, M.J., Hartmann, M., Willing, B.P., Thorson, L., & Wlodarska, M. (2012). Early life antibiotic-driven changes in microbiota enhance susceptibility to allergic asthma. *EMBO Rep*, 13, 440–447.

Salva, S., Villena, J., & Alvarez, S. (2010). Immunomodulatory activity of *Lactobacillus rhamnosus* strains isolated from goat milk: impact on intestinal and respiratory infections. *Int. J. Food Microbiol.,*141, 82–89.

Silva, D.R., Sardi, J.C.O., Pitangui, N.S., Roque, S.M., da Silva, A.C.B., & Rosalen, P.L. (2020). Probiotics as an alternative antimicrobial therapy: Current reality and future directions. *Journal of Functional Foods*, 73, 104080.

Serhan CN, Brain SD, Buckley CD, Gilroy DW, Haslett C, & O'Neill LA. (2007). Resolution of inflammation: state of the art, definitions and terms. *FASEB J*, 21, 325–332.

Shida, K., Suzuki, T., Kiyoshima-Shibata, J., Shimada, S., & Nanno, M. (2006). Essential roles of monocytes in stimulating human peripheral blood mononuclear cells with *Lactobacillus casei* to produce cytokines and augment natural killer cell activity. *Clin. Vaccine Immunol.,* 13, 997–1003.

Soares, A.C., Souza, D.G., Pinho, V., Vieira, A.T., Nicoli, J.R., & Cunha, F.Q. (2006). Dual function of the long pentraxin PTX3 in resistance against pulmonary infection with Klebsiella pneumoniae in transgenic mice. *Microbes Infect.,* 8, 1321–1329.

Song, J.A., Kim, H.J., Hong, S.K., Lee, D.H., Lee, S.W., & Song, C.S. (2014). Oral intake of *Lactobacillus rhamnosus* M21 enhances the survival rate of mice lethally infected with influenza virus. *J. Microbiol. Immunol. Infect.,* 1–8.

Thornburn, A.N., Macia, L., & Mackay, C.R. (2014). Diet, metabolites, and "western-lifestyle" inflammatory diseases. *Immunity*, 40, 833–842.

Timmerman, H.M., Niers, L.E., Ridwan, B.U., Koning, C.J., Mulder, L., Akkermans, L.M., Rombouts, F.M., & Rijkers, G.T. (2007). Design of a multispecies probiotic mixture to prevent infectious complications in critically ill patients. *Clin. Nutr.*, 26, 450–459.

Trompette, A., Gollwitzer, E.S., Yadava, K., Sichelstiel, A.K., Sprenger, N., & Ngom-Bru, C. (2014). Gut microbiota metabolism of dietary fiber influences allergic airway disease and haematopoiesis. *Nat. Med.*, 20, 159 – 166.

Vareille-Delarbre, M., Miquel, S., Garcin, S., Bertran, T., Balestrino, D., Evrard, B., & Forestier, C. (2019). Immunomodulatory effects of *Lactobacillus plantarum* on inflammatory response induced by *Klebsiella pneumoniae. Infect. Immun.*, 87, 00570–19.

Verheijden, K.A., Willemsen, L.E., Braber, S., Leusink-Muis, T., Jeurink, P.V., & Garssen, J. (2015). The development of allergic inflammation in a murine house dust mite asthma model is suppressed by synbiotic mixtures of non-digestible oligosaccharides and *Bifidobacterium* breve M-16V. *Eur. J. Nutr.*, 54, 1–11.

Vieira, A. T., Rocha, V. M., Tavares, L., Garcia, C. C., Teixeira, M. M., Oliveira, S. C., et al. (2016). Control of *Klebsiella pneumoniae* pulmonary infection and immunomodulation by oral treatment with the commensal probiotic *Bifidobacterium longum* 5(1A). *Microbes Infect*. 18, 180–189.

Vieira, A.T., Teixeira, M.M., & Martins, F.S. (2013). The role of probiotics and prebiotics in inducing gut immunity. *Front Immunol.*, 4, 445.

Vissers, Y.M., Snel, J., Zuurendonk, P.F., Smit, B.A., Wichers, H.J., & Savelkoul, H.F.J. (2010). Differential effects of *Lactobacillus acidophilus* and

Lactobacillus plantarum strains on cytokine induction in human peripheral blood mononuclear cells. *FEMS Immunol. Med. Microbiol.,* 59, 60–70.

Vizoso Pinto, M.G., Rodriguez Gómez, M., Seifert, S., Watzl, B., Holzapfel, W.H., & Franz, C.M.A.P. (2009). Lactobacilli stimulate the innate immune response and modulate the TLR expression of HT29 intestinal epithelial cells in vitro. *Int. J. Food Microbiol.,* 133, 86 –93.

Wilson, E.H., Wille-Reece, U., Dzierszinski, F., & Hunter, C.A. (2005). A critical role for IL-10 in limiting inflammation during toxoplasmic encephalitis. *J. Neuroimmunol.*, 165, 63-74.

Yan, R., Lu, Y., Wu, X., Yu, P., Lan, P., Wu, X., Jiang, Y., Li, Q., Pi, X., Liu, W., Zhou, J., & Yu, Y. (2021). Anticolonization of Carbapenem-Resistant *Klebsiella pneumoniae* by *Lactobacillus plantarum* LP1812 Through Accumulated Acetic Acid in Mice Intestinal. *Front. Cell. Infect. Microbiol*., 11

Zhang, P., Summer, W.R., Bagby, G.J., & Nelson, S. (2000). Innate immunity and pulmonary host defense. *Immunol. Rev.*, 173, 39–51.