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April / May 2021



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Black Seed (*Nigella sativa*) usage in Ayurveda to restore the body's health and harmony led Sabinsa to investigate and isolate its most active compounds, thymoquinone (TQ) and thymohydroquinone (THQ). Extraction with eco-friendly and selective supercritical carbon dioxide yields material that independent researchers discovered out-performs cold-pressed and other preparations in a head to head assessment.[†] Black Seed's recent popularity surge is sure to continue, and Sabinsa's Nigellin® Black Seed Extract, in Amber (oil), and unique Onyx and Pearl (powders) are quintessential to progress it.

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[†] Koshak AE *et al.* Comparative Immunomodulatory Activity of *Nigella sativa* L. Preparations on Proinflammatory Mediators: A Focus on Asthma. Front Pharmacol. 2018;9:1075. Published 2018 Oct 2. doi:10.3389/fphar.2018.01075

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Spokesperson: Chris Lee, Managing Director,
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foreword

The year no one could have predicted – reflecting on changes in the nutraceutical industry amidst the global pandemic

At the time of writing this, we have passed the one-year milestone since COVID-19 lockdowns began in the UK, so it seemed a fitting time to reflect on the strange and unprecedented previous 12 months.

Business operations and supply chains in particular have experienced extreme challenges over the last year – from protecting workforces and material supplies, and for some the entire modus operandi was flipped on its head. Embracing change and adapting has been key to business resilience, and the nutraceuticals industry has always been highly innovative and exceptional at responding positively to change. So, it's not a surprise to learn that this year the sector has continued to grow, if not thrive. Consumer awareness around the benefits of dietary supplementation is at an all-time high, with heightened awareness globally around the importance of health. And with a forecasted CAGR of over 20% for 2020-2024, the future looks bright for nutraceuticals. With this in mind, we look back at the challenges and changes to some of the industry's key sectors in light of COVID-19, and the potential lasting impact for the future.

First and foremost, it is impossible to ignore the meteoric rise in the demand for immune health supplements. The increase in consumer awareness in this area was noticeable immediately and was unsurprising, as consumers looked for ways to proactively protect themselves from the virus – several reports highlighted the huge uplift in sales



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AND EVEN STRONGER
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for products with immune health claims from the outset of the pandemic. Some of the most popular products contain the likes of vitamins C, D, and K - due to their reported potential links to relieving COVID-19 infection or symptoms. However, the pandemic has placed a renewed spotlight on the microbiome too, with the immune health and wider benefits for consumers from gut health products also a major focus over the last year. An increased awareness from consumers on their health and wellness is certainly great news, now we need to harness that energy and interest by continuing to invest in robust science to deliver effective products that provide real consumer benefits to this newly receptive audience.

Another area that has understandably received increased interest over the →



past year is mental and cognitive health. The increase in stress caused by the COVID-19 pandemic globally, due to changes or renewed pressures on our work, home, and social lives, as well as health of course, has led to mental wellbeing and cognitive performance being more important than ever. From supplements to foods and beverages and beyond, blends of vitamins, minerals, probiotics, and new natural nootropic ingredients to help boost mental health or performance are flourishing, and this can only be a good thing for wellbeing, both now and in the future.

With lockdowns forcing facilities like gyms to close, sports nutrition has also seen significant changes in light of the pandemic. As consumers searched for ways to stay fit at home, opportunities opened up for brands to adapt to the emerging home-based active consumer. From home-schooling to working from home and running a household,

regular schedules were significantly affected too, meaning that for some sport nutrition consumers convenient nutritional or nutraceutical solutions were even more desirable.

The healthy ageing category also continues to evolve in the face of the pandemic, with adults of all ages looking for products to support joint, skin, and overall health. Mobility remains a key focus for healthy ageing, and continues to broaden its demographic appeal outside of just Boomers. Unique ingredient combinations in the joint health space are gaining ground too, creating accessible and convenient products that address mobility as a whole. And after a year of reduced mobility due to lockdowns, these products will be key to getting many of us back on our feet.

The pandemic has not only had a huge effect on our personal and business lives,

but it has also changed the way we do business. Without being able to travel and meet one another face-to-face, virtual events have provided a new platform for connections, innovation, and growth. Creating and maintaining a space to facilitate networking, knowledge sharing, and community-building is key to our industry. At the upcoming Vitafoods Insights Virtual Expo on 10-13 May, our aim is to do just that - to inspire the nutraceuticals industry by providing the latest insights and consumer trends, market-leading product developments, as well as invaluable networking. After a challenging year for all we hope to emerge a better connected and even stronger industry. We hope you can join us in May. ●

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Nutraceuticals Now is a technical review providing the latest information on functional products and ingredients which are defined as having a disease preventing and/or health promoting benefit in addition to their nutritional value.

It is targeted at manufacturers of food and drink, who are producing finished products aimed at the ever increasingly health conscious consumer.

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CONSUMERS ARE BOOSTING THEIR IMMUNE HEALTH

Over the past 12-months, consumers have become more concerned about their immune health more than ever before. This has been a direct result of the COVID-19 pandemic as consumers begin to re-evaluate their lifestyles and diets in order to be less vulnerable to disease as well as the dangers of viruses and bacteria in surrounding areas. So how is this consumer shift changing the food and beverage industry and are consumers actively seeking out new products in order to combat this concern?

COVID-19 has significantly impacted consumers confidence towards their immune system alongside their overall health. FMCG Gurus consumer insights show that a total of six in ten consumers across the globe say that they have become more conscious about their health and wellness, with 64% of consumers also stating they are now more concerned about their immune health. This shows that concern over vulnerability to disease is not only restricted to consumers associated with being more vulnerable but has impacted society overall.

However, although COVID-19 has heightened consumer concern towards their immune health other lifestyle factors are also seen to be contributing to poor immune health across the globe. As such, 44% of global consumers say that they have experienced health problems in the last twelve months that have impacted on quality of life. Consumers believe that there are several day-to-day and long-term issues that impact on overall levels of health and wellness. Many of these day-to-day attributes are something that consumers will link to the frantic nature of modern life and levels of professional obligations and time-scarcity.

Due to deteriorating confidence towards immune health, consumers are beginning to adopt a holistic health approach to life. FMCG Gurus research shows that 77% of global consumers recognize the link between their immune health and overall health. This means that consumers will see good immune health as important to protecting heart, bone and joint, and digestive health, whilst also recognizing that issues such as stress and anxiety, poor sleep health, and excess weight is something that can negatively impact on immunity.

In order to address their immune health, consumers are most likely to adapt their diets. FMCG Gurus insights shows that the two most popular types of changes have been to increase intake of fresh fruit and vegetables and reduce sugar intake. Increasing intake of fruit and vegetables is something that will be a popular option amongst consumers for several reasons. These are products that consumers know and trust and associate with recognized ingredients that boost health. Whereas sugar is still seen as the number one dietary evil due to its associated link with health issues such as weight gain and diabetes.

As consumers look to change their diets in order to boost their immune health, they will begin to actively seek out new innovative products which helps aid this issue. Functional food and drink products are seen as highly attractive to consumers and are more favourable compared to nutritional supplements. FMCG Gurus research shows that 50% of consumers have turned to food to boost their immune health with 72% of global consumers stating they would rather consume immune supporting food and beverages than supplements. Functional food and drink products will be seen as easier to incorporate into daily diets and more appealing from a sensory perspective. In comparison, consumers can have concerns towards nutritional supplements over issues such as taste, cost, ease of digestion, ingredients used in products, and safety. These are concerns that the nutritional supplements market needs to address.

There is a major opportunity to position products at consumers who are looking to address their immune health. Therefore, claims around the topic of boosting the immune health must be clear and transparent for consumers.

Many consumers are more sceptical of the health and wellness industry than before. This is because consumers can feel that brands may not have their best interests at heart and can make misleading health claims in order to charge a premium price. This highlights the importance of clear messaging and being transparent with consumers.

Ingredient claims can also be highly appealing when it comes to immune boosting food and drink. FMCG Gurus insights show that 45% of global consumer would be more likely to purchase immune supporting products if they contained a branded health ingredient. Consumers associate a number of ingredients with boosting the immune system, with the top three being Omega 3 (77%), Protein (77%), and Probiotics (72%). The popularity of probiotics as a way of boosting immune health shows that awareness and appeal of such products is growing and that consumers do not associate the ingredient exclusively with digestive health but overall wellness. Therefore, highlighting that consumers are concerned about their immune health but understand that by boosting overall health and wellness they will also be boosting their immune health and feel less vulnerable to future viruses and disease. ●

This article is based on FMCG Gurus: What's Next for Immune Health in 2021- Global Report. For more information, please contact info@fmcggurus.com



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Guidelines for physical health are well known: exercising, healthy eating, good hygiene and now, social distancing. Then, to help reach psychological well-being, yoga, mindfulness meditation and a balanced lifestyle are tools to keep in mind. In parallel, there are some ways to proactively reinforce natural defenses and mental health. The use of food supplements will help fulfill both physical and psychological gaps. Probiotics will bring additional assistance to keep the right balance. Beyond gut health support, probiotics have been abundantly studied and have shown significant results in strengthened immunity, and more recently in mental health areas. How can probiotics multitask to that extent? Everything connects to the gut, and this is where the magic happens. Actually, not magic, but science!

The immune system

The gut-associated lymphoid tissue (GALT) is the largest immune network in the body. In fact, 70% of the immune system resides in the gut. The immune system's main function is to protect the body by ensuring that any 'non-self' antigens are cleared from the body; this is done by the immune system recognizing itself and other common environmental antigens (food, airborne substances,

clothing, etc.) as 'self' and not a threat. In a perfect world, the immune system performs these two roles perfectly; this is homeostasis, or a healthy state. A proper balance is needed, an over aggressive immune system is not beneficial and counterproductive, and an under aggressive immune system is weak.

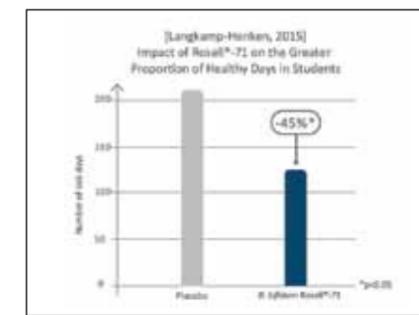
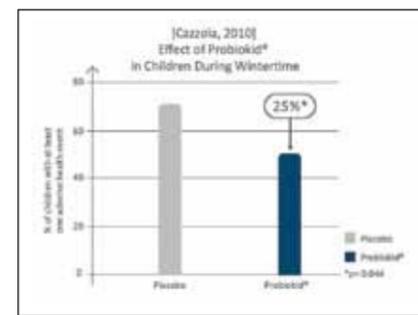
The relationship between the immune system and the gut microbiota is supported by a wide array of scientific evidence. The digestive microflora plays a key role in the development and maintenance of immune defenses. In the same way as the immune system, the digestive microbiota evolves through life, and its balance is impacted by many factors including stress, diet, age, etc. In this context, the use of probiotics, through their ability to balance and interact with the host microbiota has appeared as a potential strategy to positively influence the immune response [Harper, 2020].

The brain-gut axis

The brain and the gut communicate through a vast network of 500 million neurons innervating the gut. That's why the gut is sometimes referred to as the 'second brain' due to its hosting the enteric nervous system (ENS), a neural network that allows the gut to work without instruc-

tions from the brain [Liang, 2018]. The ENS maintains control of the digestive system; it plays an important role in peristalsis, digestive enzyme secretion, and pain perception. Being home to intestinal microflora, there is now evidence the gut and its microbiome work together to affect not only gut function and immunity, but also endocrine functions and neurotransmission. This is the microbiota-gut-brain concept. The benefits of probiotics for the brain-gut axis are now described in several studies and meta-analyses. A recently published meta-analysis showed a significant improvement in depression and anxiety with the use of probiotic or symbiotic interventions [Liu, 2019].

Nowadays, the connection between probiotics and the brain-gut axis is increasingly well understood. Scientifics can draw a good picture of the pathways involved in this bidirectional communication. As an example, these mechanisms have been monitored in several mechanistic studies with the probiotic formula, Cerebiome®, showing specific modes of action, including but not limited to: the modulation of neurotransmitters synthesis like serotonin from dietary amino acid like tryptophan, a positive impact on behavior, the support of a healthy brain structure, the modula-



tion of the HPA axis and the modulation through the vagus nerve. Cerebiome® (L. helveticus Rosell®-52 & B. longum Rosell®-175) is the most documented psychobiotic in the world, with five clinical studies and nine preclinical studies in the brain-gut axis area and approved health claims in Canada and Brazil on mood, feelings of anxiety and stress-related gastrointestinal discomfort.

The underlying interactions between stress and immunity

Stress is a worldwide concern, and its impacts on general health and well-being are well known. Gut discomfort and associated symptoms are easily perceived by the consumers; however, they may not be aware that stress also takes a toll on the immune system. Over the past 30 years, more than 300 studies have been conducted on stress and immunity in humans, and together they have shown that psychological challenges can modify various features of the immune response [Segerstrom, 2004]. Stress can influence the severity of infectious disease, decrease the immune responses to vaccines or reactivate latent herpes viruses.

Top solution for infant and child immunity

Probioid® (L. helveticus Rosell®-52, B. infantis Rosell®-33, B. bifidum Rosell®-71 and FOS) is backed by 11 clinical studies on infants and children and is renowned to support immune system maturation and baby-specific microflora. This super formula is Generally recognized as safe (GRAS) and each strain has been authorized in infant food in China.

Probioid® and its single strains have showed their beneficial effects in babies during their first year of life. In a study of 132, three-and-a-half-month to six-month-old healthy, formula-fed babies, Probioid® was able to maintain SIgA levels, compared to the placebo group,

supporting and maintaining a normal intestinal immunity [Xiao, 2019].

Cazzola et al. published a study in 2010 involving 135 healthy, school-age children who had at least three episodes of cold-like symptoms during the previous winter. A three-month supplementation with Probioid® was able to decrease the risk of occurrence of cold-like symptoms in these children by 25% vs. placebo (p=0.044) and to significantly limit school absenteeism by 40% (p=0.043).

Documented solutions for immunity in stressed students

Teenagers and young adults' lifestyle and occasional stress can also be concomitant to suboptimal immunity. Researchers were interested in academically stressed students as a model of acute psychological stress, which is associated with increased incidence of cold and flu-like symptoms. A large probiotic study conducted in 581 stressed students at University of Florida during final exams for the autumn semester [Langkamp-Henken, 2015] showed that the students who received B. bifidum Rosell®-71 had a higher proportion of healthy days around the exam period compared to the placebo group. Researchers saw a 45% reduction in the percentage of participants who became ill (p<0.05 vs. placebo) and fewer episodes of cold/flu-like symptoms when compared with the placebo (p<0.05). In a post hoc analysis, [Culpepper, 2016], it was also demonstrated that B. bifidum Rosell®-71 had a positive effect on self reported stress scores (p=0.0086) and reduced stress-induced occasional diarrhea (p=0.006).

ACTIVE ADULTS' IMMUNITY ALSO NEEDS TO BE CARED FOR

In overtrained athletes or even in people exercising more than they previously would, particularly during winter or at the

seasonal transitions, chronic stress and high intensity exercise could reduce immune defenses. A pre-post intervention study was conducted with L. helveticus LAFTI® L10 in two groups of well-trained recreational athletes: eighteen healthy athletes and nine fatigued athletes, with recurrent cold-like symptoms and impaired performance. The study showed that L. helveticus LAFTI® L10 helped to recover a healthy immune balance: after one month of L. helveticus LAFTI® L10 administration, CD4+ T cells secretion of IFN-γ in fatigued athletes was restored to the levels found in healthy athletes [Clancy, 2006]. The results of this study are correlated with previous in vivo studies whereby L. helveticus LAFTI® L10 induced the production of IFN-γ in challenged animals [Elahi, 2005].

Ready-to-market probiotic solutions for immune and mental health for the whole family

Choose from Lallemand Health Solutions scientifically substantiated Rosell®, LAFTI® or Harmonium probiotic strains portfolio to build your own formula to support immunity and mental health. Pick from a list of compatible ingredients, including vitamins B6, B9, C, D, and minerals such as magnesium, selenium and zinc for extra claims. Expert in yeast production, Lallemand Health Solutions allows you to stand out in your market by adding a selection of yeast-based ingredients to further support natural defenses. Over the years, Lallemand Health Solutions has developed a large range of innovative dosage forms such as powder, capsules, sachets and sticks, drops, room-stable chewable tablets, and packaging options to fit all needs. ●

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A healthy mind in a healthy body is a widely used mantra, now even more relevant than ever before. Since 2020, consumers' behavior has evolved: 64% are now more conscious about their immunity and 43% about their mental well-being (FMCG Gurus). People are very aware of the importance of putting both physical and mental health on an equal footing. But where to start?

HOW WILL YOU TAKE CARE OF YOUR NEW SELF THIS YEAR?





RESTORING THE GUT MICROBIOTA BALANCE: WHY IS DIVERSITY SO IMPORTANT?

By Stephen O'Hara, CEO at OptiBiotix

There are more than 10,000 different microbial species that are known to inhabit the human ecosystem. Following scientific investigation into the human microbiome, we know now that the cells in the microbiome significantly outnumber those in the human genome – our collective DNA. While originally it was believed that microbes outnumbered human cells by 10:1, this is now thought to be much closer to 1:1 with 1.3 microbial cells for every one human cell¹. The largest population of these micro-organisms, approximately 100 trillion, exist in the human gastrointestinal tract² and collectively forms the gut microbiota.

Due to its unique composition, the gut microbiota can be easily influenced through diet, cultural and environmental factors, impacting the way it regulates metabolic processes, cholesterol, inflammation and the body's immune responses. When these micro-organisms live in relative balance, it's known as 'normobiosis'. This routine state can be achieved when individuals follow a healthy lifestyle through eating a balanced diet, performing regular exercise

and making sure they get enough sleep each night. However, not all routines can be sustained long-term. External stressors also influence the gut microbiota with many microbiologists discovering new evidence that indicates a relationship between the gut, neurobiochemistry and emotional behaviour, including stress, sleep deprivation, anxiety and depression³.

This internal influence manipulating our emotional behaviour is more commonly known as the 'second brain', or the Enteric Nervous System ('ENS'). Containing approximately 500 million neurons, the second brain is embedded in the lining of our gastrointestinal system and can often choose to act independently of its own accord or work in conjunction with our Central Nervous System ('CNS') to emphasise shifts in our emotion via a bidirectional link. When the ENS and CNS systems communicate, we call it the 'gut-brain axis', where complex pathways between cognitive and emotional areas of the brain link with the endocrine, immune and Autonomic Nervous System ('ANS'). When we disrupt the signals between the ENS, CNS and ANS by, for example, eating a larger meal than usual, by avoiding regular exercise or simply feeling anxious or stressed, we can easily shift the state of balance of this important gut-brain relationship. So, when this multifactorial relationship between an individual's gut microbiota, the gut-brain axis, and the chosen lifestyle becomes imbalanced, it's known as 'dysbiosis'.

The Gut Imbalance: Dysbiosis

Gut dysbiosis typically occurs when one or more micro-organisms has grown out of proportion to the other bacterial species that inhabit the gastrointestinal tract. This imbalance can cause a loss of beneficial bacteria, potentially expand harmful bacteria and can result in an overall loss of microbial diversity. Common symptoms of dysbiosis include flatulence, bloating, abdominal pain, diarrhoea and constipation, many of which are associated with irritable bowel syndrome (IBS), irritable bowel disease (IBD), coeliac disease and SIBO (small intestinal bacterial overgrowth). Moreover, recent studies have suggested that there is a direct link between these gastrointestinal conditions and dysbiosis, par-

ticularly in connection to depression⁴. While a lower diversity in microbial species is also considered a marker of dysbiosis and has since been tied to certain autoimmune diseases, obesity and other cardiometabolic conditions⁵. Even modern medicine like antibiotics have been found to cause gut dysbiosis by causing neurobehavioural changes in the gut-brain axis⁶.

Treating dysbiosis to restore the gut microbiota balance is often as simple as changing our diet. Traditional western diets often rely heavily on sugars and highly processed foods, which follow FODMAP (fermentable oligosaccharides, disaccharides, monosaccharides and polyols) food groups. Those who follow a high fat diet will find their gut microbiota is high in *Bacteroides*, while those who eat a diet rich in carbohydrates will find that *Prevotella* dominates. For example, a study that chose 21 healthy volunteers to follow a gluten-free diet discovered that each had a lower abundance of several key beneficial microbial species in their gut microbiota⁷. In studies like these, an unbalanced diet often delivers a knock-on effect to the gut since it prevents the metabolism of short-chain fatty acids (SCFAs), thus weakening the inflammatory response and causing microbial imbalance. It's why consuming a balanced diet is so vital in achieving great gut health – it provides a much more diverse microbiota that's robust against environmental influences.

Probiotics and Prebiotics: The Key to Restoration?

Preventing the onset of dysbiosis by consuming a healthy, balanced diet is one approach to achieving a diverse microbiome, though it is not the only route. Probiotics can also be used to both prevent dysbiosis and act as a therapeutic agent to rebalance an ongoing condition. They can easily manipulate the composition, enhance the function of existing microbial communities and improve the integrity of the intestinal barrier. *Lactobacillus* probiotic strains are a great example of this, having demonstrated their immune tolerance capabilities, specifically in gastrointestinal conditions such as IBS and IBD⁸. For example, a clinical study discovered that IBS patients showed decreased

pain and flatulence when receiving a rose-hip drink containing *Lactobacillus plantarum*⁹.

More recent studies have also suggested that *Lactobacillus* strains could reverse the symptoms of dysbiosis. Researchers that induced dysbiosis in the gut microbiome of mice treated each with three different strains of *Lactobacillus* bacteria: *L. plantarum*, *L. casei* and *L. rhamnosus*. The results concluded that all three strains were effective in restoring balance to the gut microbiota, particularly those microbial families that produce SCFAs, such as acetate and butyrate¹⁰. Many other clinical trials have also concluded that administering *Lactobacillus plantarum* and inulin can improve gut dysbiosis. Researchers have since found that the probiotic strain's IBD-alleviating effect may be related to the increase in butyric acid-producing genera in the intestine¹¹.

Alongside probiotics, prebiotics and dietary fibres can also be instrumental in tackling dysbiosis. For example, fucosylated oligosaccharides derived from chicory root are being used in creams to fight dermal dysbiosis, while many studies have also shown that fructooligosaccharides can suppress the hunger signal, promote satiety and control weight gain. Recent research has shown that when inulin-type fructooligosaccharides are fed to mice, the number of *Bifidobacteria* – usually found in leaner individual's gut microbiota – increase significantly, helping to prevent adiposity and inflammation¹². Moreover, research from the University of Roehampton has proven that fibre and mineral formulations, which include glucomannan and oligofructose, can positively impact the gut microbiome with significant increases in *Christensenellaceae*, *Bacteroides* and *Actinobacteria*¹⁴. Since prebiotics help to change the microbial landscape of the gut, helping feed the good bacteria, it means this two-pronged approach can increase microbial diversity and help prevent long-term conditions, which are developed from dysbiosis, from effectively taking root.

Science-backed Microbiome Modulation

At OptiBiotix, we are committed to developing science-backed approach- →

es to improve consumer health and wellbeing. As a leading life sciences company, we develop compounds to tackle obesity, cardiovascular disease and diabetes. These compounds work within the gut microbiota to support the growth of beneficial bacteria and improve overall wellbeing. Revolutionary functional fibres and mineral blends, such as WellBiome®, which human studies have shown increases microbiome diversity, is specifically targeted towards the health and wellbeing market. This blend works in synergy to harness the health positive bacteria found in the gut microbiota, delivering real benefits in three primary areas: digestive, heart and metabolic health.

Helping to maintain a healthy digestive system, the vegan-friendly prebiotic supports regular bowel habits¹⁵ by significantly increasing essential bacteria – such as *Bifidobacterium*, *Bacteroides* and *Christensenella* – with its 94% fibre content. In addition, the lactose- and gluten-free ingredient is backed by several EFSA health claims, alongside showing an ability to improve mood and reduce systolic blood pressure, leading to improved heart health. So, by modulating the microbial communities found in the gut microbiota, functional fibre and mineral blends like WellBiome can help to combat metabolic disorders as a result of dysbiosis, such as cardiovascular disease, type 2 diabetes and obesity⁸.

The Importance of Balance

If the microbiome is now believed to be a virtual organ of the body, it needs to be treated like one. This includes feeding the gut with beneficial bacteria through a range of nutritionally rich foods to promote a healthy microbial balance. The challenge for many will be finding what dietary lifestyle works for them, depending on whether they are treating an ongoing health condition like IBS and IBD, preventing potential metabolic conditions in later life, or by switching to a new diet due to allergies or intolerances. Yet restoring this balance doesn't have to be difficult, it just requires individuals to 'go with their gut instinct' and understand what food works best for their microbial makeup. Diversity, then, is not just important for our gut, it's also the key to unlocking a healthier lifestyle. ●



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2021 BUZZWORD “IMMUNITY”: Brands are making hay out of the immune consciousness

By Maggie McNamara,
Marketing Director at Gencor



Understandably, people want to do everything they can to support their immune system and stay healthy — especially considering that we just went through and are still dealing with a global pandemic. With the pandemic sweeping the globe, many industries and sectors took massive economic hits, however, one industry that did unquestionably prosper and continues to prosper through the insanity — Dietary supplements, in particular immune-support supplements.

FMCG Gurus¹ reports that in the past year alone, consumers worldwide are making changes to their diets and lifestyles to improve their immunity—61% in North America, 56% in Europe, 50% in Africa, 48% in the Asia Pacific, and 45% in South America. The most common reason for making changes was the desire to be proactive about their health (as opposed to suffering from a health condition). Eight out of the top ten sup-

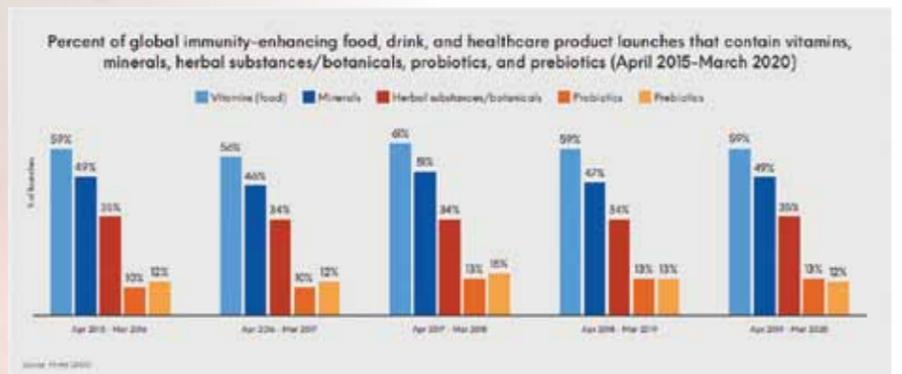
plements selling on Amazon in March 2020 were for immune support,² and with no cure for the virus in sight and vaccines a long way away from development, people were frantically searching for options to keep healthy. A month later, on Amazon, the top 20 vitamin category products in sales were immune related supplements.³

Immunity supplement sales growth was projected to spike above 25% in 2020, up from 8.5% growth to \$3.3 billion overall, according to Nutrition Business Journal (NBJ).⁴ Historically, growth has tended to spike in years with a severe cold and flu season and drop off in years with lower rates of illness. In keeping with this trend, growth peaked in 2017 to 9.9%, the highest growth rate in a decade, as the U.S. faced the worst flu season it had seen in years. Even less surprising is how all previous growth potential in the category has paled in comparison to the demand driven by the coronavirus pandemic.⁵ The final sales figure for immunity supplements reached \$5.2 billion in 2020, with a growth of 51.2% over 2019. In other words, nearly 10% of all U.S. supplement sales in 2020 were for immune support.⁴

FMCG Gurus consumer insights showed that only 54% of consumers indicate they were satisfied with their immune system mid-way through the pandemic.⁶ Then in one of their latest reports, FMCG Gurus research shows that 64% of global consumers say that they have become more conscious about their immune health as a result of COVID-19 and this has risen by 7% in a matter of months.⁷

While the category cannot expect to maintain a growth rate over 50%, NBJ does project a lasting boost for immunity supplements. Even with the growth curve normalizing in the coming years, they expect a lasting increase of \$1.5 billion over pre-COVID forecasts for cold, flu and immunity.⁸

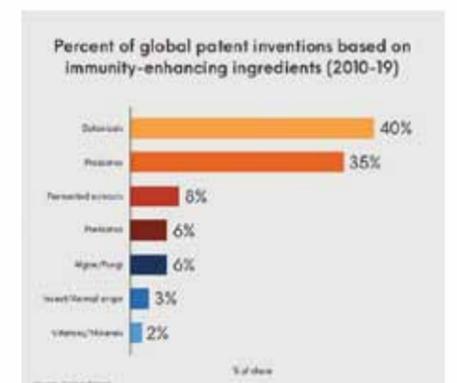
According to a report by Market Research.com, herbal extracts are the



fastest-growing ingredient, which are expected to grow at a CAGR of over 12% from 2020–2025.⁹ Herbal immunity supplements such as echinacea, elderberry, astragalus, garlic, and andrographis are expected to pose additional sales with the growth of the vegan population and flexitarians.⁶ But the spike in immunity boosting products is not limited to supplements and botanicals, it has also spurred a big jump in retail sales across several segments.

Immunity-strengthening products, including ginger and curcumin, are predicted to be prominent food trends in 2021, according to specialty food purveyors Natural Grocers and The Fresh Market.¹⁰ The pandemic has provided a clear boost to products that improve consumers’ well-being, both mental and physical. The Natural Grocers’ nutrition trends, predicted by a team of health and wellness experts in consultation with the grocer’s buyers and analysts, include a breadth of items focused on improving long-lasting health and immunity. In fact, for both The Fresh Market and Natural Grocers, the overall trend is one of healthy, long-term immunity boosting and nutrient-rich foods.⁶

Simply put, the coronavirus pandemic accelerated the trend toward food that supports the immune system. Innova Market Insights reports that 45% of global consumers are consuming more food and beverage products that boost their immune system since COVID-19.¹¹ One of the big formulation trends for 2021 has consumers placing an increased emphasis on food as medicine as they seek to fight what ails them. When the pandemic began disrupting Americans’ lives last March, about 36% of “clean label enthusiasts” (CLE consumers) began making changes to their diets to



boost their immune systems and keeping themselves healthy, according to research from InsightsNow.⁸

ADM has identified health and immunity among its top five global food and beverage trends for 2021. About 31% of consumers are buying more products tailored for their health, and 50% prefer foods and beverages that naturally contain beneficial ingredients based on in-depth research from ADM’s proprietary OutsideVoiceSM consumer insights platform.¹² The desire to influence health and wellness through foods and beverages is creating new opportunities for nutrient-dense products with functional health benefits aimed at supporting immune systems.¹³

IMMUNE HEALTH SUPPLEMENTS MARKET SEGMENTATION

According to MarketResearch.com, which looked at the global outlook and forecast for the Immune Health Supplements Market for 2020–2025¹⁴, the market is segmented by ingredient. The vitamin segment accounted for over 26% of the total revenue in 2019 and is still strong in 2021. The wide availability and proven health benefits of vitamin A, D, C, K, E, and B complex in supporting the immune system is driving the segment. The sale boost in vitamin C has →

been high since the outbreak of COVID-19, especially in APAC, Europe, and North America. The surge is expected to continue through 2025, as consumers pursue preventive measures.

The herbal and botanical extracts segment is expected to be the fastest-growing one in the market with a CAGR of over 12%.¹⁴ The growth in the vegan population, flexitarians, and consumers seeking plant-based alternatives with fewer side-effects is driving the demand for the segment. The growth is also associated with the importance of clean labels and health claims. These consumers want to know how to boost the immune system naturally but still expect ingredients with well-researched, evidence-based benefits like (Elderberry, Curcumin, Echinacea extract and Reishi mushrooms).

A low level of zinc, iron, copper, and magnesium in the body decreases the resistance against infections, thereby negatively impacting the immune system. The encouraging results related to the consumption of minerals is expected to generate a surge in mineral-based supplements. Mintel¹⁵ reports that the most recognized mineral by consumers as providing immunity benefits was zinc. However, FMCG Gurus found that in Europe, the Asia Pacific, and Africa, iron was the ingredient most frequently associated with improving the immune system, while magnesium was rated the highest in South America.⁶

Besides vitamins, minerals and botanicals, key players need to aim to gain competitive edge by developing Novel Immunity Boosting Supplements. The companies present in the market are mainly focusing on scientific research activities to develop innovative immune health supplements for generating more sales. Palmitoylethanolamide (PEA) is a natural support for the immune system. In 1993, Nobel laureate Dr. Rita Levi-Montalcini discovered that PEA is used in the body to regulate certain immune cells in parallel with the endocannabinoid (ECS) system. PEA is a cannabinoid-like molecule that is naturally produced by your body. It interacts with the endocannabinoid system to enhance balance in all kinds of ways. In fact, it appears that PEA exists at low



levels in every mammalian cell and is helpful for a healthy immune response. Backed by immense clinical research, with more than 3,000 participants taking part in six double-blind, placebo-controlled clinical trials demonstrating that PEA has clear benefits for immune health.¹⁶ In addition to studies on immune health, multiple studies have demonstrated that PEA is safe and effective in supporting a balanced inflammatory response and improved gut barrier defense.

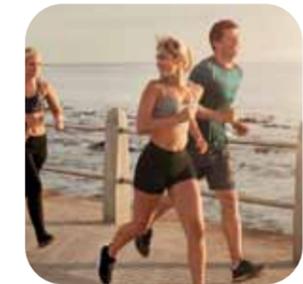
Finally, even if the COVID crisis fades into history, it seems likely that immunity-boosting foods and supplements will remain on-trend. Globally, immunity-boosting products are expected to grow over the next five years and surpass \$17 billion by 2025, according to market researcher ReportLinker.¹⁷ Innova Market Insights has identified immunity as one of its top 10 trends for 2021.¹⁸ Six out of 10 global consumers are increasingly looking for food and beverage products that support their immune health, says Innova, with one in three saying concerns about immune health increased in 2020 over 2019.

The global immune health supplements market share is highly competitive, and clinically proven formulas and scientific research are the major differentiating factors in the market that can substantially increase the segment. Functional foods and beverages are posing a threat to the consumption of immune ingredients in the supplement form, but factors such as innovations, research, competitive landscape, availability of substitutes, stringent

regulations from standard bodies and the adaptability of supplements into functional foods and beverages can further intensify the market dynamics. Ultimately, immunity-boosting ingredients will play a significant role in the coming years. ●

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HOW CURCUMIN, IRON, SELENIUM, ZINC, VITAMINS C, B2, B6, AND B9 FROM VEGETAL ORIGIN COULD HELP IN PANDEMIC

The conjuncture of the SARS COV 2 epidemic that has swept the world for over a year now would be one of the most current illustrations of Hippocrates' famous quote: "Let your food be your first medicine".

In general, low levels or intakes of micronutrients such as vitamins and minerals have been associated with adverse clinical outcomes during viral infections. It has been confirmed in a recent review¹ which highlighted that certain vitamins and minerals should be considered in the management of COVID-19 patients. Prevention, diagnosis, and treatment of malnutrition should be therefore included in the management of this epidemic. For that, the European Society for Clinical Nutrition and Metabolism (ESPEN) provided practical recommendations for nutritional management of COVID-19 patients².

Vidya Herbs' range of high-quality plant extracts is enriched with a specific essential trace element and a range of vitamins. Extracted from plants using a gentle water-based process, these ingredients are suitable for food supplements and food enrichment.

Curcuma longa (Turmeric)*

Turmeric is no doubt the most known plant from Ayurveda. Its main component is curcumin, which is well-known for its anti-inflammatory properties and has been shown to be a potent immunomodulatory agent. Curcumin is not only stimulating the immune system, but it also exerts anti-virus activities, demonstrating in vivo activity against Dengue³, Influenza A⁴, Hepatitis B⁵ and Herpes Simplex⁶ viruses. And now, with the COVID-19 pandemic, curcumin is presenting new and interesting potentials.

How curcumin helps the immune system modulation

In response to infection, infectious diseases, or biological intrusion, our biological defences may fight by liberating cytokines. Because an uncontrolled cytokine liberation by the immune system



may lead to the development of a lot of auto-inflammatory diseases, it is more appropriate to consider immune system modulation rather than only immune system stimulation.

Known as a strong anti-inflammatory compound, curcumin can reduce the production of various proinflammatory cytokines including TNF, IL-1, IL-2, IL-6, IL-8, IL-12, and chemokines, most likely through inactivation of the transcription factor NF-κB. That is why curcumin anti-inflammatory profile may be useful in both acute and chronic inflammation.

But curcumin can also modulate the activation of innate and adaptive immune cells such as T-cells, B-cells, macrophages, neutrophils, natural killer cells (NK cells), and dendritic cells and can also interact with molecular components involved in the inflammatory processes, such as cytokines and various transcription factors with their downstream signalling pathways, as mentioned above. Interestingly however, curcumin at low doses can also enhance antibody responses⁷. In vitro and in vivo experiments showed that curcumin's anti-inflammatory and immunomodulatory effects are combined to sustain the immune system and all its health properties⁸.

Curcumin and pulmonary damaging viruses

Even if inflammation under physiological conditions is a protective mechanism, when the negative regulatory mechanism is suppressed, a persistent and extensive inflammatory response occurs,

which can reach pathological levels causing fatal systemic damages. This triggered over-reaction of the immune systems may cause severe lungs damages and acute respiratory distress syndrome resulting in mortality. The same adverse effects of this type of immune overreaction have been observed in highly pathogenic avian influenza viruses and the novel coronavirus (SARS-CoV2) of the Severe Acute Respiratory Syndrome Coronavirus (SARS-CoV). This cytokine storm which results in acute lungs injuries may be counteracted by curcumin due to its capacities to exert protective effects by regulating the expression of both pro-inflammatory and anti-inflammatory factors and by eliminating the reactive oxygen compounds that exacerbates the inflammatory response⁹.

Because of the great impact of the SARS-CoV2 on airways, curcumin has been considered on Nrf2 pathway. This nuclear factor erythroid-2-related factor 2 (Nrf2) has an essential protective role in the lungs against oxidative airway diseases. It has been recently published that curcumin could significantly increase its nuclear expression levels and promote its biological effects. The authors are expecting that curcumin may be considered as a therapeutic candidate against a broad range of oxidative stress-related diseases, including type 2 diabetes, neurodegenerative diseases, cardiovascular diseases, cancers, viral infections, and more recently SARS-CoV-2¹⁰, the COVID-19 disease.

Curcumin and COVID-19

Since December 2019 and the first cases reported from Wuhan, COVID-19 has not received any treatment, and a lot of pharmaceutical molecules have been tested in vain. Due to its identified clinical effects such as antiviral, antinociceptive, anti-inflammatory, antipyretic, and antifatigue effects, curcumin could be effective to manage the symptoms of the infected patient with COVID-19. Due to its several molecular mechanisms including antioxidant, antiapoptotic, and

antifibrotic properties with inhibitory effects on Toll-like receptors, NF-κB, inflammatory cytokines and chemokines, and bradykinin, curcumin could play an important role in the management of the disease^{11,12}.

Based on various immunity-boosting steps concerning Ayurveda, and the broad-spectrum of antiviral properties of curcumin, its combination with Zinc is hypothesised by some authors as a therapeutic approach of a nutritional complex with a concerted antiviral action¹³. Zinc in combination with polyphenols like curcumin may form ionophore complex that can boost individual immunity.

According to the hypothesis presented just above, it could be interesting to combine curcumin with natural zinc. But other minerals are also interesting to support or boost our immune system such as Iron and Selenium that could also be combined with curcumin (see below).

Recent research has highlighted the strong potential of curcumin as a complementary therapy or nutritional approach to viral diseases and more particularly today of COVID-19. However, low bioavailability, absorption, permeability, and rapid metabolism still obstruct curcumin's use. To improve curcumin bioavailability, Vidya Herbs developed a naturally enhanced bioavailability curcumin. Vi-Active™ bioavailability is 2.2-times higher than standard curcumin.

Curcumin could be safely consumed at 1,200 mg/day in 3 x 400 mg doses¹⁴, or at higher levels according to clinical trials results¹⁵.

Marketed under the brand name Puremeric™ Vidya Herbs turmeric extracts are characterized by three curcuminoids profiles. HPLC characterisation, isotopic C14 analysis and DNA testing guaranteeing the natural origin and the absence of synthetic substitutions. The botanical variety is guaranteed by a botanist and complete traceability is ensured through the Full iD™ internal quality label. Puremeric™ extracts also benefit of SFT™ natural technology that combines an easier formulation of the product and streamlined production while maintaining clean labelling.

Vitamin C*

Vitamin C helps to maintain the structural and functional integrity of the cells of our mucosal barriers such as the skin and the respiratory system. This vitamin is essential for the immune system for the differentiation, the proliferation, and the function of the immune cells. In addition, it plays a powerful antioxidant role. Finally, vitamin C participates in the development and production of antibodies.

Vidya Herbs makes an extract containing 15% natural vitamin C from Amla (*Emblia officinalis*). Amla tannins are also recognized for their involvement in the immune response. Just over 530 mg of extract provides the recommended 80 mg / d.

Vitamin B6

Vitamin B6 is involved in the immunity linked to our intestinal barrier mediated by migration of lymphocyte. It is also involved in their proliferation, their differentiation, and their maturation. It is also involved in maintaining or increasing the cytotoxic activity of NK cells. In terms of inflammation, this vitamin is required to produce cytokines and the regulation of inflammation. Vitamin B6 also participates in the production and metabolism of amino acids necessary for the constitution of antibodies.

Vitamin B6, which is officially recognized to carry a claim relating to the proper functioning of the immune system, can be found at 0.1 to 0.5% in our Vitamin B Complex extract, which also provides vitamins B1, B2, B3, B5, B7 and B9. An herbal blend of guava, lemon and holy basil is used to provide this extract, 200-1,000 mg of which provides the 1.4 mg of vitamin B6 required daily.

Vitamin B9 (folate)*

Vitamin B9 is involved in the regulation of the immunity of our intestinal barrier by acting for survival and regulation of T lymphocytes in the small intestine. Folate is also involved in the modulation of the cytotoxic activity of NK cells. Foliates are also used to support the immune response mediated by T Helper 1. They are necessary for the production and the metabolism of antibodies, ensuring a sufficient response to antigens.

Folic acid is obtained from lemons (*Citrus limon*) and the content of 5% of this

extract allows the contribution of RDA in 4 mg only.

Vitamin B2*

Vitamin B2, for which EFSA has validated many physiological functions, is particularly interesting for its action necessary for iron metabolism. Our extract is obtained from the fruits of the guava tree (*Psidium guajava*). Its 2% riboflavin content allows ingestion of RDA in just 70 mg.

Iron*

Vitamin C is officially recognized at European level to improve the absorption of iron, which is an important mineral for the immune system.

Like vitamin C, iron is essential for our barrier cells and helps to maintain their integrity as a cofactor of metalloenzymes. Iron is also involved in innate immune cells as a factor involved: in the destruction of bacteria, as a component of enzymes necessary for the functioning of immune cells and in the regulation of cytokines and the inflammatory response.

We have developed an extract from Curry leaves (*Murraya koenigii*) containing 3% Fe that achieves 100% of the recommended daily allowance in less than 500 mg.

Zinc*

Zinc (Zn) is an essential micronutrient because its deficiency leads to suppress the immune response, both innate and adaptive, leading to an increased susceptibility to many infectious agents and an increase in the duration of the infection. The European Commission officially recognizes the role of Zn in protecting the immune system.

Indeed, Zn also participates in maintaining the integrity of the cells of our



mucosal barriers since it is a cofactor of the metalloenzymes necessary for their maintenance. Zn is necessary for NK cells and for the growth and differentiation of immune cells. It increases the phagocytic activity of certain macrophages. It is an anti-inflammatory agent which participates in the modulation of the inflammatory response of cytokines.

This Zn-rich extract from guava (*Psidium guajava*) leaves is standardized at 4% Zn, and achieves the daily dose in less than 300 mg.

Selenium*

Selenium (Se) is the other micronutrient essential for proper immune function. It is present in the form of selenoproteins important for antioxidant defences, acting at the level of leukocytes and NK cells. Selenium is also involved in the differentiation and proliferation of T lymphocytes and helps to maintain antibody levels. Selenium deficiency is linked to the risk of mortality and severity, especially in cases of serious illness and sepsis.

Our extract is obtained from Indian mustard (*Brassica juncea*). By a fine selection of soils for its cultivation, associated with a gentle extraction process, we obtain an extract of 0.5% of Se which allows to obtain the recommended daily dose with less than 20 mg.

Conclusion

Barrier measures such as hand washing and wearing a mask help to reduce the spread of the virus and the impact of infections. But the burden of this pandemic is heavy and nutritional prophylactic measures may be considered, as necessary.

Indeed, there is no lack of clinical data to show how vitamins and minerals such as those described above participate in the support and functioning of our immune system. Inadequate intakes of these nutrients are unfortunately quite widespread, leading to less resistance to infections, thus increasing the burden of epidemics.

With this 100% natural offer, these vitamins and minerals included in their natural food matrices will allow them to supplement effectively and thus support their immune system, for better prophylaxis against current and future infections. ●



*(Available in organic quality with monitoring of 471 pesticides by third party laboratory)

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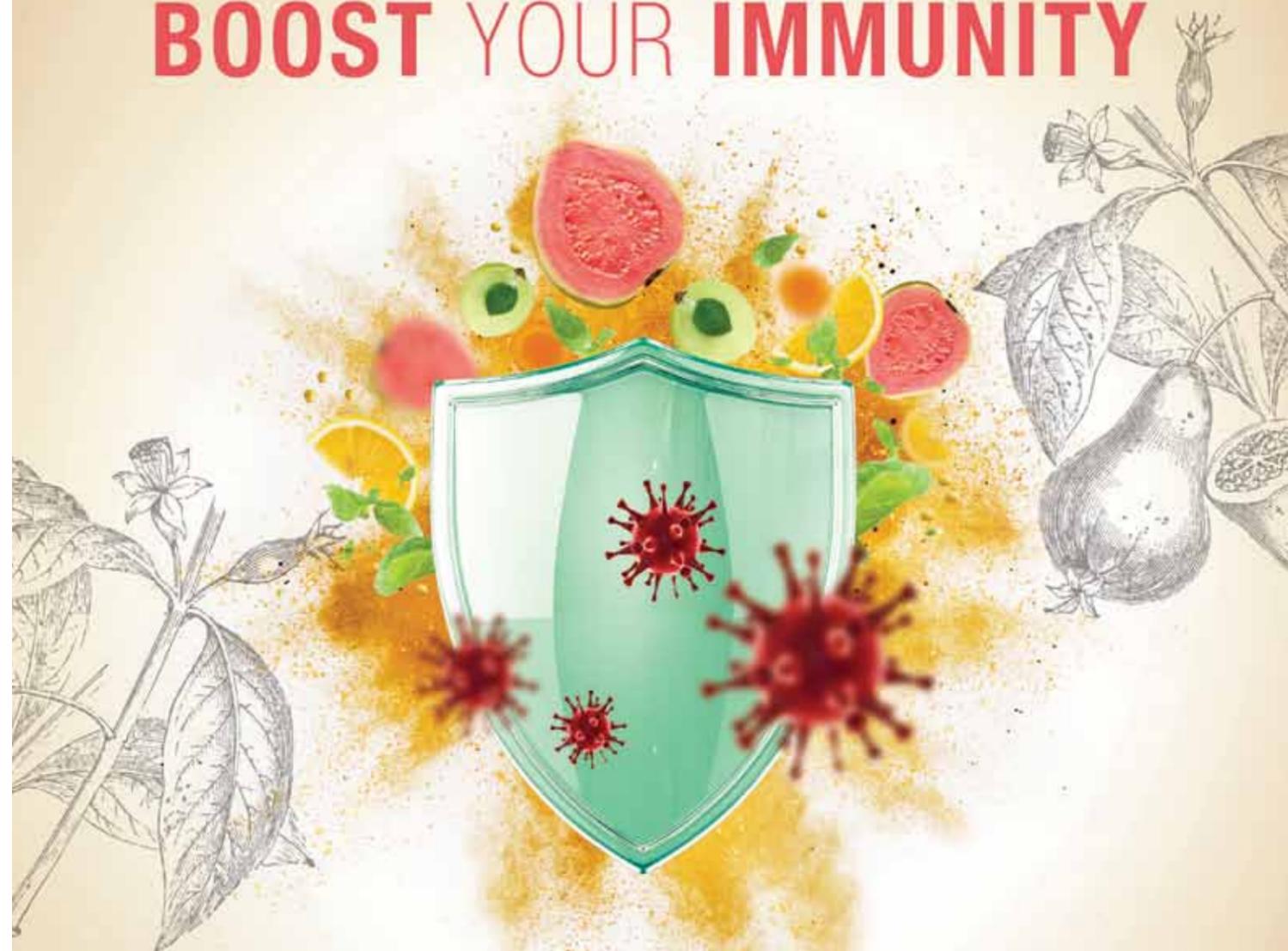
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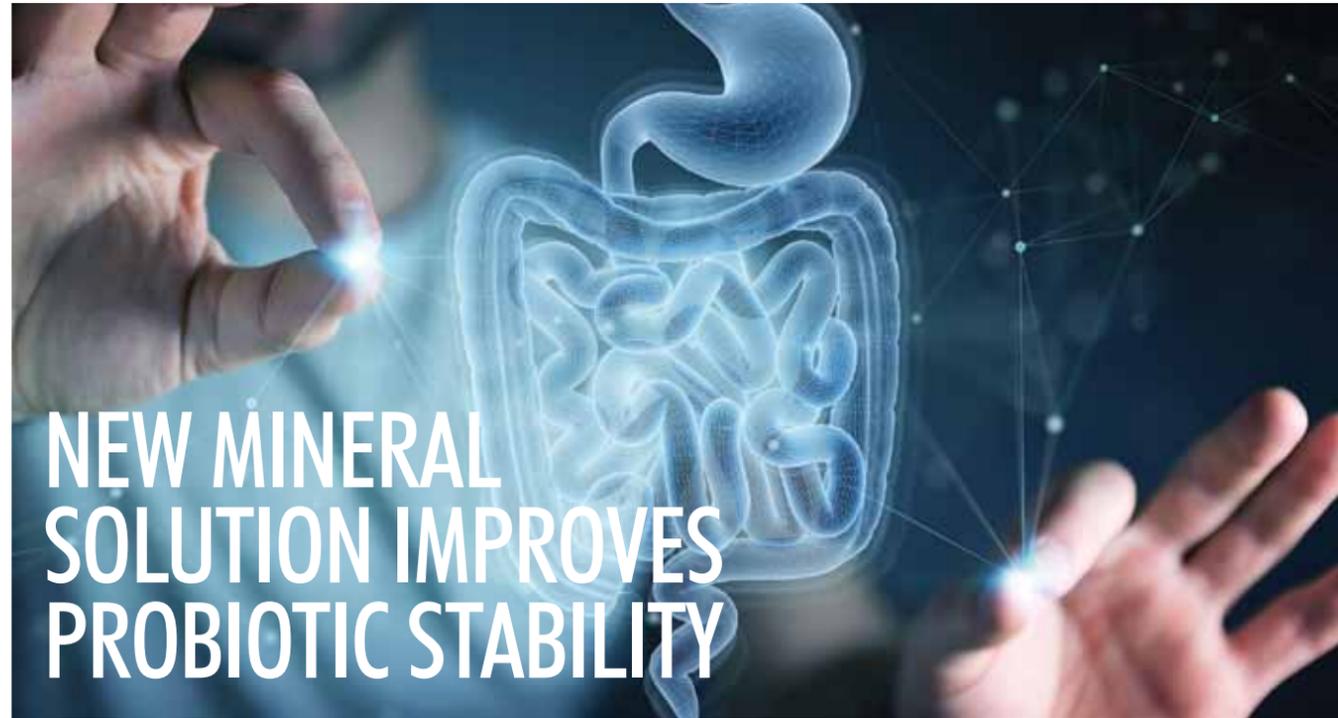


BOOST YOUR IMMUNITY



- CURCUMINOIDS / *CURCUMA LONGA*
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- ANDROGRAPHOLIDS / *ANDROGRAPHIS PANICULATA*
- VITAMIN B COMPLEX / *OCIMUM SANCTUM (HOLY BASIL) PSIDIUM GUAJAVA & CITRUS LEMON*
- VITAMIN B2 / *PSIDIUM GUAJAVA*
- VITAMIN B9 / *CITRUS LEMON*
- TANNINS / *EMBLICA OFFICINALIS (AMLA)*
- VITAMIN C / *EMBLICA OFFICINALIS (AMLA)*
- WITHANOLIDES / *WITHANIA SOMNIFERA (ASHWAGANDHA)*
- URSOLIC ACID / *OCIMUM SANCTUM (HOLY BASIL)*
- TANNINS / *SALACIA RETICULATA*

Omya has developed a new functionalized mineral solution for greater stability and performance of probiotics. Together with leading contract research company NIZO, Omya studied the mineral's influence on probiotic viability during production and delivery processes. *Nutraceuticals Now* talks to Lalit Sharma, Innovation Manager at Omya, and Kevin van Koerten, Senior Scientist at NIZO, about their cooperation and the new mineral solution.



NN: Could you briefly outline how you came together to study a mineral as stabiliser for probiotic formulations?

Lalit Sharma: We have recently developed an inorganic agent for enhancing the stability and performance of probiotic formulations. With its strong water-binding properties and significant buffering capacity, our new mineral solution is a promising inorganic probiotic carrier. We learned about NIZO as the leader in probiotic topics through their ongoing research and publications in this field. From lab to production scale, they have the necessary microbiological, processing and analytical equipment all under one roof, along with the expertise to help companies successfully address their particular food challenges. For us, it was important to learn more about the most appropriate bacteria strain to use for a representative gut model. So we reached out to NIZO for scientific validation that our mineral concept works.

Kevin van Koerten: When Omya approached us, we were fascinated by the topic right from the start. We are continually looking for new ways to improve food products, and this was the first time we carried out probiotic stability tests

“ USING A MINERAL IN PROBIOTIC STABILISATION IS A GROUND-BREAKING APPLICATION CHANGE.”

with inorganic material. As we were able to gain a lot of experience in handling functional minerals, the joint project enabled learnings on both sides.

NN: Why is a stabiliser required for probiotics?

Kevin van Koerten: It helps overcome production challenges. Probiotics are live bacteria that need to be incorporated into foods and nutraceuticals. To increase their shelf-life, probiotic formulations are generally dried to a powder before further processing. A stabiliser helps prevent possible damage during

drying, and the subsequent loss of beneficial effects.

NN: What makes this research so special?

Lalit Sharma: Using a mineral in probiotic stabilisation is a ground-breaking application change. Our new solution is the first inorganic agent for enhancing probiotic stability and performance. Thanks to the collaboration with NIZO, we got confirmatory research data in less than six months.

NN: How did you test the mineral and what were the results?

Lalit Sharma: For the research at NIZO's lab, *Lactobacillus plantarum* (strain WCFS1), one of the most studied probiotics, was used as a model organism. The lactobacilli cultures were mixed with either maltodextrin – the organic benchmark excipient – or our new mineral solution, and spray dried to evaluate their survival rates. To assess the efficacy of the stabilisers during digestion and accelerated shelf-life experiments, the resulting powders were separately blended with skim milk powder or pressed into tablets with lactose as an excipient. A representative in-vitro digestion model

demonstrated a proof-of-principle: our solution outperformed maltodextrin in both matrices – milk powder and lactose tablets – delivering up to 1000 times the amount of probiotic bacteria. In line with the digestion results, our product also showed significantly better stabilising effects during shelf life compared to maltodextrin – both in the milk formulation and lactose tablets.

Kevin van Koerten: The study's main goal was to confirm that Omya's inorganic solution performs as well as existing products already on the market. In the end, we found that it even outperforms current organic solutions. In addition to excellent gut delivery, we have also been able to show that the mineral offers high shelf-life stability for probiotics, paving the way for new expertise in probiotic production, supply chain and usage.

NN: What's the current market potential for probiotic formulations?

Lalit Sharma: Public awareness of gut health and its importance for wellbeing and immune health is growing. Furthermore, interest in supporting the immune

system has increased massively, particularly in light of the pandemic. So clearly, now more than ever, consumers are appreciating the scientifically supported immune benefits of probiotics. However, as these microorganisms are highly sensitive, product development can be challenging. That's why a proven stabiliser such as our mineral solution is vital. The results demonstrate the mineral's huge potential for probiotic applications in the food, nutraceutical and pharmaceutical industries, which means numerous possibilities for innovative products and positionings. ●

About Omya Group

Omya International AG is a leading global producer of calcium carbonates and a worldwide distributor of specialty additives, premium services and solutions. Founded in 1884 in Switzerland, Omya has a global presence extending to more than 175 locations in over 50 countries with 9,000 employees. Omya provides sustainable added-value products and services from responsibly sourced materials to meet current and future generations' needs. Omya offers innovative solutions based on high purity natural minerals and complementary ingredients that comply with the most stringent regulatory and quality standards in the Consumer Goods sector.

About NIZO

NIZO's wide-ranging expertise helps companies successfully address their food challenges: from managing the protein transition or delivering real health benefits to maintaining food safety and upscaling to industrial production. Through multidisciplinary teams and a unique pilot production plant, NIZO brings all the expertise together to deliver cost and time-to-market savings. It can also support customers through the entire innovation process: from R&D to (pilot) production.



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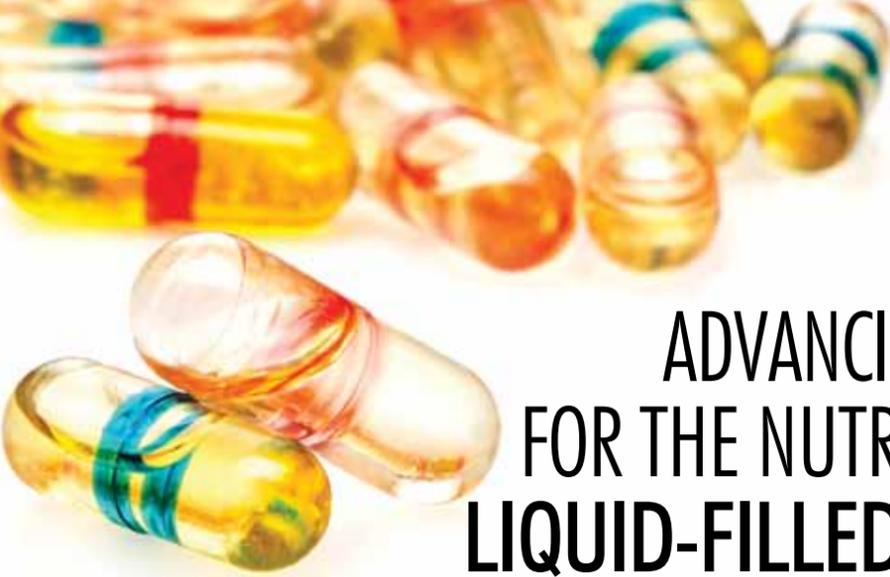
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By Dr. Jnanadeva Bhat, Head -
Formulation R&D (Pharma & Nutra),
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ADVANCING ENCAPSULATION FOR THE NUTRACEUTICAL MARKET: LIQUID-FILLED HARD CAPSULES

The nutraceuticals sector has seen significant growth and development over the last decade. This is a result of several factors, including increasing awareness about nutrition, busy lifestyles, ageing populations, increasing incomes in some societies and recent pandemic outburst. It is yet to be seen, but is likely, that the pandemic will prove a catalyst for stronger growth over the next few years, with Covid-19 having further highlighted the importance of immunity and health.

Globally, the nutraceuticals market is projected to grow at a CAGR of 7.5% during the period 2020 to 2025¹. The demands are two-fold. Firstly, on the consumer side, there is a greater demand for a range of products that meet the vegan and vegetarian market, as well as being user-friendly. On the manufacturers side, products need to be developed that offer manufacturing efficiency, enhanced bioavailability, trending ingredients and strong consumer appeal.

When we look at dietary supplements, the first dosage form that comes to mind is hard capsules. Capsules encapsulate formulation in a shell and are generally easier to formulate than other dosage forms. As a dosage form, capsules offer a range of benefits above tablets, such as helping to improve customer experience and patient compliance. Capsules are not only smoother and easier to swallow, but they can also mask unpleasant tastes.

Despite the significant benefits of existing capsules, nutraceutical manufacturers are always exploring opportunities for new

dosage forms for delivery. The development of novel encapsulation technologies that extend beyond stable formulations to liquid and semi-solid formulations play a key part in meeting the demands of manufacturers and customers. In this article we will look into an emerging dosage form in this area; 'Liquid-filled hard capsules', and review the benefits, properties, manufacturing and possibilities of this form.

Liquid-filled hard capsules

Liquid encapsulation is a technology which is emerging and gaining interest across the globe in the dietary supplement sector. The liquid-filled hard capsules dosage form encompasses products or compounds that are inherently liquids filled into hard capsules and can be band sealed. These capsules are either made from gelatin or hydroxypropyl methylcellulose (HPMC).

Gelatin, as an animal origin polymer, does not meet the increasing need for vegetarian or vegan-friendly nutraceuticals. Plant-based alternatives, such as HPMC capsules (Hydroxypropyl methylcellulose) have been developed to cater to the growing needs of consumers. As a result, there has been a shift in manufacturing towards HPMC polymer as the material of choice for capsules, particularly in the nutraceutical segment.

Comparing Hard and Soft Gel Capsules

In the dietary supplement sector, liquid-filling in hard capsules is gaining widespread interest due to its myriad advantages. In particular, when we compare the benefits of liquid-filling in hard cap-

sules, to soft gel capsules, there are a huge range of positives for manufacturers and consumers. These include:

Ease of development and manufacturing

In comparison to soft gel capsules, liquid-filling in hard capsules is usually more straightforward. It allows a simpler, more streamlined manufacturing facility, and also supports small-scale batches during development phases. The process is easier as it requires fewer steps during development and manufacturing, which can facilitate a shortened product development stage, and therefore an expedited route to market.

In addition to the potential for a streamlined development phase, hard liquid-filled capsules also provide an easier option for scaling-up operations.

Lower Oxygen/Gas Transmission Rates

One of the foremost advantages of hard capsule liquid-filling is its lower oxygen transmission rates (OTR). Soft gel capsules have comparably elevated OTRs, primarily due to the larger amounts of plasticizers needed for the gelatin polymer film flexibility.

Higher OTRs result in greater taste and aroma escape. This can be an issue, particularly when used for liquid formulations with strong odours or pungent ingredients. Hard Gelatin Capsule can therefore be a more appealing option for formulations such as fish oil, garlic oil and mint oil as they better prevent scent or flavour escaping.

In some cases, traditionally powder-based products like Curcumin, L-carnitine, Ashwagandha and CoQ10 are gaining traction as liquid formulations in liquid-filled hard capsules, since this format increases the solubility and therefore enhances bioavailability.

Consumer appeal

Aesthetics are becoming an increasingly crucial part of improving consumer appeal and the acceptance of nutraceutical products. As the market expands and evolves, we are seeing a trend for visually appealing products that entice consumer engagement and enhance brand image

Conventional capsules can be transformed into aesthetically appealing ones through new technology. Liquid-fill and band-sealing technologies allow for otherwise ordinary nutraceutical products to have real product identity and differentiation. Preprinted capsules are another growing trend in this area, as they can be customised as desired with logos or other designs for brand recognition. This useful marketing tool is not available when using soft gel capsules.

Flexibility in Filling

Thermostable products have a flexibility to fill over a wide range of temperature.

Maximum fill temperature for hard liquid-filled capsules is 70°C, in comparison to soft gel capsules at just 35°C. This flexibility is available from both hard capsules, as well as with encapsulation machines.

This demonstrates the stability of hard capsules even at higher temperatures. If certain formulations need higher temperature filling for viscosity modification or ease of operation, then it is possible to encapsulate these in hard capsules.

Greater possibilities

Apart from standard liquid formulations and oils, brands are seeking to offer a range of modified release profile products. This dosage form is able to handle a wide range of viscosities, including semisolids, and can help achieve a range of modified release profiles.

There are wide-ranging options for formulation available for nutraceutical manufacturers through utilising liquid-filled hard capsules as a dosage form.

Possibilities

Oil-filling

Hard capsules can allow natural, edible oils to be directly encapsulated. This is especially beneficial because it eliminates the need for synthetic excipients, which increasing numbers of consumers prefer to avoid.

Previously, some oily products, like DHA, Vitamin E, or Vitamin A had to be formulated into powders and then filled into capsules. With the availability of liquid-fill technology, these can now be directly filled into hard capsules. Additionally, for other oils such as garlic oil, fish oil and coconut oil, being able to offer these in hard capsule format is a big plus.

Perhaps most importantly of all, two products with exceptionally high growth curves, hemp oil and cannabidiol (CBD), can be delivered in their oil forms, without synthetic excipients, via encapsulation in hard capsules.

Simplified, or 'clean-label', products are increasing in popularity in the dietary supplement sector. As a result of developments in the capsule area, nutraceutical manufacturers can opt to pair their products with suitable hard capsule types. For example, fish oil can be incorporated in fish gelatin capsules, whereas natural and vegetarian ingredients would be perhaps better suited to clean-label certified HPMC capsules. Synthetic and animal origin ingredients can continue to be incorporated into traditional gelatin capsules, where vegan designation is unnecessary or unimportant.

Liquid-Solid combination filling options

Beyond the standard liquid-filled hard capsules, there are further possibilities for expanding the utilisation of this dosage form by developing combined formulations.

Combination filling is an exciting area. It enables hard capsules to offer multi-dose and multiphasic delivery. This is not possible, to the same extent, with soft gel capsules. Combinations include capsule-inside-capsule, tablet in liquid-filled capsule, and pellets in liquid-filled capsule. Each of these have their own benefits and can offer increased ingredient compatibility and delivery options.

Capsule inside liquid-filled capsule – In this combination two different incompatible active ingredients are incorporated into one capsule to avoid stability or incompatibility concerns. One active ingredient is dissolved or dispersed in a solvent, while the other is encapsulated in a smaller capsule and placed into the liquid-filled capsule. This segregates the two active ingredients.

Tablet in liquid-filled capsule – Two different nutraceutical active ingredients are incorporated into one dosage form to obtain customized release profiles. This form allows for a multiphasic release profile, as the ingredient in solution form can deliver immediate release, while the other can be in delayed-release tablet form.

Pellets in liquid-filled capsule – Pellets can be filled into a capsule to obtain sustained release profiles, with one active ingredient dissolved in a liquid for immediate release.

Conclusion

Liquid-filled hard capsule technology is helping meet the demands of a steadily growing nutraceutical industry. Development in this area has supported the expansion of the nutraceutical sector by providing opportunities for easier manufacturing, shortened product development, and enhanced brand image. With HPMC and gelatin options, a huge range of products can now be produced that not only have enhanced bioavailability, but are also more user-friendly and convenient. The possibilities with liquid filled hard capsules are widening with diverse filling options. ●

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GREEN TEA EXTRACTS: A NATURAL DEFENSE AGAINST CORONA AND OTHER VIRUSES

By Dr Stefan Siebrecht,
Managing Director Taiyo GmbH

The viral load in the upper respiratory tract is one of the decisive factors that affects the spread of SARS-CoV-2. New studies suggest ways to effectively reduce the viral load at key entry points: the mucous membranes.

In the second year of the global coronavirus pandemic, humanity is hoping for the resounding success of vaccinations. However, there is still no singularly effective drug for most sufferers and the best way to fight COVID-19 is to prevent SARS-CoV-2 infection. After the transmission of SARS-CoV-2 via respiratory aerosols or droplets from infected individuals, the virus must enter human cells by passing through the body's cell membranes to start multiplying and causing an infection (Anfinrud et al. 2020). The primary aim of the rolled-out vaccines is to produce antibodies that block the spike proteins of the virus (which are used to attach to the cell and invade). There are also natural plant substances available in our food that have similar antiviral properties and also prevent adhesion and invasion.

It has long been known — and demonstrated in numerous studies — that green tea catechins have antibiotic and antiviral properties. Green tea catechins are effective against many viruses that affect human health (herpes, Zika, Dengue and hepatitis, for example), influenza A and

B, and many more (Calland et al. 2012, Carneiro et al. 2016, Colpitts and Schang 2014, Nakayama et al. 1993, Yang et al. 2014). Green tea is especially effective against influenza A and B viruses, which are also coronaviruses. It was shown in several in vivo studies that drinking and/or gargling with normal green tea decreased the incidence infections in healthy humans, children, students, nursing home residents and healthcare workers (Table 1, Furushima et al. 2018). This is surprising because influenza viruses multiply in the lower respiratory tract regions, which are less accessible by gargling.

Recent findings on the antiviral effects of green tea extracts

Like influenza, SARS-CoV-2 is also a coronavirus and, as it multiplies in the upper regions of the respiratory tract, it was speculated that using green tea catechins — either as a supplement or as a gargling solution — could potentially act against SARS-CoV-2 viruses. In November 2020, three different studies independently tested whether green tea catechins were effective against the new human SARS-CoV-2 virus.

Frank and Conzelmann, CogniVerde

A German study showed that green tea infusions and juices such as elderberry or pomegranate were able to reduce the viral infectivity of influenza and SARS-CoV-2 virus titers in vitro (Frank et al. 2020). The results demonstrated that the green tea infusions were able to reduce both the influenza virus titer and, albeit to a much lesser degree, the SARS-CoV-2 virus titer. The reason for this could be the strongly different and varying content of catechins and polyphenols in the different tea infusions.

Yano, Nara University

Independently, laboratory experiments at Japan's Nara Medical University also demonstrated that green tea extracts are effective against the SARS-CoV-2 coronavirus. Professor Hisakazu Yano and his team from the Department of Microbiology and Infectious Diseases confirmed the inactivation of the new SARS-CoV-2 coronavirus by tea (Yano 2020). Using ten different varieties of commercially available tea, sold in plastic bottles, the virus was mixed with a sample of each one and subsequently monitored for viability and/or growth. Pursuant to Dr Yano's theory that tea could be used to detoxify the virus in humans, it was noteworthy that the teas were able to reduce the toxicity of the virus by 99% and 99.9% in one and 10 minutes, respectively.

Table 1: Characteristics of major studies on gargling with tea against influenza infection

| Source | Study Design/ Observation Period | Analyzed Population | Observation Period | Measurement Outcomes |
|----------------------|-------------------------------------|--|-----------------------|--|
| Noda et al. 2011 | Observational study | 19595 children in nursery school; age: 2 - 6 years | 20 days | The low fever onset absence was associated with gargling with green tea in comparison with tap water. (OR (95% CI): 0.29 (0.16 - 0.55) in the green tea group, OR (95% CI): 0.74 (0.62 - 0.88) in the tap water group) |
| Yamada et al. 2006 | Interventional study | 124 nursing home residents; mean age: 83 years | 3 months | Significantly lower incidence of influenza infection in the group gargling with green tea than in the group gargling with water (OR = 15.7; 95% CI 1.88 - 399.7) |
| Yamada et al. 2007 | Randomized-controlled trial | 395 healthy adults; age: 20 - 65 years | 3 months | Incidence of influenza infection was 1.0% of participants in the catechin group and 2.0% in the control group (P=0.84) |
| Toyozumi et al. 2013 | Randomized-controlled trial | 307 high school students; age: 15 - 17 years | 3 months | Incidence of influenza infection was 7.1% of participants in the catechin group and 7.9% in the control group (P=0.96) |
| Ide et al. 2014 | Randomized-controlled trial | 747 high school students; age: 15 - 17 years | 3 months | Multivariate logistic regression indicated no significant difference; incidence of influenza infection was 4.9% in the green tea group and 6.9% in the water group (OR=0.69; 95% CI 0.37 - 1.28) |

Source: Furushima et al. 2018

Taiyo Kagaku

Based on Frank et al.'s and Yano's findings, Taiyo Kagaku Japan performed an in-house in vitro dose response study to verify their results by using a highly potent green tea extract with a known and defined quantity of catechins. For the study, human fetal lung fibroblasts were mixed with active coronaviruses and green tea catechins before the solution was cultured at 37°C for 96 hours to evaluate virus-derived cytotoxicity. As a result, the viruses were inactivated. The scientists used 62.5 ppm of a specific Sunphenon® green tea extract and found that even this quite low concentration of catechins was able to inactivate the SARS-CoV-2 virus in vitro and could reduce the cytotoxicity of the SARS-CoV-2 virus by 99.99%. However,

although these results are very encouraging, additional work is needed to confirm the findings.

Shedding light on polyphenols and catechins

Polyphenols and catechins can interact and inactivate viruses by several mode of actions:

1. Catechins can act like natural antibodies and react either with the viral spike proteins and/or with the cellular binding sites (anti-adhesion and anti-invasion effects) (Kawai et al. 2003)
2. Catechins can also enforce virus excretion by agglutination
3. Catechins can inhibit enzymes that are needed for the multiplication of the virus
4. Catechins can destroy the virus (Yamaguchi et al. 2002)

Polyphenols and catechins thus act similarly on living bacteria and, as such, are often called "natural antibodies" and "natural antibiotics." The effects observed during the studies are attributable to the polyphenols and catechins in the tea. By being able to prevent the process that enables viruses to invade and infect human cells, it is therefore concluded that green tea catechins have anti-adhesion, anti-invasion and antiviral properties.

As experimental studies have revealed that green tea prevents influenza infection in students (Ide et al. 2014) and hospital staff (Matsumoto et al. 2011), these results may suggest a protective effect

against viral entry and, consequently, coronavirus infection. It remains undisputed that the most effective defense strategy consists of vaccination and compliance with the hygiene and isolation rules (distance, hand washing, mask wearing).

Oral care mouth spray concept

It has been shown that gargling with green tea reduces the incidence of influenza by up to 60% (Table 1). Because the SARS-CoV-2 virus infects the upper respiratory tract, it is more infectious than influenza; but, by contrast, it is more accessible and easier to treat by gargling. It has also been demonstrated that some oral care mouthwashes can kill the SARS-CoV-2 virus as well. However, many of these products comprise chemicals that should not be swallowed and are impractical for on-the-go use.

Based on these observations, Taiyo GmbH, Germany, developed a concept for an oral care antiviral mouth spray. Taiyo created a convenient, 100% natural and safe oral care mouth spray that can be used on-the-go and in situations that might pose a risk of infection. Different kinds of food-grade green tea extracts were combined in this new oral care mouth spray to ensure a convincingly pleasant taste:

- Teavigo®, which is rich in EGCG
- Sunphenon®, a special and highly fermented green tea extract that's high in EGC, which is particularly effective against many different viruses and bacteria compared with EGCG.

The green tea product combines all the advantages of an antiviral oral mouth spray solution with an oral care mouthwash: it has an antiviral effect against coronaviruses (influenza and SARS-CoV-2), inhibits caries formation and also has an antibacterial effect. In addition, it has an oral deodorant effect and prevents bad breath. Furthermore, it's free from alcohol and other antiviral chemicals.

The product can be used immediately before or in a critical situation — such as on public transport, while shopping or at school or work — and provides additional protection against virus particles that might pass through a mask. The spray is a food product and is safe for human consumption. →

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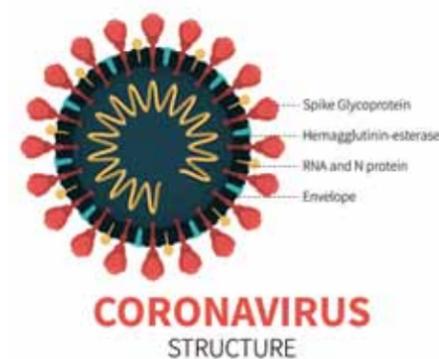


Figure 1: Because viruses do not metabolize, they cannot be killed by antibiotics. Anti-adhesive products block the adhesion and subsequent invasion of bacteria into cells like antibodies

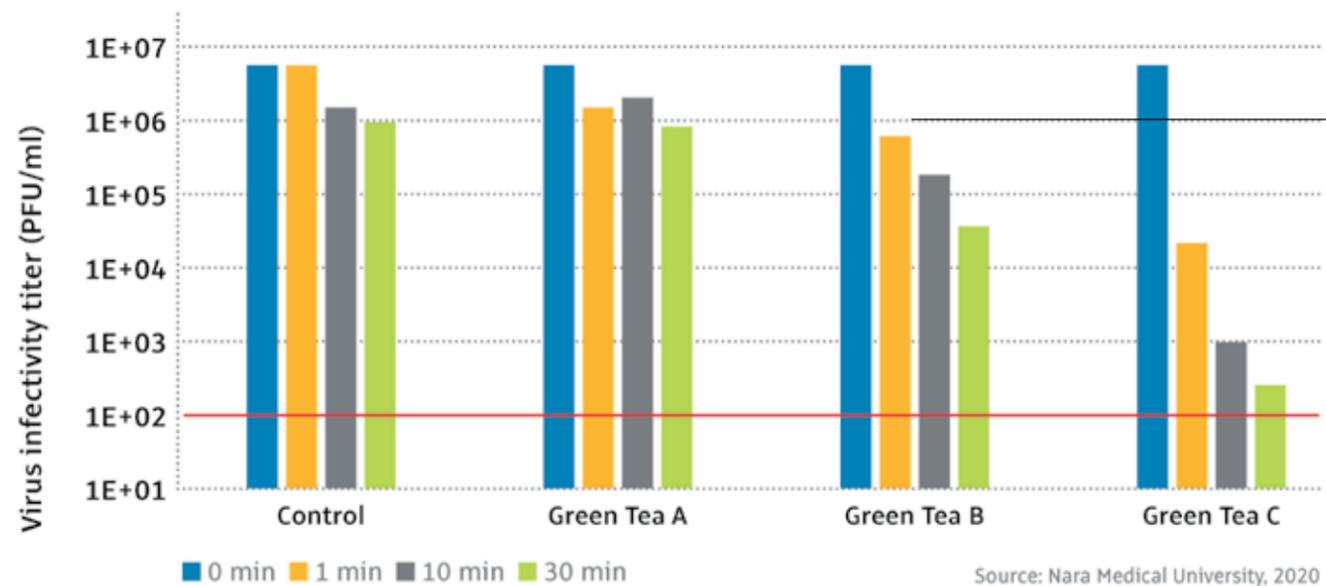


Figure 2: In vitro tests showed that some green tea infusions are able to decrease SARS-CoV-2 infectivity effectively, whereas others had no effect.

This spray, in addition to the distance and hygiene rules and wearing a mask, may constitute another layer of defense and could inactivate any coronavirus particles that are already in the mouth and body. Because the polyphenol content of commercially available green tea extracts varies considerably, depending on their origin, quality is important. Taiyo's tea extract, as used in the study and for the new product concept, comes from known sources and is produced in its own factory according to the most stringent quality standards (FDA guideline 40CFR180). Moreover, these high purity extracts of whole tea leaves are guaranteed to be free from solvents, pesticides and other residues. ●

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Figure 3: Different types of Taiyo's green tea extract (Copyright: Taiyo)

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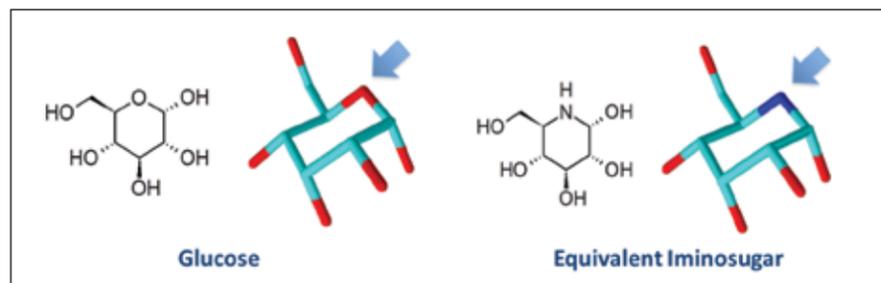
IMINOSUGARS: highly functional but elusive natural ingredients

By Robert J. Nash and Yana B. Penkova
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Plants produce sugars by photosynthesis and also produce a wide range of iminosugars to prevent herbivores and pathogens using those sugars efficiently. Iminosugars in their simplest forms can be monosaccharide analogues with a nitrogen atom replacing the oxygen in the ring of the sugar (Figure 1). Like sugars, iminosugars are colourless, very water-soluble and stable in solution, but, unlike most sugars, iminosugars are tasteless and appear not metabolised by mammals (1). The iminosugars show great diversity in biological activity and are arousing interest as treatments for a wide range of diseases including diabetes, viral infections, cancer, lysosomal storage disorders, inflammation and for weight control (2). The iminosugars show great stereoselectivity in biological activity which is not surprising when one considers just glucose which has 2×10^5 forms in the pyranose and furanose forms; each form is recognised by biological systems and highlights that sugars far surpass the structural and biological information shown by amino acids of equivalent molecular weight. Sugars and their control are crucial to good health. Every type of cell in our bodies has a unique sugar coating and aberrations in these coatings and messaging occurs in many if not all diseases (3). There is also good evidence that imbalances in glycosidases (enzymes that breakdown complex sugars) are associated with many diseases including Alzheimer's, depression, and cancers and indeed these imbalances are often used as markers of disease.

The sugar-based language is very difficult to understand and control but iminosugars offer great potential to specifically correct defects. Most important of their activities seem to be inhibiting or stabilising glycosidases or interacting with sugar receptors. It is remarkable that there are many iminosugars in our

Figure 1. Iminosugars



foods and medicinal plants but they are rarely seen or identified because they are hidden by common sugars and amino acids which are usually present in higher quantities and have similar analytical properties. The affinity of these sugar analogues for the glycosidases and receptors can be very potent, coupled with good oral availability, distribution and stability in vivo, it makes their presence in many fruits and vegetables of potentially great significance in the diet of people and other animals. Other types of natural products are more easily seen such as the coloured flavonoids and so tend to be focused on despite many of them having low relative activity or showing non-specific binding activity. The iminosugars may be the elusive active compounds of many herbal medicines.

Perhaps the best examples of major foods containing iminosugars are potatoes and rice. We were the first to find the iminosugars in potatoes in 1993 and they are in all of them (4). The iminosugars in rice were only recently discovered and are not in all types of rice (5). The nor-tropane calystegines of potatoes are potent glucosidase and galactosidase inhibitors while the iminosugars of rice (e.g. fagomine) can inhibit a wider range of enzymes. It is notable that selection of food plants for shelf-life or other commercial attributes seems to have altered their sugar analogue content without anyone knowing and, for example, each potato variety has a distinctive

iminosugar profile with wide variation in amounts and which ones are present. Since the iminosugars of potatoes inhibit glucosidases the different amounts present means that they will differently slow the release of glucose from the potato in the diet and from other foods eaten at the same time. It is also notable that iminosugars such as those in potato and rice are stable on cooking and our research shows that they go through the body of humans and dogs unchanged and are excreted eventually in urine (1).

A group looking into the basis of the anti-diabetic activity of mulberry in TCM identified the first plant iminosugar, DNJ (1-deoxynojirimycin) in 1976 (2). As a potent inhibitor of various glucosidases it has formed the basis of the diabetes drug Glyset™. Quality controlled mulberry leaf products (e.g. Reducose™) are being developed by the UK company Phynova. DNJ is probably the most commonly naturally-occurring and studied iminosugar and it and a derivative Zavesca have been shown to also inhibit infection by viruses such as HIV and SARS-CoV-2 by altering surface glycans (6). In May 2019, a team of Chinese researchers found that the compound could also ameliorate symptoms associated with angina pectoris, such as chest pain, in patients with coronary heart disease (7).

Maintaining a balance of sugars is crucial to good health and losing good control seems involved in the ageing process. Perhaps due to their main presumed

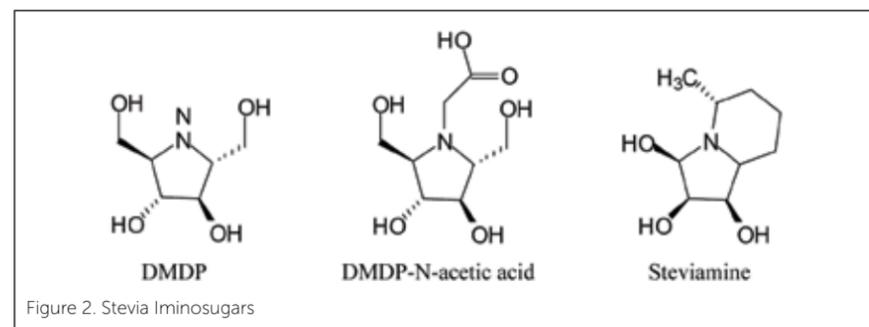


Figure 2. Stevia Iminosugars

evolutionary purpose to protect sugars such as glucose, the iminosugars of plants and microbes that resemble glucose appear able to help to maintain this balance. While some such as DNJ are potent intestinal glucosidase inhibitors and can cause gastrointestinal problems at high concentrations, there are others that appear able to control blood sugars without being enzyme inhibitors. One such example occurs in the Indian Ayurvedic medicinal plant *Gymnema sylvestre*. It contains one very major iminosugar (BR1) that controls blood sugar in mouse studies by itself (8). This plant has some clinical evidence that over time it can have restorative effects on insulin responses and beta cell health. Probably mistakenly, most *Gymnema* products concentrate a group of saponins to the total exclusion of the BR1.

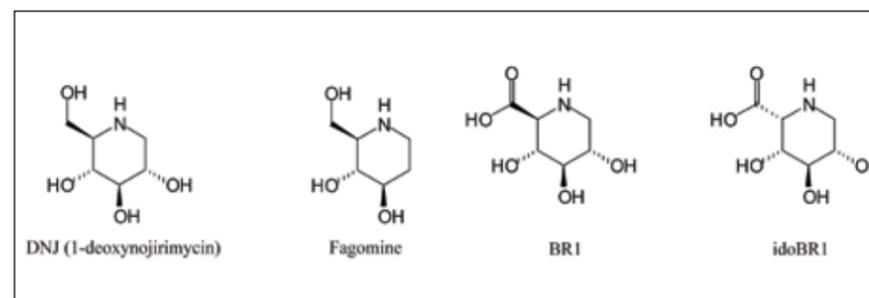
If the body regulates sugar levels well there are many benefits in terms of energy balance and preventing tiredness and craving for sweet foods; many natural iminosugars seem to have evolved with this beneficial effect even if unintended by the plants. For the roughly 422 million people worldwide who have diabetes, sugar is dangerous. Too much glucose in the blood and the risks of long-term health problems are heightened. Reducing sugar intake is one way of alleviating diabetes but selecting foods that have sugar analogues such as

iminosugars is another potential way of slowing glucose release into the blood and also probably removing glucose more quickly from the blood stream. The body seems to have many ways of controlling glucose in the body and even advanced glycation end products (AGEs) (produced by too much sugar in the body), when given orally can surprisingly control blood sugar and lipids (9).

Artificial sweeteners or highly purified sweet compounds like Steviosides (from *Stevia rebaudiana*) are one alternative to refined sugars but it is probably better to use natural sugar sources with other components such as iminosugars still present. *Stevia* plant, for example, contains glycosidase-inhibiting iminosugars (e.g. DMDP and DMDP-N-acetic acid) but they are removed from the processed products; the natural *Stevia* may, therefore, be better for health than the highly processed steviosides (and related compounds) (10). One of the isolated iminosugar compounds from *Stevia* (steviamine), also shows potential anti-metastatic activity in assays by inhibition of an enzyme specially produced by cancer cells to aid their spread (11).

Cucumber is one example of how the active component remained unknown because it was an iminosugar and difficult to detect by usual analytical methods. Known since Roman times

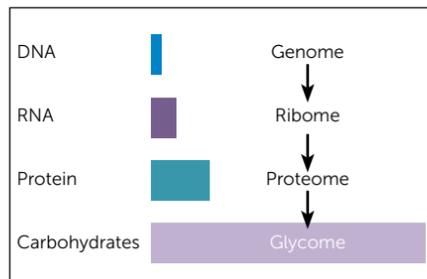
Figure 3. Common piperidine iminosugars. DNJ from Mulberry fruit and leaves, fagomine from Buckwheat and some Rice grains, BR1 from *Gymnema* and idoBR1 from certain cucumbers



to have beneficial anti-inflammatory effects and used by women to improve puffiness and redness around the face, many groups investigated cucumbers but failed to find an active molecule. We now know that certain varieties contain one iminosugar, idoBR1, and it has potent anti-inflammatory activity via a probably novel mechanism (1). Breeding of cucumbers seems to have removed idoBR1 from most modern varieties. IminoTech Inc in the USA has produced a quality-controlled cucumber extract containing measured idoBR1 (Q-actin™) that gave good results in osteo-arthritis from oral use and required over ten times lower doses than glucosamine and chondroitin. Interestingly, our recent research shows that humans and dogs both excrete the idoBR1 eventually unchanged.

Buckwheat and rice contain one iminosugar (D-fagomine) which is related to DNJ. Fagomine if used as a dietary supplement or functional food component is reported to potentially reduce the risks of developing insulin resistance, becoming overweight and suffering from an excess of potentially pathogenic bacteria (12). Interestingly certain rice varieties have more fagomine than buckwheat and can have a wider range of related iminosugars (5). So rice may be more healthy than buckwheat but only if you eat the right variety!

We know the glycome is far more complicated than the genetic code which has just four biochemical letters strung together in lines. We are only just beginning to understand how manipulating the sugar code can be medically useful. For example, with cancer we have known for decades that sugars on cancer cells change and this can make the cells less recognisable to medicines. Studies are underway by Professor Miriam Dwek at the University of Westminster to see if cancer cells dosed with an iminosugar that impedes the growth of the sugar forest on the cancer cell surface can make drugs more effective. Some iminosugars seem also able to induce stronger immune responses (T and NK cell) to cancer cells in animal models and may have wider immunomodulatory benefits (2). It is probable that iminosugars are going to be recognised more and more as health-promoting components of our diet →



Molecular Information

Figure 4. The Role of Carbohydrates. Carbohydrate complexity and diversity greatly exceeds that of proteins and genes. Carbohydrates and associated receptors present excellent targets and growing market opportunities for iminosugars.

and may be the reason why we and other animals selected foods such as potatoes and cucumbers in the first place. The steeping of plants in hot water to make teas/beverages is the most common way of preparing herbal medicines and this favours the extraction of the stable and water-soluble iminosugars. The water-soluble components of plants comprise most of the weight of plant extractable material but are the least well studied. Many more iminosugars remain to be identified in our common food plants and teas.

As shown earlier, each iminosugar molecule has a nitrogen atom in its ring instead of the usual oxygen atom. It is amazing that such a small change, replacing an oxygen atom in a sugar molecule with a nitrogen atom, can give such wide ranging therapeutic and nutritional benefits. These simple natural molecules promise to open up more avenues for the discovery of new medicines, cosmetic ingredients, health products and supplements. ●

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PROBIOTICS, PREGNANCY & VAGINAL MICROBIOTA:

How New Microbiome Research is Sparking Growth in the Women's Health Supplement Market

By Liisa Lehtoranta, R&D Manager, IFF Health

Women are taking charge of their health like never before. As consumer awareness around the benefits of preventative health practices grows, the women's health and beauty supplement market continues to rapidly expand, with the global market projected to reach \$68.9 billion by 2026.¹

Market demand is driven in part by emerging new research on feminine health, including how a healthy microbiota can play a critical role in women's vaginal and urinary health. As science develops around the gut microbiota's impact on various body sites -- such as vaginal microbiota -- and the impact specific probiotic strains can have on the microbiota and health, consumers are beginning to understand that probiotics offer diverse benefits, beyond traditional digestive health. In turn, women are looking to probiotics to provide natural solutions to specific health concerns, such as combatting common vaginal infections or boosting prenatal health.

Manufacturers and formulators seeking to meet market demand can con-

sider developing probiotic supplements tailored specifically to women's health needs. By developing efficacious products, targeted to women's life stages and concerns, they'll stand out on the shelves while helping women achieve optimal vaginal and prenatal health.

It's all about (vaginal microbiota) balance

For many women, vaginal infections are a life-long concern. About 30-50% of women suffer from bacterial vaginosis annually², while 70% suffer from vulvovaginal candidiasis in their lifetime³. Women of reproductive age are most susceptible to bacterial vaginosis, and it's especially common during pregnancy -- typically, between 10-30% of pregnant women experience infection.⁴

Vaginal infections commonly result from vaginal microbiota imbalances caused by atypical vaginal bacterial overgrowth. Antibiotics and antifungal medicines are the primary treatments for vaginal infections, but in many cases, they can cause unpleasant side effects. Oftentimes, bacterial vaginosis or vulvovaginal candidiasis recurs. A more natural solution,

like probiotics, may help.

The research community is sharpening its focus on what keeps vaginal microbiota healthy, what specifically causes dysbiosis and how probiotics can help. Within the last ten years, studies have revealed that the vaginal microbiota can be categorized into several different bacterial community types. A key indicator of a healthy human vagina is a high number of *Lactobacillus* species. Specifically, the lactobacilli types predominantly colonizing the vaginal microbiota, especially in healthy women, are *L. crispatus*, *L. jensenii*, and *L. gasseri*. Reduction in the proportion of lactobacilli in the vaginal microbiota is associated with disease or increased disease risk, and women lacking abundance of these lactobacilli types in the vaginal tract are typically more prone to infection.

Probiotics containing certain strains of lactobacilli may help women deficient in lactobacilli to restore healthy bacteria balance. Women can take these probiotic strains daily, or during times of dysbiosis to promote healthy vaginal micro-

biota balance and boost recovery from potential disruption.

However, formulators seeking to develop a women's health product must keep in mind that probiotic strains are not a one-size-fits-all solution. Probiotic solutions for feminine wellness should include strain-specific formulations and accurate dosing of each strain to support women through key life stages such as pregnancy, pre- or post-menopause.

Products may contain the same strains with different dosing, to address specific health needs. For example, HOWARU® Feminine Health combines *Lactobacillus acidophilus* La-14® and *Lactocaseibacillus rhamnosus* HN001™ to target vaginal microbiota balance while HOWARU® Protect Prenatal+ features different quantities of the same strains to benefit women's prenatal health. In addition to evaluating the efficacy and safety behind a product, formulators must evaluate the strains and dosing, to fully tailor the end product to their target consumer's life stage.

The proof is in the probiotic clinical trials

Formulators seeking to develop a probiotic specifically for women's vaginal health can consider incorporating HOWARU® Feminine Health into their formulations. Researchers found that when consumed orally, the strains within HOWARU® Feminine Health can migrate to the vaginal tract and balance vaginal microbiota.

In a randomized, double-blind, placebo-controlled clinical trial⁵, a group of healthy women consumed two HOWARU® Feminine Health capsules once daily for 14 days. At the end of the study, women experienced a rise in vaginal *Lactobacillus acidophilus* and *Lactocaseibacillus rhamnosus* levels, which continued to increase for at least one week when compared to the placebo group.

In another clinical trial, 40 women with signs of vaginosis and an intermediate Nugent score, which indicates a perturbed vaginal microbiota, reported an increase in healthy vaginal bacteria after consuming HOWARU® Feminine Health consistently for 15 days⁶. Interestingly, results showed significantly higher

lactobacilli counts in the probiotic group compared to the placebo group -- indicating probiotics' benefits for balancing vaginal microbiota. The women in the probiotic group also experienced a decrease in self-assessed vaginal symptoms like itching or discharge.

HOWARU® Feminine Health's effect on clinically diagnosed vaginal infections was investigated in two other separate trials. Women with either bacterial vaginosis⁷ or vulvovaginal candidiasis⁸ consumed HOWARU® Feminine Health, in addition to an antibiotic^{vii} or antifungal treatment^{viii}. The women then continued to take the probiotic or placebo for six months as a maintenance. Both studies showed that the probiotic supplement provided significant benefits in bacterial vaginosis and vulvovaginal candidiasis management and recovery, when taken along with antibiotic or anti-fungal therapy.

The clinical trial results reveal HOWARU® Feminine Health's targeted ability to support healthy vaginal microbiota and address symptoms of recurring vaginal infections, such as bacterial vaginosis and vulvovaginal candidiasis, when used with antibiotic or anti-fungal therapy. By incorporating products like HOWARU® Feminine Health into their own formulations, manufacturers can create an efficacious end-product, tailored specifically to women's health needs.

Probiotics meet pregnancy

Mothers and their newborns can benefit from probiotic supplementation during pregnancy, birth and post-natal stages. Formulators developing a probiotic tailored specifically for women's prenatal health can consider HOWARU® Protect Prenatal+. This probiotic product provides benefits to help promote vaginal health, which is essential in reducing risks such as miscarriage or vaginal infections during pregnancy. It also supports the mother and child's immune health and promotes the mother's happiness and calmness.

A placebo-controlled clinical trial studied infants and their expecting mothers, with an allergy history, taking probiotic *Lactocaseibacillus rhamnosus* HN001™. The strain was delivered in capsules to mothers and infants, starting around six

days post-birth up to 2 years of age¹⁰. The capsule's powder was delivered to infants via syringe or teaspoon undiluted or mixed with fluid -- once infants began with solid food, the powder was sprinkled on top. Mothers received the probiotic or placebo daily from five weeks pre-term to six months post-term, if breast-feeding, and blood and breast milk samples were collected to assess biomarkers related to immune health¹¹. Results showed the probiotic's benefits in bolstering mother's immune marker levels and reducing cumulative prevalence of eczema in 2-year-olds -- this effect continued up to 11 years of age¹².

In another study, breastfeeding mothers received a probiotic supplement with *Lactocaseibacillus rhamnosus* HN001™ or placebo prenatally from 14-16 weeks of pregnancy to delivery and postnatally for six months, if breast-feeding. The results showed *Lactocaseibacillus rhamnosus* HN001™'s consumption was associated with a significant reduction in the prevalence of gestational diabetes mellitus (GDM), especially in mothers over 35 years old with a history of GDM; and reduction in postnatal depression and anxiety scores¹⁴.

Clinical studies have long supported that probiotic supplementation provides mothers and their children with benefits throughout pregnancy, birth and beyond¹⁵. Additionally, recent studies suggest probiotics could potentially affect breast milk composition¹⁶ and may support breast health in women with mastitis¹⁷, painful breast tissue inflammation while breastfeeding. Staying healthy through these stages is vital to optimal infant development, and manufacturers can help women do so naturally by incorporating clinically documented probiotic strains such as those found within HOWARU® Protect Prenatal+ into their prenatal supplement formulations.

Strain stability over formula creativity

Besides selecting tailored, efficacious strains, there are a range of other factors to consider when developing a high-quality end-product for women's health. One of the main considerations brand owners must keep in mind is how to stand out in a marketplace crowded with similar products. →

Combining healthy bacteria with popular herbal or botanical solutions is an emerging trend in probiotic supplements, and a savvy way to create a unique, personalized product. For example, cranberry is well-known for its natural benefits to lower urinary tract infection risk. Formulators can consider combining cranberry with strains such as *Lactobacillus acidophilus* La-14® to help women support vaginal and urological health, for a holistic women's health product.

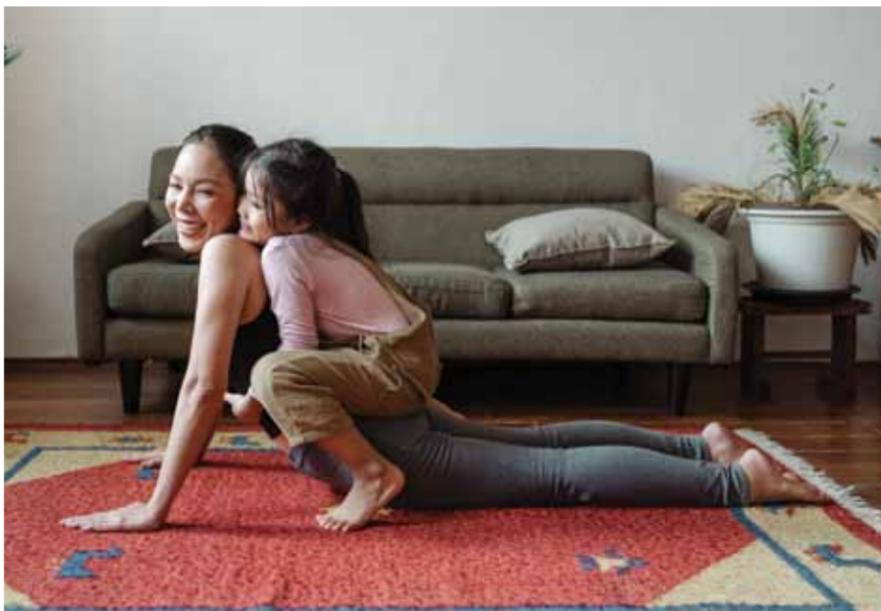
However, formulators should be aware of how combining certain ingredients can affect strain stability. More clinical research is needed to truly understand the potential synergistic benefits of various botanicals and strains and how they interact. While incorporating well-known botanicals will attract consumers, formulators must be certain that the combination has synergistic benefits and will not inhibit strain stability and efficacy.

When looking to develop tailored combination probiotic products for women's health, it's important to work with a supplier who emphasizes strain stability, product quality and safety. Emerging formats and combinations require expertise in probiotic formulation to ensure the claims on the package are valid through the end of the product's shelf-life. By partnering with a supplier experienced in developing innovative probiotic blends, formulators will be well-equipped to develop high-quality, personalized products, that remain effective throughout their shelf-life.

The future is female health

When it comes to understanding how specific probiotic strains benefit vaginal microbiota, researchers have just scratched the surface. As new research emerges, probiotic supplements for women are likely to become even more personalized. In the coming years, women may be able to take a test to discover their individual vaginal microbiota, allowing them to take probiotic supplements crafted specifically for their vaginal microbiota health.

Women are increasingly taking charge of their health and lives – and they're doing it via probiotics tailored to their health concerns. This is not only a trend, but a



movement that will continue to develop into the future. Manufacturers can stay ahead of this rapidly evolving market by prioritizing clinically documented strains and collaborating with a trusted, experienced strain supplier to develop effective supplements that allow women to prioritize their personal health. The future of female health, empowered by innovative probiotic solutions, is looking bright. ●

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EXPLORING THE TOP 5 INNOVATIONS AND TRENDS FROM DSM EXPO 2021



By Kristina Tahiri, Director Specialty Nutrition EMEA, DSM

It's no secret that research, development and knowledge sharing is crucial for ensuring the continual growth of the nutrition and health industry. It enables important discussions around meeting the latest consumer trends and allows industry experts to debate global issues, such as how to keep the world's growing population healthy. But at a time when face-to-face meetings are not possible, how can we ensure these conversations continue to progress? DSM Expo 2021, hosted via a virtual environment, allowed key opinion leaders from across the nutrition and health industries to come together safely to discuss a variety of topics – providing a much-needed platform for nutrition and health professionals during uncertain times. Here, we explore key takeaways from the event, including insights shared by experts from across the early life nutrition, dietary supplements, food and beverages, nutrition improvement and medical nutrition markets.

A boost for early life nutrition

Growing consumer concerns on immunity and health following the pandemic placed early life nutrition firmly at the top of the agenda at DSM Expo 2021. Nutrition in the first 1,000 days of a child's life – from the onset of pregnancy to the second

year of life – has long been established as a vital part of growth and development, but COVID-19 has prompted many to reconsider their dietary and lifestyle choices. In the UK, for example, 32% of parents to children under the age of four reported that COVID-19 resulted in them placing greater importance on ensuring adequate nutrition.¹ Manufacturers have been quick to address these concerns, with the creation of 'smart', targeted products that offer high nutritional value and support cognitive immune development in children. These products typically feature key nutrients such as omega-3 and omega-6 fatty acids, including a combination of arachidonic acid (ARA) and docosahexaenoic acid (DHA) for brain and eye development² and vitamin C for immune support.²

Attendees at the expo had the opportunity to learn more about the wider scientific benefits of these nutrients in the support of both maternal health and infant development. DHA, for example, may reduce the risk of preterm birth and improve brain and eye development. DHA and ARA in combination may also be key for immune function.^{4,5,6,7,8,9,10} Meanwhile, experts explored the science behind human milk oligosaccharides (HMOs) – the third most abun-

dant component of breast milk that is considered important for infant growth and development – particularly for brain and digestive health. This growing bank of research is leading to further innovation in the development of high-quality, safe infant nutrition products for mothers who are unable, or choose not, to breastfeed.

Dietary supplements: what's next?

With interest in health and wellness at an all-time high, presenters at DSM Expo 2021 examined the top trends in dietary supplements, including the latest innovations that support gut health. This comes following growing consumer awareness of the link between a healthy digestive system and immunity; one in three people now take dietary supplements to support their digestive wellbeing.¹¹ Innovation is therefore growing in the digestive health space, as manufacturers look to develop new dietary supplement solutions that meet evolving consumer needs. Highlighted at the event was DSM's new vitamin solution, V-DIRECT, which uses targeted delivery systems to allow for optimal absorption into the colon, improving the balance of the gut microbiome with vitamins C, B2 and B3.

Another key topic of discussion at the event was plant-based omega-3 innovation. While fish oil has typically been used as a source of omega-3s, pressures on marine resources and biodiversity have caused mounting concerns across the globe and led to searches for other sources. Plant-based alternatives made from fermented non-GM algae have emerged as a sustainable option – providing a single source of pure, potent eicosapentaenoic acid (EPA) and DHA.

Experts in the field, including Professor Philip Calder from the University of Southampton, led an interesting discussion on how these nutritional ingredients are helping brands create purpose-led, science-backed and sustainable solutions for a new generation of consumers.

Fortifying food and beverages to support immunity

Opinion leaders at DSM Expo 2021 explored different ways in which producers can enhance food and beverage products through food fortification to appeal to health-conscious consumers in the current climate, where interest in immunity has grown exponentially. They shared insights on the top ingredients associated with boosting immunity in the EMEA region, including vitamin C (78%), vitamin D (63%) and omega-3 fatty acids (54%). In addition, insights revealed that consumer concerns go beyond immune health – day-to-day stress and tiredness cause many to now look for products containing ingredients that support energy levels, such as B vitamins and magnesium.

Presenters also discussed how fortification of food and beverages offers flexibility in product application, providing plenty of opportunity for innovation – with options to add vitamins and minerals to juice drinks, bread and snack foods.

Staple food fortification to end malnutrition and world hunger

Hidden hunger, a form of malnutrition, affects two billion people worldwide¹³ and can seriously impact human health through conditions including blindness, anemia, weakened immunity and the onset of non-communicable diseases.^{14,15,16,17} Fortified staple foods, such as rice and flour, have an important role to play in increasing nutrient intake in vulnerable populations and tackling malnutrition, particularly following the disruptions caused by the COVID-19 pandemic. Widespread food shortages and people with weakened immune systems due to insufficient nutrient intakes have exacerbated the crisis on a global scale. DSM Expo 2021 provided an important platform on which to discuss the growing problem, with discussions concluding that public and private sectors must work together to ensure that all people have access to the nutritious food they need to stay healthy and thrive.

Exploring the benefits of medical nutrition

Not only has the pandemic worsened the malnutrition crisis, but it has left a significant impact on the health of vulnerable people, such as patients and

the elderly. Often immunocompromised, these individuals are at a greater risk of serious repercussions after contracting COVID-19. The European Society for Clinical Nutrition and Metabolism (ESPEN) has outlined 10 practical recommendations for nutritional management before and during infection, including identification of individuals at risk of malnutrition, and details how medical nutrition products can provide support.¹⁸

Exploring the latest science, leading experts at DSM Expo 2021 discussed how manufacturers can support optimal immune function in the elderly, as well as how concept-specific nutritional therapies can promote the recovery and independence of patients. A key area of growing scientific interest highlighted at the event was the link between vitamin D and immune health in patients. A recent study revealed by experts suggests that individuals with higher levels of vitamin D may have a lower risk of developing serious symptoms from COVID-19.¹⁹ These findings are promising in the fight against the ongoing pandemic, indicating the vast potential for medical nutrition to improve patient care and health outcomes globally.

Standing together

Despite the world slowing down in the past year, events such as DSM Expo 2021 have helped to underline the importance of continued collaboration, to drive forward the discussion on some of the most important topics today. New, cutting-edge research and purpose-led innovations have never been more vital, to help accelerate products from concept to consumer, keep the world's growing population healthy and, ultimately, create brighter lives for all in a sustainable way. ●

For more information, get in touch: PartnerWithDSM.com

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UNIBAC PROBIOTICS: USING CLINICALLY STUDIED BACTERIA TO SUPPORT THE GUT MICROBIOME

By Dave Smith, Design and Marketing Director at Sweet Cures

Probiotics are seeing a surge in popularity due to the impact of Covid-19. On top of concerns about protecting ourselves and others from the virus, the stress and strains of lockdown over the last year are having a negative impact on mental health for many people.

But what is positive is that we have witnessed a renewed focus on health and wellbeing as a result. As part of this, many people are realising the power of probiotic bacteria and how it can help to maintain all-round general health.

Building on the success of its Probiotic Blend Capsules, world-leading natural health food supplement manufacturer and retailer Sweet Cures has launched an all-new range of probiotics in collaboration with global market leader Danisco Nutrition & Biosciences.

The new UniBac probiotic range contains a unique blend of up to 17 strains of friendly gut bacteria clinically proven to survive transit to the gut and support all-round general health by helping to maintain that delicate balance of gut microbiota.

BANT registered Sweet Cures' Nutritionist Serena Coan, said: "Prioritising our personal health and wellbeing is so important right now, and a healthy gut is key to almost all aspects of this, including the gastrointestinal tract, immune system, urogenital tract and even your mental health.

"An attractive aspect of the UniBac range is the variety of live bacteria in the products, akin to the natural diversity of our gut microbiome, making it ideal for daily support.

"The abundance of Lactobacillus and Bifidobacterium strains are promising for supporting mental health. Recent research into the use of "psychobiotics" (probiotics that influence the central nervous system and gut-brain axis) has



shown the power of specific probiotic strains on management of inflammation and neurotransmitter production involved in health conditions."

Studies show the microbial balance in the gastrointestinal tract enhances not only intestinal health, but the immune system and various other wide-ranging physiological functions throughout the body; and the ingestion of probiotic bacteria is known to work in favour of maintaining this balance. (de LeBlanc and LeBlanc, 2014)¹; (Kechagia et al, 2013)²; (Vandenplas et al, 2015).³

The first two products launching from the new range are the UniBac Advanced 17 Probiotic Blend, one of the most comprehensive probiotic blends available, and the Essential 9 Probiotic Blend, a blend of nine strains of friendly bacteria designed for everyday use to support a healthy gut.

The live bacteria used in the Advanced 17 and Essential 9 Probiotic Blends includes:

Lactobacillus acidophilus (La-14) – At the forefront of groundbreaking research, La-14 has been found to significantly stimulate the production of anti-inflammatory cytokines, small proteins respon-

sible for regulating immunity and inflammation, in the body's immune response (Giardina et al, 2014)⁴. Research even goes as far as to suggest that supplementation with La-14 stimulates an improved primary immune reaction following oral vaccinations (Paineau et al, 2008)⁵.

Lactobacillus casei (Lc-11) – Commonly found in the human gastrointestinal tract, clinical studies from DuPont Danisco report Lc-11 demonstrating the ability to inhibit selected pathogens in vitro, including E.coli and salmonella. Additional data also supports Lc-11's ability to help maintain good oral health by inhibiting dental plaque causing the growth of bacteria linked to tooth decay (DuPont Danisco)⁶.

Lactobacillus plantarum (Lp-115) – Like many Lactobacilli bacteria, this strain is well-suited for intestinal survival due to its high tolerance to acid and bile (DuPont Danisco)⁷. In addition to supporting immune system modulation (Paineau et al, 2008)⁴, Lp-115 has also been picked up on by academics for its properties in decreasing risk factors for cardiovascular morbidity. One study on postmenopausal women with metabolic syndrome found consuming fermented milk treated with Lp-115 demonstrated beneficial effects on their glycemia and homocysteine levels compared to that of the control group (Barreto et al, 2014)⁸.

Lactobacillus rhamnosus (Lr-32) – One of the most widely researched strains, Lr-32 is known for its anti-inflammatory properties and strong adhesion to the intestinal cell walls, giving it a better chance of survival in GI tract. Studies assessing Lr-32's impact on intestinal inflammation found that Lr-32 led to a reduction in colitis symptoms in vivo, and demonstrated its ability to support the immune response at the mucosal membranes of the intestines (DuPont Danisco)⁹; (Foligne et al, 2007)¹⁰.



Lactococcus lactis (Ll-23) – Following evidence suggesting that the gut microbiome could be involved with the development of obesity, and therefore its modulation may aid in the treatment of it, researchers have assessed the effects of probiotic mixes containing Ll-23 alongside dietary intervention. Experimental groups ingesting the probiotic mix reported a reduction in abdominal adiposity, as well as increased antioxidant enzyme activity, in a more effective way than the control group receiving dietary intervention alone (Gomes et al, 2016)¹¹. Further analysis supports this idea that probiotic supplementation including Ll-23 could potentially reduce weight gain and improve some of the metabolic parameters linked to obesity in adults (Wang et al 2019).¹²

Bifidobacterium bifidum (BB-06) – BB-06 was another strain included in the probiotic mix assessed in Gomes et al's double-blind study on reducing obesity risk factors (2016). Another double-blind, randomised placebo-controlled study from Gomes et al (2020)¹³, which also utilised DNA profiling to establish which bacteria in the human gut are associated with metabolic risk factors and evaluate the role of probiotic supplementation on the modulation of the gut microbiota. The results of said study further supported Gomes' earlier findings, reporting positive changes to BMI, weight, fat and lean mass among other adiposity markers. As a wider species, it's also worth pointing out that Bifidobacterium bifidum strains have been of recent research interest in influencing the development of tumours and the efficacy of cancer treatments, after noting that this species was abundant in the gut of lung cancer patients who were responsive to therapy (Lee et al, 2021)¹⁴.

Bifidobacterium breve (BB-03) – Typically one of the most abundant probiotic strains present in breastfed infants, BB-03 is known for contributing to the normal function of the immune system, respiratory tract health and reducing pathogens associated with digestive upset. Upon its discovery in 1899, it was even considered a primary reason behind the babies' greater resistance to disease (Dupont Danisco)¹⁵. Since then, studies have also explored the potential of BB-03 in the prevention of chronic diseases linked to obesity (Minami et al, 2015)¹⁶.

Streptococcus thermophilus (St-21) – This strain is of particular research interest for its uses in supporting healthy digestion, notably in assessing its role in the relief of diarrhoea. Studies on infants with acute diarrhoea (including that caused by antibiotics - AAD) have found that control groups using formula treated with St-21 reported significantly fewer incidences of AAD (Saavedra et al, 1994)¹⁷; (Corrêa et al, 2005)¹⁸.

Both UniBac Probiotic Blends are available to order online from www.sweet-cures.com, with two further UniBac products due to launch later this year.

About Sweet Cures

Sweet Cures is one of the world's leading experts in natural health supplements, driven to provide the highest quality products and customer service experience.

For over 19 years, Sweet Cures has specialised in using healthy and essential sugars as an effective and safe approach to maintaining good health across a range of areas, from bladder health and friendly bacteria, to digestive health

and energy levels. Sweet Cures boasts a wide product range of natural health supplements using monosaccharides, such as Waterfall D-Mannose®, High Energy D-Ribose™, L-Arabinose Plus™ and Xylotene®.

The Sweet Cures team are experts in their field, ensuring the purity of products is always ahead of competitors, made from the finest ingredients at the optimal dosage, without unwanted excipients, binders and fillers.

The team also prides itself as being one of the few natural supplement manufacturers you can contact directly for product information, and have helped thousands of customers from across the globe.

From its HQ in York, Sweet Cures handles the whole process directly, from enquiries and manufacturing, to packaging and deliveries. For more information, visit www.sweet-cures.com or find Sweet Cures on Facebook www.facebook.com/sweetcuresyork, Twitter @sweetcures and LinkedIn www.linkedin.com/company/sweet-cures/

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LEVERAGING LACTOFERRIN: CAN A GLYCOPROTEIN FOUND IN MILK SUPPORT IMMUNITY?

Marieke Schoemaker, Global Development Specialist – Adult Nutrition, FrieslandCampina Ingredients

Consumers today are increasingly aware that the best medicine is preventative and are therefore taking a more active role in both preserving and improving their immune health. As such, they are also increasingly careful when choosing what goes into their bodies. A world of knowledge is just a click away, and they are easily able to find out everything about the ingredients in the products they consume, including functional food and drinks and supplements.

Before the COVID-19 pandemic, 47% of consumers said they regularly researched ingredients to help decide their best options.¹ As the pandemic struck, this preference took on new urgency and the focus turned to immune health support. In fact, the number of consumers that actively wanted to improve their immunity rose from 53% in 2019 to 70% in 2020.² Contemporary consumers want immune health solutions that contain scientifically proven ingredients, backed by clinical evidence.

Supporting immunity

Encompassing a complex set of defence mechanisms, the human immune system is honed to protect itself from both external and internal threats. Crucially, it must perform strongly enough to avoid infection, constantly alert and continually evolving to track down, identify and destroy new and recurring pathogens – while also distinguishing pathogens from harmless or beneficial substances.

However, the strength and variety of an

immune response is completely unique to each person, depending not only on genetic factors, but also on environment, age, body composition and other factors.^{3,4,5} This is why more consumers are relying on functional foods, drinks and supplements to obtain some of the nutritional benefits their diets may lack and to help support their immune systems.²

Lines of defence

In order to create solutions that address this need, manufacturers are taking a closer look at the sites where the human body is directly exposed to pathogens – such as the mucosal surfaces of the upper respiratory tract and the gut. The body protects these areas with the mucosal immune system, made up of a physical coating of mucus, layers of epithelial cells and lymphoid tissue cells – which play an important role in identifying pathogens and providing an appropriate immune response to them.

In addition, in order to function correctly, the gut mucosal immune system relies on the interaction between the intestinal immune system and gut microbiota. ‘Microbiota’, or the collection of microbial cells which live in and on the human body (although most abundantly in the gut), can synthesise vitamins⁶ and short-chain fatty acids⁷ to create beneficial nutrients that support the maturation of the intestinal immune system.⁸

The gastrointestinal (‘GI’) tract provides an optimal environment in which gut microbiota thrive and are nourished. With the gut mucosal immune system

and the broader immune system as a whole influenced by the interaction of microbiota with environmental factors, it is clear that diet is an essential element of supporting immunity.

The power of milk

As the first and only form of nutrition available to mammals when they are born, the importance of nutrient-dense mammalian milk cannot be overstated. The immune system needs to be ready for action from the moment of birth, so it is unsurprising that breast milk plays a vital role in supporting immune health from the very beginning. A key component of milk is protein – the building blocks for several bodily tissues as well as immune cells. Interestingly, some dairy proteins are not actually used as building blocks at all but have functional properties instead – take an immune active glycoprotein like lactoferrin, for example.

Lactoferrin is already much studied and is known primarily for its antibacterial effects.⁹ For example, its iron-binding capability enables it to compete with siderophilic bacteria to bind ferric iron,¹⁰ which can reduce the risk of bacterial infection. However, it additionally offers strong antiviral activity against a broad spectrum of both naked and enveloped DNA and RNA viruses.¹¹ Effective in the inhibition of binding and invasion of these viruses, by binding the virus directly or by binding to the receptor the virus uses to gain access to target cells, lactoferrin can also boost innate immune responses to support antiviral defence.^{12,13,14,15,16,17,18}

The antiviral effects of lactoferrin have been explored in a number of clinical studies. A study of Australian adults who frequently suffer from common cold-associated symptoms, for example, showed that a combined daily dose of 400mg of bovine lactoferrin plus 200mg of whey protein significantly reduced the incidence of colds and the cumulative number of cold-related symptoms in comparison with a placebo.¹⁹ This suggests that the right dose of bovine lactoferrin may act as a prophylactic, reducing the symptoms and duration of upper respiratory tract infections.

Guarding the gut

Naturally, these clinical studies have also led to interest in lactoferrin’s potential benefits against GI infections. A limited number of studies in adults has so far been performed to investigate the effect of bovine lactoferrin supplementation on GI infection such as *H. Pylori* or Norovirus. So far, the evidence indicates that supplementation with bovine lactoferrin might suppress the colonisation of *H. Pylori* and may also play a role in suppressing infectious gastroenteritis.²¹

This hypothesis has been tested in a recent study considering the GI symptoms of childcare workers in Japan, who are exposed to a higher risk of infection when working with small children. The study showed that lactoferrin supplementation correlated with reduced acute GI symptoms in winter, as well as significantly shorter average duration of diarrhoea, as compared to a placebo.²²

The goodness of milk

Research is continuing apace, but already all the signs point to lactoferrin being a vital tool for any manufacturer in the immune health space. This glycoprotein shows exciting potential for supporting immunity in both the gut and the upper respiratory tract – helping product development teams globally meet rising demand from health-conscious consumers.

As the world’s largest dairy cooperative, FrieslandCampina Ingredients has always strived to lead the way in illuminating the benefits of milk to customers, so they can pass on those benefits to their customers. With Biotis™ Immune Health, the company is leveraging its expertise in lactoferrin to expand custom-

ers’ opportunities in the adult immune health market. Find out more at biotis.com/immune-health. ●

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DO PREBIOTICS OPEN NEW ROUTES FOR 'HEALTHIER SNACKING'?

By Gareth Clark,
European Sales &
Marketing Director at
Clasado Biosciences

The successes of the food manufacturing sector are inherently linked to how well brands and food developers can anticipate and meet the evolving needs of the consumer market. When we think of 'consumer trends', we often go straight to manufactured goods such as clothing and technology, but the wider FMCG sector is just as susceptible to shifts in demand.

One particular area of interest is the renewed market interest in health and nutrition. More specifically, consumers are looking for products that combine food and nutrition on a much closer level than has been seen before. The nutraceutical and food categories are becoming more intertwined than ever before as brands on both sides look to meet the evolving needs of shoppers.

In essence, this change is creating new opportunities for food products with heightened nutritional value. We are seeing brand new categories being created with significant commercial opportunity and everyday snacking products, that form part of the routine diet for many, have a role to play. In addition, some consumers may be resistant to the idea of 'popping pills' as part of a dietary routine. For this demographic, different delivery methods, such as functional or fortified foods, may provide an appealing alternative to achieving their nutritional reference intake (NRI%) goals.

A question that must be asked as we look towards the expanding functional foods market is – can the health and nutrition industry better support the food sector as the two become more closely linked? Furthermore, where can the health and nutrition industry provide food manufacturers with the opportunity to blend creativity with consumer appeal?

Gut health nutrition moves mainstream

When we talk about functional foods, we cannot discount the rapid accelera-



tion of public awareness of gut health. We have seen this in action for a number of years with probiotics, as products such as kefir and live culture yoghurts capture attention on the store shelves.

Consumers are taking a much closer look at physical health and wellbeing. In particular, areas such as immune function and mental health have become such a key point of focus that brand new product categories are emerging in response.

One of the most abundant opportunities for brands is to harness microbiome science and gut health within product formulations. As well as aiding digestion, 'good' gut bacteria exert influence over other areas of health and wellbeing too, including cognition and brain health, immune function, the body's response to sport and athletics – and even how well we sleep. Digestive health is therefore a market full of retail potential. What's more, as we are only beginning to scratch the surface of gut health as a key selling point for functional foods, the path is open for brands to be first to market in new segments.

For example, one of the world's largest breakfast product brands recently launched a prebiotic cereal; the technology to make this happen has been in de-

velopment for a long time. This launch reflects that the health and nutrition sector is now at a tipping point where it can diversify product applications and support brands and their manufacturers with innovation opportunities.

Where do prebiotics fit in for food developers?

For developing functional snack foods that engage the consumer, brands are seeking two core elements; the scientific backing that instils confidence and the versatility to fit into diverse manufacturing processes.

Probiotic ingredients such as kefir or lactobacillus are well-known to the public, but they have application constraints. As live bacteria, they need to survive the manufacturing process intact, as well as the journey through the human digestive system. In contrast, prebiotics offer a more flexible alternative path for developers. Where probiotics add good bacteria to the gut, a prebiotic ingredient fuels and nourishes the good bacteria that already exist within the gut microbiome and therefore increase their numbers. These good gut bacteria are known through extensive study to positively influence a diverse range of the body's natural functions and processes, which creates powerful marketing potential for brands.

Prebiotics, or dietary fibre, are found naturally occurring in a wide range of foods. Increasingly however, the food and nutrition sectors are harnessing prebiotics, such as Bimuno® our proprietary GOS ingredient, as a standalone ingredient for recipes and formulations.

As a substrate rather than a live organism, prebiotic ingredients do not need to account for heat or acid survivability, making them more stable for use in food products that are baked or heat-treated. This quality alone creates space for the baked goods category to be involved in the gut-health conversation. Significantly, this stability also means prebiotic ingredients can be introduced to products at any stage of the manufacturing process, creating simpler avenues of inclusion for existing recipes and formulations.

Trust is essential, and the consumer wants to know that the functional food snack products they are purchasing can do what they claim. At Clasado, we have put this ideology to the forefront of the business with Bimuno. As the most studied prebiotic of its kind, Bimuno is supported by over 90 scientific publications, including more than 20 clinical trials.

Designed to be intrinsically versatile, Bimuno offers a way for brand owners and functional food developers to build proven gut health science directly into their next generation of products.

It is becoming increasingly clear that as the line between food and nutrition is blurring, and the market potential of gut-oriented functional food is becoming wider than ever. By exploring the mani-



fold benefits of prebiotics, there is a great deal of opportunity for brands to create functional snack foods shaped by today's and tomorrow's consumer needs. ●

For more information on Clasado Biosciences and its activities, please contact PHD Marketing Ltd. The Cavalier Suite, The Barracks, Wakefield Road, Pontefract, West Yorkshire UK WF8 4HH. Tel: +44 (0) 1977 708 643 or Email: hello@phdmarketing.co.uk

BIOIBERICA AND APSEN REINFORCE PARTNERSHIP WITH NEW HOLISTIC MOBILITY PRODUCT – MOTILEX HA

Apsen introduces Motilex HA – including Bioiberica's Mobilee® and b-2Cool® ingredients – in the Brazilian market. The innovative product follows the publication of recent scientific evidence supporting the enhanced efficacy of Bioiberica's joint health ingredients when combined.

Bioiberica, a global Life Science company, has partnered with multinational health and pharmaceutical expert, Apsen, to develop an innovative mobility product for the Brazilian market. Apsen's Motilex HA combines two of Bioiberica's leading joint health ingredients, b-2Cool® native type II collagen and Mobilee® – a patented ingredient that synergistically combines a high concentration of hyaluronic acid with polysaccharides and collagen – to effectively maintain joint function and support overall mobility. The launch of Motilex HA follows recent scientific research published in Osteoarthritis and Cartilage, which highlights the benefits of combining Bioiberica's native (undenatured) type II collagen, b-2Cool®, with other key ingredients for joint health, including chondroitin sulphate, glucosamine

hydrochloride and Mobilee®.

This latest development is born from Bioiberica's long-standing partnership with Apsen – the companies previously collaborated to produce Motilex, a powdered food supplement containing b-2Cool®, which has since become a marketing-leading product – and comes after Mobilee® was authorised as a novel food ingredient in Brazil in early 2020.

Discussing the product and its position in the market, Jaume Reguant, Healthcare Director at Bioiberica, said: "Following the successful development of Motilex, we recognised an opportunity in the market to leverage our combined technical and market expertise and respond to the growing trend for holistic mobility solutions. Rather than focusing on joints and muscles in isolation, we've worked closely with Apsen to expand its range and create a new product which uses a powerful combination of hyaluronic acid, polysaccharides, and collagen in the form of Mobilee®, alongside native type II collagen to provide health-conscious consumers with an effective solution that supports overall mobility and enables them to achieve their health goals."

Kleber Vargas, Vice President of New Business at Apsen, comments: "Brazil is a priority market for both Apsen and Bioiberica, where Motilex, containing b-2Cool®, is currently the market leader. The mobility market continues to evolve rapidly in the region and it's for this reason that we choose to partner with organisations, like Bioiberica, which can support us in the development of cutting-edge solutions with market standout through the provision of high-quality, science-backed ingredients."

A leading source for innovation in the sector, Bioiberica has over 45 years of expertise and experience in joint health and mobility. As part of its mission to provide holistic, on-trend mobility solutions, the company continues to seek collaboration with global partners, through which it can share extensive marketing, regulatory and scientific knowledge and help facilitate brands in bringing exciting new products to the market. ●

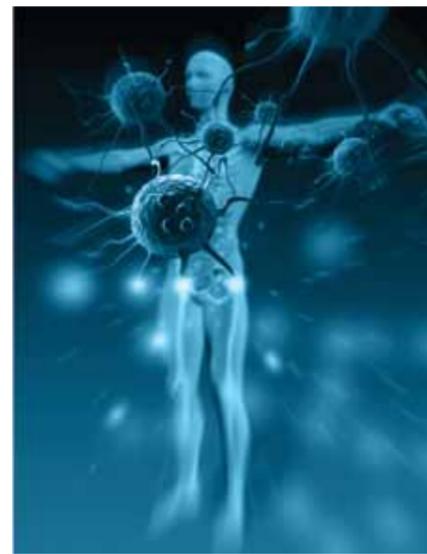
To discover more about Bioiberica, its innovative ingredients and strategic partnerships, visit: www.bioiberica.com

A HEALTHY IMMUNE SYSTEM MEANS SO MUCH MORE THAN NOT BEING SICK

By Susan J Hewlings PhD, RD Director of Scientific Affairs Nutrasource/GRAS Associates

According to a report by Fortune Business Insights, the immune health global market size increased 7% from 2019 to 2020. According to a report by Fortune Business Insights, the immune health global market size will increase 7% from 2019 to 2020. The report also indicates that there is increased demand globally and in the US for immune products such as elderberry, zinc, vitamin c and vitamin D. Probiotics, prebiotics and omega-3s are also in high demands. The report further states that the immune health supplements market size was USD 16.32 billion in 2019 and is projected to reach USD 29.40 billion by 2027, exhibiting a CAGR of 7.4% during the forecast period.¹ The report also indicates that there is increased demand globally and in the US for immune products such as elderberry, zinc, vitamin c and vitamin D. Probiotics, prebiotics and omega-3s are also in high demands. The report further states that the immune health supplements market size was USD 16.32 billion in 2019 and is projected to reach USD 29.40 billion by 2027, exhibiting a CAGR of 7.4% during the forecast period.¹ Data from SPINS (Chicago) on the U.S. dietary supplement market during the year ending November 29, 2020, show that vitamin D sales in both the mainstream and natural retail channels increased by double-digits. In the mainstream channel, vitamin D sales grew 34.4% to \$544 million.² Two surveys sponsored by the Council for Responsible Nutrition (CRN) in 2020 confirm that more consumers relied on vitamin D last year to support health. The first, a COVID-19-focused survey conducted by Ipsos from July 31, 2020, to August

4, 2020, polled more than 2000 existing U.S. supplement users to determine how their supplement use changed during the pandemic. 37% of supplement users said they had increased their use of vitamin D.³ Another survey, CRN's annual Consumer Survey on Dietary Supplements, polled more than 2000 U.S. adults from August 27-31, 2020, and found 42% of respondents used vitamin D.⁴ What this doesn't say is what consumers think defines a "healthy immune system". According to research conducted by FMC gurus, globally, the majority, 61% of people surveyed believe that being easily susceptible to day-to-day illness such as catching a cold is a key sign to a poor immune system.⁵ However, a healthy immune system is much more than the absence of illness. Considering all aspects of a healthy immune system may open the market to a more diverse immune category.



Defining a healthy immune system is more challenging than it seems. Immunologists are attempting to determine different ways to directly investigate immune status. One of the most promising ways to determine this is through a field of study called systems biology or systems vaccinology.⁶ This approach considers that there are a lot of factors that can disrupt the human immune system, and how these factors influence the various parts of the immune system can help define a healthy immune system. The most convenient factor to study is the response to common vaccinations such as influenza virus vaccines. Studying the response of the many known aspects of the immune system to a vaccine can reveal which components of the immune system change and how they change. This information helps to define a healthy immune system and helps to answer

how different people respond differently when exposed to both pathogens and vaccines. It is easiest to focus on markers in the blood that might be different when a person is ill compared to when they are not.⁷ Such studies have revealed that immune systems remain stable for as long as 6 years in healthy individuals.⁸ This suggests that individuals have a baseline state of immune system composition in which the components of the immune system are well regulated, and in balance. When the person is exposed to a challenge, such as a virus, there is a response aimed at bringing the system back to balance. How the response occurs and how it is brought back to balance is still being revealed and is undoubtedly influenced by a complex interaction of factors including genetics. However, we do know that people respond differently to these challenges for different reasons that are not all genetically dictated.⁷ For example, it is well understood that diet and lifestyle influence immune function. While overall diet is important, it has been determined that certain nutrients are crucial to keeping the immune system in balance and are key to helping the system retain balance after being challenged by infections. This evidence is so compelling that the European Food Safety Authority (EFSA) states that six vitamins (D, A, C, Folate, B6, B12) and four minerals (zinc, iron, copper and selenium) are essential for the normal functioning of the immune system.⁹ In addition to diet and lifestyle, certain populations are more at risk for poor immune function. For example, elderly people tend to respond differ-



ently to immune challenges and vaccines compared to younger adults. While the exact reasons for this are not completely known, the low-grade systemic inflammation often associated with aging has been suggested as a reason for the differences.¹⁰ Additionally, men and women demonstrate different immune responses. For example, when presented with an immune challenge, women tend to show their greatest response 3 days after exposure while in men the peak response occurs during the first day.¹¹ Another factor that has been identified to influence immune response is the human microbiota. Disruption in the balance of the microflora in the gut has been linked to initiating and maintaining inflammation, immune response and even response to vaccines.¹² While more research is needed to clarify the differences in immune response associated with age and gender, identifying that there is a difference can help to identify target groups for intervention and prevention strategies and can help public health officials establish specific guidelines surrounding immune related public health concerns. What does this mean for the dietary supplement market? While defining a healthy immune system may not be as straight forward as it seems, identifying that immune response potentially involves chronic inflammation and the microbiome as well as nutritional factors such as vitamin D, allows for the development of multiple combinations of multi-ingredient formulas to target multiple consumer concerns. For example, a product could support gut health and support a healthy immune system or support a healthy inflammatory response and a healthy immune system. While research is ongoing to more clearly define exactly what a healthy immune system is, it is clear that it is much more complex than just not being sick. ●



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WHY RESEARCH AND CLINICAL STUDIES ARE KEY TO SYSTEMATIC CHANGES IN THE HERBAL SUPPLEMENT INDUSTRY

By Krishna Rajendran, CEO of Karallief, Inc

According to the 2019 CRN Consumer Survey on dietary supplements more Americans than ever (77 percent) reported using some type of dietary supplements. While the most popular category was vitamins and minerals, nearly 40 percent of those surveyed used herbal and botanical supplements. While herbal supplements are still on the periphery of American healthcare, the World Health Organization found that 80 percent of the global population uses herbal supplements as a component of their primary healthcare.



While supplements are not regulated by the FDA in the same way pharmaceuticals are, they still need to meet quality standards. For the herbal supplement industry to continue to grow and gain credibility in the healthcare community and with consumers, more research and clinical studies are needed to prove the safety and efficacy of products. A 2016 report from Mintel showed that more than a third of consumers want more clinical studies of supplements, yet very few ingredient suppliers actually conduct clinical trials of the products they sell.

For herbal supplement manufacturers, a reason they often cite for not doing clinical trials is that their extracts have been used successfully for centuries. While that may be true, it really doesn't answer the question of the safety and efficacy of a specific brand's product. In order to establish credibility for herbal use in modern healthcare, traditional usage must be complemented by rigorous clinical studies. Right now, too many companies shy away from conducting clinical trials because it would cost more money and take more time to bring a product to market. However, I believe that science, not sales, needs to drive market strategy decisions.

While many manufacturers ignore clinical trials entirely, others try and leverage research conducted by other companies selling similar herbals. One issue with this is that companies are less likely

“THE GLOBAL PANDEMIC HAS PUT AN EVEN GREATER FOCUS ON WELLNESS AND CONSUMERS TAKING AN ACTIVE ROLE IN THEIR HEALTH

to invest in high quality R&D and safety testing, if another company can just easily copy and undercut them on price. This discourages innovation and high-quality testing which, in the long-run, is detrimental to formulators' desire to give consumers high quality products. High quality formulators want to work with companies who have originally developed a product with original research. This is because only the scientists who are involved in developing the product (especially in the case of a synergistic combination herbal extracts) will un-

derstand the intricate details of how the product was created and finalized. A company trying to copy the original developer is only able to guess how the product was developed. They may be 70-80% correct, but they most likely will not have all the details. Thus, they end up developing a less accurate, inferior, and potentially less-safe product that hasn't been tested properly.

The herbal supplement industry is also full of single ingredient products, where this piggybacking on one company's study is commonplace. While single ingredient supplements aren't necessarily bad, they aren't as effective because they don't leverage the synergies that exist between herbal ingredients. A manufacturer like Karallief that has a robust team of Naturopathic doctors and herbal scientists that are able to develop highly innovative synergistic multi-ingredient extracts.

For example, we recently commissioned a clinical study for Easy Climb, our joint health product. It was a four-month, randomized double blind, placebo-controlled study with different standard industry knee tests used to determine the efficacy of the specific formulation. It is this kind of scientific study that should be the gold standard in the herbal industry to push it forward and gain legitimacy and consumer confidence.

The global pandemic has put an even greater focus on wellness and consumers taking an active role in their health. These educated customers will gravitate towards products with research that backs up their efficacy. As they start to choose these better products, it will force the companies who are left out to either perish or step up their game and invest in more scientific research and testing. ●

Krishna Rajendran is the CEO of Karallief®, Inc., a company that researches, develops and distributes combination, custom and single herbal extract formulas to companies around the world in the dietary supplement, skincare and food industries.

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OXIDATIVE STRESS AND RECOVERY IN SPORTSPEOPLE: HOW BOTANICALS CAN HELP THEIR CELLULAR HEALTH

By Thomas Ughetto,
Sales & Marketing
Director, Robertet
Health & Beauty

The sports nutrition market is very dynamic. Initially focused on bodybuilders and athletes, it has gradually opened up to mainstream consumers, who consider sports and nutrition as a means to a healthy lifestyle. The global sports nutrition is estimated at 42 billion dollars in 2022 compared to 23 billion in 2015 according to market studies. With a CAGR1 of 8.4% between 2015 and 2022, it is one of the strongest dynamics in the world of nutraceuticals. While the United States remains the historical leader (30% of global sales), the United Kingdom is growing and remains the European leader (3 out of 10 Britons are consumers). France is a small market, but it has potential¹.

Athletes also no longer view things solely through the prism of performance. They are looking for global solutions that cater for their performance but also their well-being and recovery.

They are paying more attention to our general health and wellness and are more demanding in terms of nutrition and supplements. They attach great importance to naturalness and transparency. Indeed, 65% of recreational users and 74% of athletes would prefer 100% natural sports supplements².

Responsible for tissue damage, poor adaptation to effort and reduced training effectiveness, oxidative stress is now a key target for sportspeople.

Indeed, protecting cells is important both in antiaging and in sport medicine and can indirectly impact energy replacement and hormonal management, as well as improving our neurotransmitters. Our antioxidant defenses prevent oxidative stress and inflammation, and also facilitate physical and mental well-being.

We are also observing that people are paying greater attention to chronobiology. This means a diet and a supplementation that are perfectly adapted to each sportsperson depending on their own specific needs and the timing of their training: who needs supplements,

what is the most suitable time to take them, and for how long?

If we take the words of Dr. Saramito, who has forged longstanding experience and used his skills with top athletes (French Olympic team at the Atlanta Olympic Games and the Subaru team at the World Rally Championship, etc.) "nutrition must be adapted to the athlete: giving a long-term antioxidant treatment without looking at the needs may disrupt cellular messaging. The dosage is more efficient when the supplementation is provided in a discontinuous treatment".

In this context, drawing on its expertise in natural ingredients, Robertet provides to athletes natural and effective solutions for tissue damage, adaptation to effort, and training efficiency.

Based on a sustainable melon juice concentrate, Melorun® has been developed specifically to counteract oxidative stress in the context of physical activity. This specific variety has an essential antioxidant enzyme, Superoxide Dismutase (SOD), in concentrations five to ten times higher than other melons.

Its efficacy has been demonstrated after 2 months of supplementation at only 40mg/day, in a gold standard clinical trial conducted on a population of recreational users as well as in a consumer study on a professional volleyball team.

Going further, 4 preclinical studies have provided a better understanding of the mechanisms behind this efficacy.

Melorun®:

- Promotes physical well-being,
- Facilitates mental well-being,
- Protects magnesium levels,
- Prevents oxidative stress and inflammation,
- Supports the integrity of muscles and joints.

In SOD supplementation, the first positive clinical effects on athletic performance and muscle rehabilitation usually start at the end of the second week. The maxi-



mum level of beneficial clinical effects is reached in week number 4. If supplementation is stopped at the end of week 4, there is an additional 2 months of effectiveness: this is called remanence. According to Dr Saramito, who has been recommending the intake of melon SOD to high-level athletes for 20 years now "remanence is very interesting when you are setting up specific action plans adapted to each sport. Let's take the example of the Tour de France to measure the importance of chronobiology and the phenomenon of remanence. Usually, professional cyclists are exhausted after a week of competition. So the first week of the Tour is usually flat. They don't lose too much energy. Next come the steep climbing stages where the muscles are constantly under assault, and athletes lose a lot of energy. Hence the importance of starting SOD supplementation 3 weeks before the Tour de France. Supplementing cyclists 3 weeks before the race allows them to be at full efficiency for the 2nd week, the one where they encounter the most difficulties. It is precisely during this 2nd week of the race that the ingredient produces its full efficiency. Then, the crucial phenomenon of remanence occurs: when the supplementation is stopped, the beneficial effect continues and is felt for some time. Remanence allows you to take breaks rather than taking continuous supplementation. Then a French sailor in the Vendee Globe, the leading round-the-world sailing race, started taking SOD three to four weeks before reaching Cape Horn. This made him fully efficient against fatigue and difficult sailing conditions (wind, temperature, stress, icebergs, currents, etc.)." ●

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