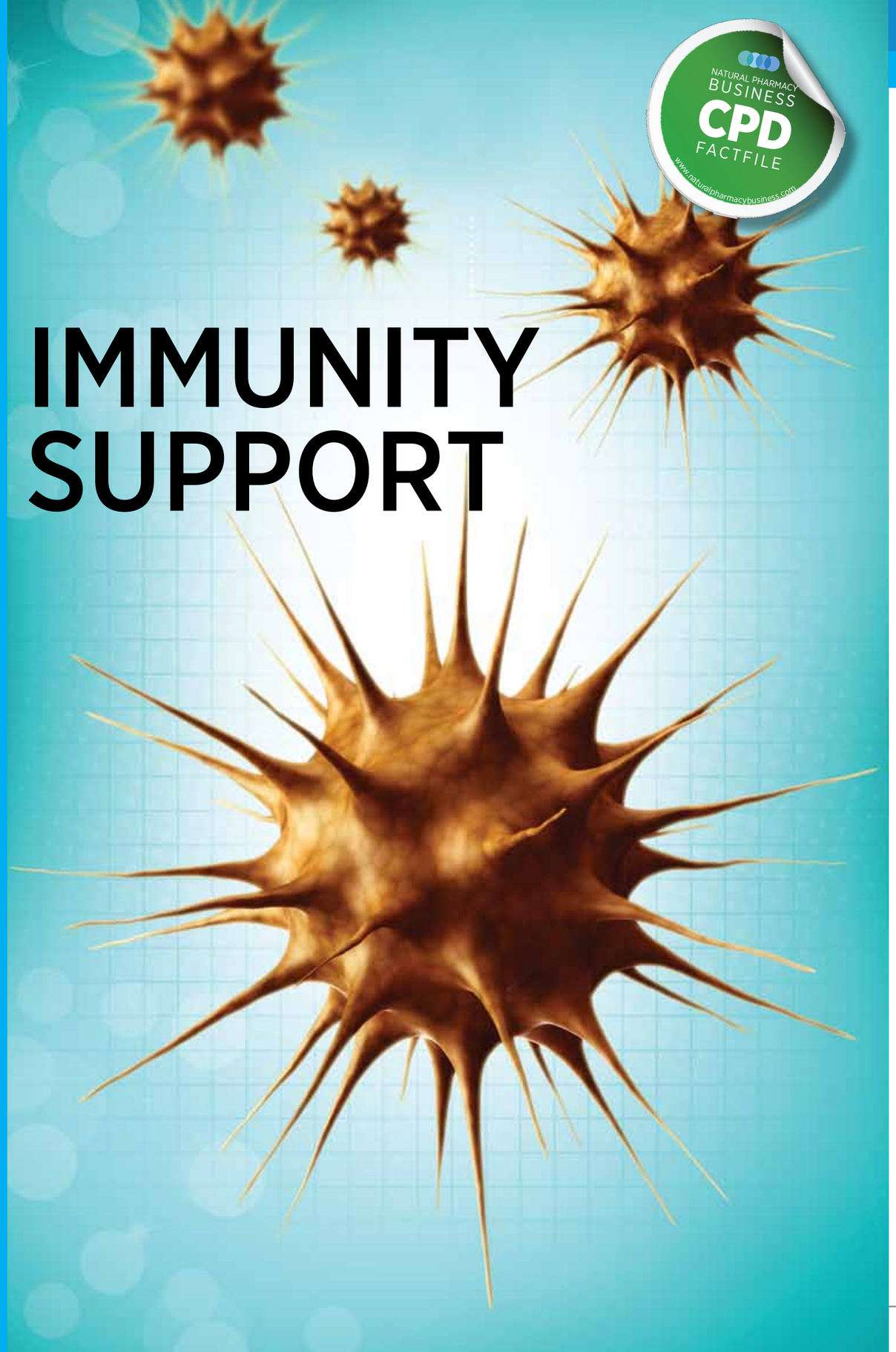
IMMUNITY SUPPORT



With the cold and flu season on the horizon, Dr Mayur R Joshi looks at the clinical landscape concerning probiotic use and immune system support.

When we are born we are presumed to be almost sterile with very little in the way of microbial colonisation. Our immune system at this stage is immature. However, after birth, the body is exposed to the maternal bacterial population as well as the external environment and we are bombarded with multiple microbes that colonise the body, thereby priming the infant immune system.

The normal function of the immune system is dependent on its complex relationship with the beneficial bacteria that inhabit the GI tract. Not all bacteria cause disease and, in fact, the interaction between the gut and bacteria is well documented, with its importance established in a variety of functions; ranging from aiding digestion to boosting immune function.

GUT BACTERIA

Up to 1,000 bacterial species inhabit the bowel with concentrations increasing further down the intestinal tract[1]. There are approximately 10 times more microbial cells inhabiting the body than there are cells making up the human body itself[2]; with the mass of bacterial cells within the colon weighing up to 1.5kg[3], similar in weight to the human liver. In addition, the collective genetic information of the gut bacteria (the microbiome or microbiota) contains over 100 times the number of genes in the human genome[4]. Consequently, the metabolic function of this microbial 'organ' is comparable to the liver and as such is as important to normal functioning. Disruptions in the bacterial population of the gut can, therefore, have profound effects on health and disease.

Much research is being carried out and we still only know a small proportion of the potential functions associated with the gut flora. Through understanding of the normal function in a healthy individual we can better understand the implications in immune system health.

MICROFLORA AND IMMUNE FUNCTION

The human gastrointestinal tract contains the largest mass of immune tissue in the body; in fact gut-associated lymphoid tissue (GALT) is responsible for 60% of antibody secretion in the body[5]. The microflora of the gut has a complex relationship with the immune system and is able to exert local and systemic effects[6].

The microflora is so important to the normal functioning of our immune system that it has been postulated that we are 200,000 times more prone to infection without our microbiota[7]. The intestinal microflora plays an integral part in host defence both through direct interactions with pathogenic organisms, as well as modulation of the immune system.

Particularly in early life, the composition of the gut flora profoundly influences the development of the gut lining and the corresponding immune system, supporting it to work effectively and offer protection against common infections.

The hygiene hypothesis proposed by Strachan in 1989 suggests that the increase in the prevalence of atopic disease

and autoimmune disease is related to reduced exposure to microbes at an early age as a result of improved sanitation and living conditions, vaccines, antibiotic therapy and smaller family sizes (in developed countries)[8]. These changes result in less diverse microbial populations, leading to altered microbiomes and immature immune system development. This, in turn, is associated with an increased incidence of allergic diseases (such as eczema, asthma and hay fever), autoimmune disease and increased susceptibility to infection.

After birth, the microbial population of the gut "primes" the local immune tissue, which has systemic effects on overall immune development. The mechanisms by which this occurs are very complex and are the focus of much ongoing research.

The mode of delivery itself can have profound effects on the microflora and subsequently immune system development. For example, babies born vaginally have a more diverse gut bacterial population compared to those born via caesarean[9, 10].The clinical relevance of these changes is still being explored, but it is well established that reduced diversity is associated with adverse changes to immune system function, for example.

PROBIOTICS

Probiotics represent a potentially excellent supplement to aid in early immune development. The accepted definition of a probiotic is a live microorganism that, when administered in adequate amounts, confers a health benefit on the host[11].

In general, probiotics have largely been associated with gut related problems and indeed they have been shown to help prevent and reduce the duration of episodes of infective diarrhoea, improve stool consistency and frequency in constipation and help in the management of infant colic.

More interestingly, probiotics have been shown to positively influence the immune system, offering protective effects against

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colds, flu and other infections as well as being used as an adjunct in the treatment of upper respiratory tract infections.

HOW DO PROBIOTICS WORK?

The beneficial effects of probiotics have been documented for over a century; initially through anecdotal evidence but now, increasingly, through rigid scientific study and clinical trial work. Multiple mechanisms of action of probiotics have been postulated and indeed identified as to how these living organisms produce their beneficial effects[12]. The overall concept is based on a redressing of any imbalance within the gut, displacing harmful bacteria with beneficial species. This also helps to increase microbial diversity and increase numbers of beneficial bacteria by helping to eliminate the pathogens.

The way they achieve this is through a number of mechanisms that have been summarised in the table below.

Modulation of Intestinal Ecosystem

↑ Beneficial bacteria

↓ Gut pH

Stimulation of gut peristalis

↓ Harmful substances

Modulation of Immune System

Stimulate local/Systemic systems via interaction with Galt

Enhanced defence response (↑ IgA, CD4+ & CD8+ T cells, NK cell activity, adjuvant effect)

DOWN REGULATION OF INFLAMMATORY & ALLERGIC RESPONSE

Improved colonisation resistance

↑ Competitive exclusion (e.g. for nutrients, adhesion sites)

↓ Harmful microbial species

↑ Epithelial cell mucin synthesis

Enhanced intestinal barrier function

Summary of main mechanisms of action of probiotic bacteria (Table taken from Baker et al 2009[13])

Not all probiotic strains will possess all of the above properties (and indeed this overview does not represent the full spectrum of properties) but it serves to demonstrate the many ways in which they are able to exert their effects.

EVIDENCE BASE

Vast amounts of time, effort and money are being invested into probiotic research in numerous clinical indications. The immune modulatory effects have been investigated extensively and yet we are still learning about the way in which the bacteria interact with the immune system. However, there is already good clinical evidence to support

further research in this area and the use of probiotics to help boost the immune system is already common worldwide.

A study in 2005 looked at 477 healthy adults who were randomly assigned to receive a daily probiotic + multivitamin + mineral supplement or a placebo[14]. The incidence of viral respiratory tract infections was lower and there was a relative reduction in flu like symptoms, fever and total symptom severity. These were statistically significant. There was no effect seen on the duration of symptoms.

In 2011 another study of 272 adults by Berggren and colleagues looked at the incidence of the common cold, duration of symptoms and the severity of symptoms over a 12-week period[15]. They were randomised to receive either a multi-strain probiotic mixture or a placebo and the results were overwhelming in their support of the use of probiotics. Incidence of the common cold was lower, duration of symptoms was lower and severity of symptoms was improved in the probiotic group. These results were statistically significant. They also found differences in certain immune markers in blood samples taken from these patients supporting the theory that these effects are due to the bacteria's ability to modulate the immune system.

A study in 2009 looked at the incidence of acute infection in 81 infants comparing a probiotic to placebo[16]. The infants were followed up for their first year of life and those taking probiotics were found to have a reduced incidence of otitis media and recurrent respiratory infections during that time.

A 2001 study by Hatakka et al looked at 571 children aged between 1-6 years old and the effect of probiotics on general illness and acute infections[17]. They found that the probiotic group had fewer days of absence from day care. They also found a relative reduction in acute respiratory tract infections (and

subsequent complications) as well as a reduction in the number of episodes requiring antibiotics.

These are a few examples of the type of research that is being carried out in the area. Of course, there are examples of human trials where no beneficial effect is seen highlighting the importance of choosing a high quality, clinically proven probiotic. Research is also strain specific so a clinical trial showing benefit with one type of probiotic cannot be used as evidence for a different probiotic. However, the positive results above serve as general support for continued research and use of good quality probiotics.

CONCLUSION

The routine use of probiotics for boosting the immune system is still a long way off in developing countries while it is still considered "alternative" medicine. They are, however, being extensively researched leading to a wider awareness of their potential benefits both in general and in specific clinical situations. Indeed, we have already seen that there is promising evidence even with the limited scope of this article.

Although more work is needed to further ascertain the properties of specific strains and formulations there is sufficient available evidence to warrant further research in the future and also to warrant the use of probiotics within specific population groups.

Dr Mayur R Joshi is Medical Advisor at Probiotics International (Protexin)

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