A good fight

How probiotics work with the immune system to support health.
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 become 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

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

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 lgA (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 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.
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 that BifidoB 019 halves the incidence of diarrhoea and reduces fever risk in preschool 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.

**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


