nzmp™

NUTRITION

A good fight

How probiotics work with the immune system to support health.

Ingredients by Fonterra™ Dairy for life

Introduction

Globally, one in two individuals worry about their immunity. But rather than leaving things to chance, most consumers actively seek out products with immune benefits to help them put up 'a good fight' against environmental factors that can impact their well-being.

Probiotics are a key ingredient in a many of these products. Consumer research indicates that desire to boost the immune system, prevent illness, reduce inflammation and prevent antibiotic associated side effects, are amongst the most common reasons for buying probiotics. (FMCG Gurus Q3 2018 Survey US)

BASIC STRUCTURE AND FUNCTION OF THE IMMUNE SYSTEM

Probiotics are live micro-organisms that if taken in adequate amounts, confer a benefit to the consumer (FAO/WHO, 2006). Alongside the **digestive benefits** associated with probiotic use, benefits to the immune system and reduction in infection rates are well supported by human clinical trials using a variety of probiotic strains.

The term 'immune system' describes a set of organs and processes designed to maintain a functioning body that can resist infections and support recovery. The components of the immune system are split into the innate or natural system, and the adaptive or acquired system (refer to Figure 1 , on page 3).

The innate immune system encompasses what is commonly described as an individual's 'first line of defence', i.e. physical barriers that prevent undesirable foreign substances such as micro-organisms, allergens or toxins from entering the body. These physical barriers include external facing surfaces of the skin, urogenital lining and the gut lining. In the gut, the epithelial surface is covered with a mucus barrier which aids in the repelling of undesirable organisms (refer to Figure 1, on page 3). Another feature of innate immunity is our own bacterial and fungal populations that live on our epithelial surfaces, actively competing with, and often destroying, pathogens before they beome dangerous. Experiments in germ free mice have shown that without the normal population of bacteria, the mucus layer is thinner and epithelial cells regenerate at a lower rate (Kim et al. 2017).

The last feature of the innate immune system are immune cells, or white blood cells. White blood cells in the innate immune system, are 'patrol' type cells that identify abnormal antigens, produce general antibodies, and help to protect the body against infections by ingesting bacteria, fungi, foreign debris, other dead or damaged cells and parasites. These innate white blood cells may also contribute to inflammatory or allergic responses, a major function of the immune system.

The adaptive immune system is a more targeted response to specific antigens which may be recognised by the body, due to prior exposure or infection. The adaptive immune response involves specialised white blood cells that are designed to explicitly attack and destroy specific antigen presenting cells. The adaptive immune system also keeps a record, or memory, of antigens it has previously encountered. Therefore, it is sometimes referred to as acquired immunity. Vaccinations work by leveraging the adaptive immune system – they provide antigens to help prepare antibody producing cells, so that when an actual infection is encountered, antibody production can be rapidly switched on to support a better immune response.

KEY DEFINITIONS

- **Antibodies (Immunoglobulins):** protein 'flags' produced by white blood cells which bind to antigens, to help the body identify undesirable foreign substances.
- **Antigen:** Chemical components from undesirable or harmful foreign substances in the body; can include allergens, toxins, viruses or harmful micro-organisms. These are recognised by antibodies.
- **Microflora:** the unique combination of micro-organisms living on an individual. The microflora is specific to the surface they live on, i.e. skin microflora is different to that found in the mouth, small or large intestine, urogenital area etc.

WHITE BLOOD CELLS

Between their role in both the innate and adaptive immune systems, white blood cells are critical to many protective processes that may include anti-infection activity. Several organs are involved in white blood cell production and development. These organs include the bone-marrow, lymph nodes, thymus and spleen. There are several different types of white blood cells each with specific functions (Table 1).

Table 1: Different types of white blood cells and their functions

Cell type	System	Function
Eosinophils	Innate	• Target layer parasites like worms • Modulate allergic inflammatory response
Basophils	Innate	• Targets parasites and bacteria • Secrete heparin and histamine • Increase blood flow to the infection site
Neutrophils	Innate	• Produced in bone marrow • Generally most abundant type of white blood cell • Target bacteria & fungi
Lymphocytes	Innate/ Adaptive	• Main cells in lymph • Natural killer cells (mainly target tumours and viral infections) • T-lymphocytes(T-cells) (several types) • B-lymphocytes(B-cells) (produce antibodies)
Monocytes (most common type)	Innate/ Adaptive	• Macrophages (engulf and destroy pathogens; alert other cells to antigen presence) • Dendritic cells (help to flag antigens to lymphocytes) • Foam cells (contain cholesterol and other fatty deposits)

IMMUNE BENEFITS OF TAKING PROBIOTICS

A well-functioning healthy immune system is a balancing act for your body. If your immune system is under prepared, then viral, bacterial and fungal infections are more likely to take hold because your immune system does not respond fast enough. However, if your immune system is over-stimulated, then the immune system can attack your own body. Examples of this over stimulation include allergies or auto-immune diseases. **NZMP LactoB 001 and BifidoB 019** are well researched strains with the following immune benefits.

Gut Associated Lymphoid Tissue & Enhanced Immune Activity

One element of the gut immune system is outward facing Gut Associated Lymphoid Tissue (GALT). The GALT consists of both fixed tissue such as lymph nodes and Peyer's patches and more 'mobile' individual lymphocytes. The development of GALT requires a microflora that interacts with those lymphoid tissues (Rhee et al., 2004), thereby training the immune system to understand what a normal safe bacterial environment looks like. Studies in germ free mice have shown less developed GALT due to the lack of a microflora bacteria to promote the immune tissue development in these specially bred animals (Kim et al., 2017). This GALT -microbiota interaction ensures that the immune system is not triggered under normal conditions, and only responds to abnormal bacterial or viral components, or fungal species that could cause disease. In this way, GALT acts like shop security personnel who need to identify a shoplifter from the sea of shoppers.

Specific probiotics seem to interact with the GALT to induce systematic changes in the immune system. This can help the immune system to maintain appropriate levels of activity and readiness to defend against pathogens (Ashraf and Shah, 2014). Prescott et al (2008) found that maternal supplementation with LactoB 001 or BifidoB 019 before and after birth, improved cord blood immune parameters such as interferon gamma (produced by specialised white blood cells, natural killer cells) and immune active compounds in the breast milk including secretory IgA (sIgA). These provide infants with protection from infection. Interferon gamma is a feature of innate immunity and helps protect against viral, bacterial and protozoal infections; while sIgA is designed to resist digestion in the intestinal tract and is the main immunoglobulin helping to protect mucosal surfaces such as the gut. Given the increase in interferon gamma it is not surprising that other studies (Arunchalam et al., 2000; Chiang et al., 2000; Gill et al., 2001) have shown that BifidoB 019 enhances natural immunity through the increase in white blood cell that trap foreign bacteria, viruses and fungi; and the activity of specialised white blood cells called T-lymphocytes that are associated with production of antibodies (an adaptive immune system response). Clinical studies using LactoB 001 also showed improved activity of foreign matter trapping white blood cells, such as natural killer cells that identify foreign cells and kill the pathogen with the help of interferon gamma (Ibrahim et al., 2010). More recently BifidoB 019 was shown to reduce elevated inflammatory markers and improve oxidative stress in subjects with and without metabolic syndrome (Bernini et al., 2018). A meta-analysis of BifidoB 019 has concluded that daily consumption

by healthy elderly adults enhances natural killer and granulocyte functions of the innate immune system (Miller et al., 2017). Both NZMP strains have proven positive impacts on the immune system at various human life stages and the evidence suggests they do this through interacting with the lymphoid tissue of the gut epithelial layer (GALT).

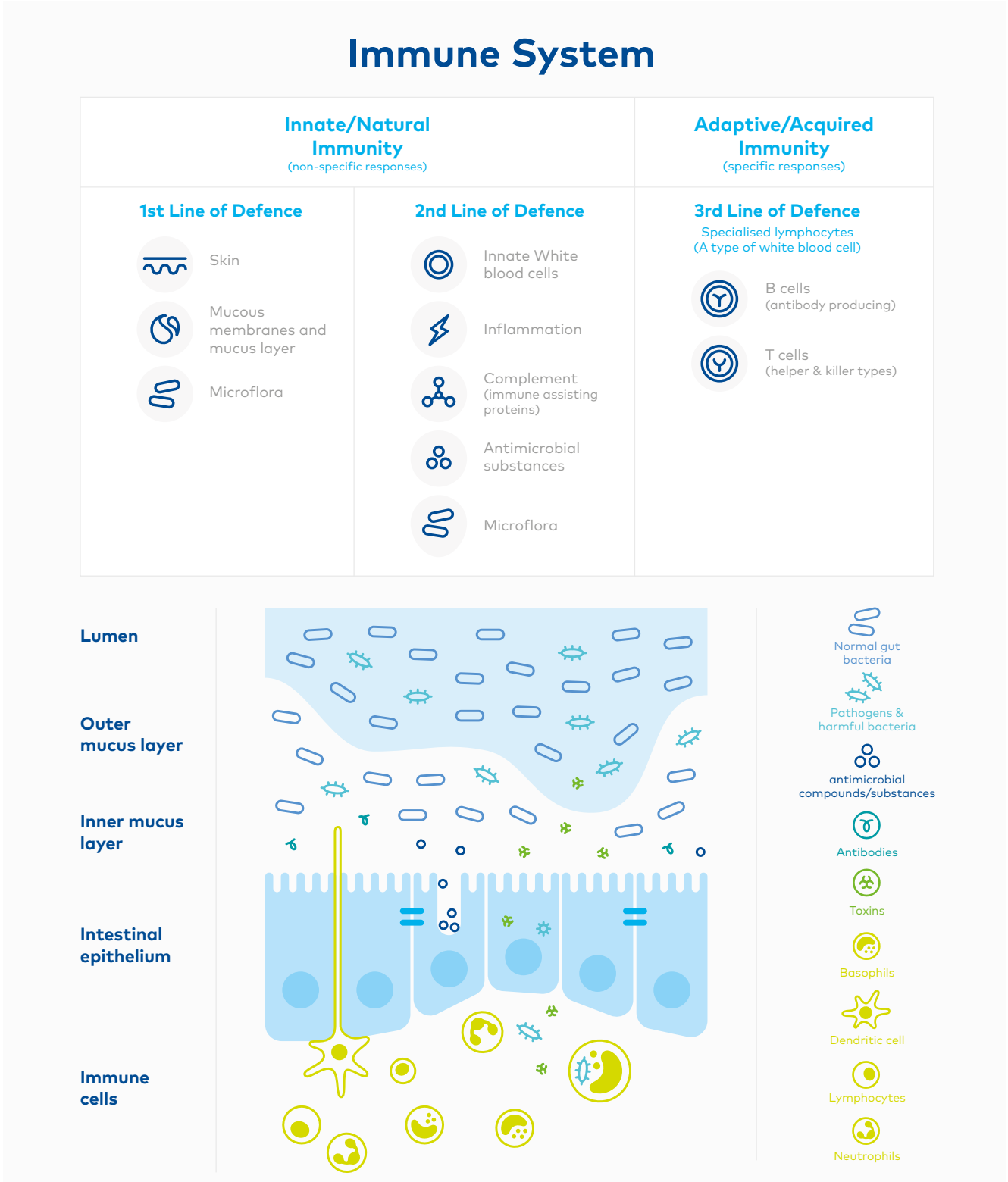


Figure 1: The gut lining (cells and mucus) is part of our innate and adaptive immune systems. Mucus keeps most harmful bacteria away from the epithelial cells. The mucus flows to wash them along and away from their binding sites. Antibodies(Y)are secreted to bind to toxins and pathogens preventing them from attaching to the gut wall and starting infection. Cells of the gut-associated lymphatic tissue (GALT) such as neutrophils and basophils from the WBC wait to engulf and destroy while dendritic cells look for new antigens to prime both the inflammatory response and the acquired immune system.

ALLERGIES

Delayed development of diverse gut microflora has been linked to development of allergies (Kalliomaki et al., 2003). An allergy is a chronic condition involving an abnormal reaction to an ordinarily harmless substance called an allergen. Allergens can include things such as dust mites, mould, and pollen, as well as food allergens such as milk, egg, soy, wheat, nut or fish proteins. Allergens are the antigens that produce the abnormal immune response.

Eczema is a very common allergic outcome. One form of eczema called atopic dermatitis, affects 7.2% of the adult population in the USA (Silverberg, 2017). When mothers and their babies are given LactoB 001 supplements, this treatment has been shown to clinically reduce eczema at 2 years of age and to maintain a reduction in eczema at 4, 6 and even 11 years of age (Wickens et al., 2008, 2012, 2013, 2018). In addition, at 11 years of age BifidoB 019 also showed significant impact on the lifetime prevalence of two other allergy conditions (atopic sensitization and wheeze) which had not been observed in earlier analyses (Wickens et al., 2018). These studies show that probiotics supplementation with LactoB 001 (and to some extent BifidoB 019) within the first two years of life can reduce allergic response and eczema, even many years after probiotic supplementation has ended. This is probably facilitated via the interactions with lymphoid tissue in the gut, to enable more normal immune development.

As well as reducing the risk of allergy development, probiotics can alleviate the condition of individuals already suffering. The combination of LactoB 001 and BifidoB 019 improved atopic dermatitis in food sensitised children (Sistek et al., 2006). Atopic dermatitis is an immune system misbalance, so improvement in this condition suggests that the probiotic combination of LactoB 001 & BifidoB 019 supports both immune re-balancing as well as preventing initial imbalances early in life (Wickens et al. 2018). Acting through the gut, probiotic supplementation with BifidoB 019 and/or LactoB 001 appears to impact the immune system throughout the whole body not just the gut.

ANTI-INFECTION BENEFITS OF TAKING PROBIOTICS

Probiotics have a well-known effect in the prevention of infection. However, it is important and scientifically more accurate to note that specific probiotic strains are only effective against specific infections. **NZMP LactoB 001 and BifidoB 0019** are well researched strains with the following published anti-infective benefits.

Respiratory Tract Infections

It appears that in sportspeople, some strains of probiotics can contribute to the prevention of upper respiratory tract infections, and improvement of symptoms (Leite et al., 2019). Leite et al (2019) specify that species, dose length of supplementation and how the probiotics are taken can play a role in effectiveness. In upper respiratory tract infections, probiotic activity seems to act through increases in interferon gamma and the secretory immunoglobulin A (sIgA). Both these immune active compounds have been shown to be increased when taking BifidoB 019 (Prescott et al., 2008). Sazawal et al. (2010) have shown that formulations including BifidoB 019 and GOS reduced severe-acute lower respiratory tract infections by 35% in 1-3-year-old children. Further research is required to see if these effects are also seen in adults, but the potential immune benefits could be hugely advantageous to both competing athletes and busy or stressed individuals.

Diarrhoea related to Infection

Diarrhoea can be caused by various toxins, but main causes are infection by viruses, bacteria and amoeba in humans and other species. Traveler's diarrhoea is a commonly acquired in sports people traveling for competition or recreation. Hemalatha et al. (2014) showed BifidoB 019 halves the incidence of diarrhoea and reduces fever risk in preschool children. Another showed that BifidoB 019 favourably altered the microflora in elderly (Ahmed et al., 2007). Preclinical animal work has shown BifidoB 019 to enhance resistance to *Salmonella typhimurium* (Shu et al., 2000) as well as rotavirus and Escherichia coli infection in piglets (Shu et al., 2001).

NZMP LactoB 001 has been shown to reduce both *Staphylococcus aureus* carriage in older male adults with a mean age of 64 (Eggers et al., 2018) and diarrhoea causing *Clostridium difficile* count in the elderly (in combination with another *Lactobacillus*; Lahtinen et al., 2012). *Clostridium difficile* treatment with antibiotics is difficult, but if it is not addressed the infection can lead to diarrhoea and gut damage. The potential for probiotics to provide an alternative and effective solution for treatment is significant.

The consistent improvement in infection related diarrhoea between animal and human studies (even across age groups) has promising implications, and builds on LactoB 001 & BifidoB 019's already strong digestive health benefits.

Urogenital Infection

The urogenital area is another site in the body where anti-infection benefits of probiotics has been demonstrated. The urogenital tract has a mucosal epithelial surface like the gastro-intestinal tract but occupied by a different microfloral population. Hanson et al. (2016) in a systematic review concluded that probiotic interventions were effective in the treatment of urogenital infections as alternative or co-treatments. Oral LactoB 001 supplementation showed, in combination with lactoferrin and *Lactobacillus acidophilus*, to improve symptoms of bacterial vaginosis and persistent candidiasis (Russo et al., 2018; Russo et al., 2019).

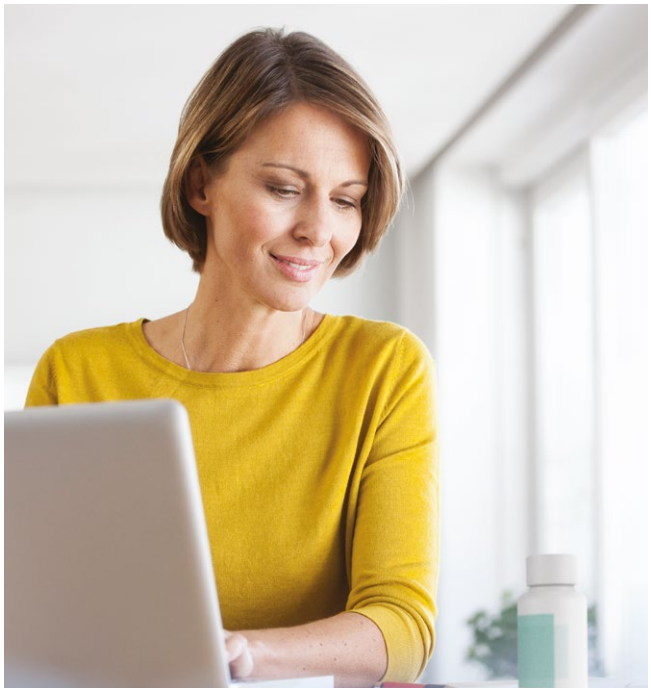
Periodontal (Gum) Disease

Periodontitis is inflammation of the gums and the structures supporting the teeth. While it is a relatively common condition, and usually experienced as redness or soreness of the gums, in serious cases it can lead to chronic inflammation, and destruction of teeth or even the underlying bone in the jaw. The inflammation is most often a response to bacterial overgrowth between the teeth and gum.

In an animal model of periodontitis, rats were induced to have periodontitis and then split into two groups that were either treated with BifidoB 019 or not (Olivera et al, 2016; Ricoldi et al 2017). While untreated mice went on to exhibit the classic symptoms of periodontitis, BifidoB 019-treated mice showed fewer symptoms, reduced proportions of gum pathogens, and better immune markers. Based on these results, the research group went on perform a randomized placebo-controlled clinical trial to test BifidoB 019-containing lozenges in human patients with generalized chronic periodontitis (Invernici et al 2018). All patients received standard treatment (scaling and root planning) and were randomly assigned to also receive BifidoB 019 (n = 20) or control (n = 21) lozenges twice daily over 30 days. Once again, those receiving BifidoB 019 had better clinical outcomes, fewer periodontal pathogens, and lower proinflammatory cytokine levels when compared to the control group. Hence, the use of BifidoB 019 in addition to periodontitis treatment appeared to reduce infection and improve patient outcomes.

Conclusion

The immune system is incredibly complex, with many components contributing to an individual's ability to maintain health. Probiotics can provide a range of potential immune benefits via their interactions with the digestive tract. NZMP's BifidoB 019 and LactoB 001 strains can modulate immunity via interaction with gut associated lymphoid tissue, and shows clinical evidence of enhancing particular immune cell activities to protect against certain types of infection. In addition, these strains support improved gut biodiversity, impacting development of allergies. With immune benefits observed across various age groups, there is strong potential for these strains to enable customers to put up 'a good fight' for immunity, as well as market opportunities.



REFERENCES

Ahmed M, Prasad J, Gill H, Stevenson L, Gopal P. (2007) Impact of different levels of Bifidobacterium lactis HN019 on the intetestinal microflora of elderly human subjects. Journal of Nutrition health and Aging 11,26-31

Arunchalam K, Gill HS, Chandra RK (2000) Enhancement of natural immune function by dietary consumption of Bifidobacterium lactis HN019. European Journal of Clinical Nutrition 54:263-267.

Ashraf R, Shah NP (2014) Immune system stimulation by probiotic microorganisms. Critical Reviews in Food Science and Nutrition 54, 938-956

Bernini LJ, Simão ANC, de Souza CHB, Alfieri DF, Segura LG, Costa GN, Dichi I. (2018) Effect of Bifidobacterium lactis HN019 on inflammatory markers and oxidative stress in subjects with and without the metabolic syndrome. British Journal of Nutrition 120:645-652

Chiang BL, Shieh YH, Wang LH, Liao CK, Gill HS (2000) Enhancing immunity by dietary consumption of a probiotic lactic acid bacterium (Bifidobacterium lactis HN019): optimization and definition of cellular responses. European Journal of Clinical Nutrition 54: 849-855.

Eggers S, Barker AK, Valentine S, Hess T, Duster M, Safdar N. (2018) Effect of Lactobacillus rhamnosus HN001 on carriage of Staphylococcus aureus: results of the impact of probiotics for reducing infections in veterans (IMPROVE) study. BMC Infect Dis. 2018 Mar 14;18(1):129

FAO/WHO (2006) Probiotics in food: Health and nutritional properties and guidelines for evaluation – FAO Food and Nutrition Paper 85

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Ghosh C, Sarkar P, Issa R, Haldar J. (2019). Alternatives to conventional antibiotics in the era of antimicrobial resistance. Trends in Microbiology 27, 323-338

Gill HS, Rutherfurd KJ, Cross ML, Gopal PK (2001) Enhancement of immunity in the elderly by dietary supplementation with probiotics Bifidobacterium lactis HN019. American Journal of Clinical Nutrition 74:833-839

Grzeskowial L, Endo A, Beasley S, Salmminen S (2015) Microbiota and probiotics in canine and feline welfare. Anaerobe 34, 14-23

Hanson L, VandeVusse L, Jerme M, Abad CL, Safdar N (2016) Probiotics for treatment and prevention of urogenital infections in women: a systematic review. Journal of Midwifery and Womens Health 61, S339-355

Hemalatha R, Ouwehand AC, Forssten SD, Babu Geddan JJ, Sriswan R, Bhaskar MV, Radhakrishna KV

(2014) A community-based randomized double blind controlled trial of Lactobacillus paracasei and Bifidobacterium lactis on reducing risk for diarrhea and fever in preschool children in an urban slum in India. European Journal of Nutrition & Food Safety 4:325-341.

Hemalatha R, Ouwehand AC, Forssten SD, Babu Geddan JJ, Sriswan R, Bhaskar MV, Radhakrishna KV

HN001 on carriage of Staphylococcus aureus: results of the impact of probiotics for reducing infections in veterans (IMPROVE) study. BMC Infectious Diseases 14:129.

Ibrahim F, Ruvio S, Granlund L, Salminen S, Viitanen M, Ouwehand AC (2010) Probiotics and immunosenescence: cheese as a carrier. FEMS Immunology and Medical Microbiology 59:53-59.

Invernici MM, Salvador SL, Silva PHF, Soares MSM, Casarin R, Palioto DB, Souza SLS, Taba M Jr, Novaes AB Jr, Furlaneto FAC, Messora MR. Effects of Bifidobacterium probiotic on the treatment of chronic periodontitis: A randomized clinical trial. J Clin Periodontol. 2018 Oct;45(10):1198-1210.

Kalliomaki M, Isolauri E. (2003). Role of intestinal microflora in the development of allergy. Current Opinion in Allergy and Clinical Immunology 3(1), 15-20

Kim D, Zeng M.Y.,Nunez G. (2017) The interplay between host immune cells and gut microbiota in chronic inflammatory diseases. Experimental and Molecular medicine 49, e339

Lahtinen SJ, Forssten S, Aako J, Granlund L, rautonen N, Salminen S, Viitanen M, Ouwehand AC (2012) Probiotic cheese containing Lactobacillus HN001 and Lactobacillus NCFM modifies subpopulations of fecal lactobacilli and Clostridium difficile in the elderly. Age 34, 133-143

Leite GSV, Resende AS, West NP Lancha AH (2019) Probiotics and sports: A new magic bullet?. Nutrition 60, 152-160

Miller LE, Lehtoranta L, Lehtinen MJ (2017) The effect of Bifidobacterium animalis ssp lactis HN019 on cellular immune function in healthy elderly subjects: systematic review and meta-analysis. Nutrients 9(3). pii: E191.

Oliveira LF, Salvador SL, Silva PH, Furlaneto FA, Figueiredo L, Casarin R, Ervolino E, Palioto DB, Souza SL, Taba M Jr, Novaes AB Jr, Messora MR. Benefits of Bifidobacterium animalis subsp. lactis Probiotic in Experimental Periodontitis. J Periodontol. 2017 Feb;88(2):197-208.

Prescott SL, Wickens K, Westcott L, Jung W, Currie H, Black PN, Stanley TV, Mitchell EA, Fitzharris P, Siebers R, Wu L, Crane J, Probiotic Study Group (2008) Supplementation with Lactobacillus rhamnosus or Bifidobacterium lactis probiotics in pregnancy increases cord blood interferon-gamma and breast milk transforming growth factor-beta and immunoglobulin A detection. Clinical and Experimental Allergy 38:1606-14.

Ricoldi MST, Furlaneto FAC, Oliveira LFF, Teixeira GC, Pischiotini JP, Moreira ALG, Ervolino E, de Oliveira MN, Bogsan CSB, Salvador SL, Messora MR. Effects of the probiotic Bifidobacterium animalis subsp. lactis on the non-surgical treatment of periodontitis. A histomorphometric, microtomographic and immunohistochemical study in rats. PLoS One. 2017 Jun 29;12(6):e0179946.

Russo R, Edu A, De Seta F. (2018) Study on the effects of an oral lactobacilli and lactoferrin complex in women with intermediate vaginal microbiota. Archives of Gynecology and Obstetrics 298:139-145

Russo R, Superti F, Karadja E, De seta F (2019) Randomised clinical trial in women with recurrent Vulvovaginal candidiasis: Efficacy of probiotics and lactoferrin as maintenance treatment. Mycoses 62, 328-335

Sazawal S, Dhingra U, Hiremath G, Sarkar A, Dhingra P, Dutta A, Verma P, Menon VP, Black RE (2010) Prebiotic and probiotic fortified milk in prevention of morbidities among children: community-based, randomized, double-blind, controlled trial. PLoS One. 5:e12164.

Shu Q, Freeman Q, Gill HS (2001. Probiotic treatment using Bifidobacterium lactis HN019 reduces weanling diarrhoea associated with rotavirus and Escherichia coli infection in piglet model. Journal of Pediatric Gastroenterology and Nutrition 33, 171-177

Shu Q, Lin H, Rutherfurd K, Fenwick SG, Prasad J, Gopal P, Gill H (2000) Dietary Bifidobacterium lactis (HN019) enhances resistance to oral Salmonella typhimurium infection in mice. Microbiology and Immunology 44, 213-222

Silverberg, J. I. (2017). Public Health Burden and Epidemiology of Atopic Dermatitis. Dermatologic Clinics, 35 (3), 283-289

Sistek D, Kelly R, Wickens K, Stanley T, Fitzpatrick P, Crane J (2006) Is the effect of probiotics on atopic dermatitis confined to food sensitized children? Clinical and Experimental Allergy 36: 629-633.

Vieco-Saiz et al. 2019. Benefits and inputs of lactic acid bacteria and their bacteriocins as alternatives to antibiotic growth promoters during food-animal production. Frontiers in microbiology 10:57

Wickens K, Barthow C, Mitchell EA, Kang J, van Zyl N, Purdie G, Stanley T, Fitzharris P, Murphy R, and Crane J. (2018). Effects of Lactobacillus rhamnosus HN001 in early life on the cumulative prevalence of allegic disease to 11 years. Pediatric Allergy and Immunology 29, 808-814

Wickens K, Black P, Stanley TV, Mitchell E, Barthow C, Fitzharris P, Purdie G, Crane J (2012) A protective effect of Lactobacillus rhamnosus HN001 against eczema in the first 2 years of life persists to age 4 years. Clinical & Experimental Allergy 42:1071-9.

Wickens K, Black PN, Stanley TV, Mitchell E, Fitzharris P, Tannock GW, Purdie G, Crane J, Probiotic Study Group (2008) A differential effect of 2 probiotics in the prevention of eczema and atopy: a double-blind, randomized, placebo-controlled trial. Journal of Allergy and Clinical Immunology 122:788-94.

Wickens K, Stanley TV, Mitchell EA, Barthow C, Fitzharris P, Purdie G, Siebers R, Black PN, Crane J (2013) Early supplementation with Lactobacillus rhamnosus HN001 reduces eczema prevalence to 6 years: Does it also reduce atopic sensitization? Clinical and Experimental Allergy 43:1048-1057.

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