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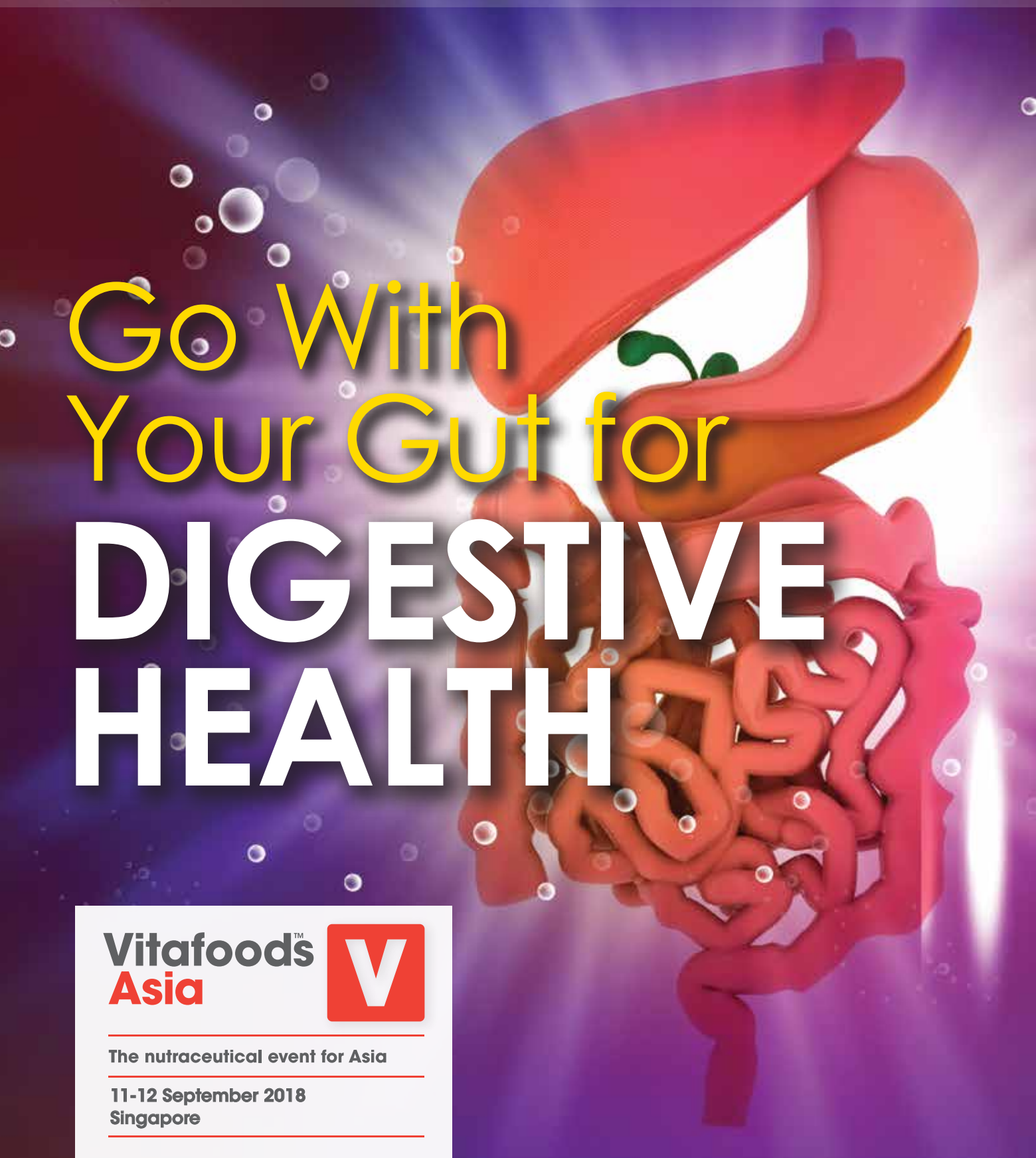

Go With Your Gut for DIGESTIVE HEALTH

Vitafoods™ INSIGHTS

CONTENT

June 2018

I've Got a Good (Gut) Feeling About This

While the microbiome may well have been the 'forgotten organ', it has certainly exploded into the mainstream for the health and wellness industry. Even more than this, gut health has become a media darling, with public perception and understanding at an all-time high. Ask your mum, ask your colleague, ask the next random person you meet how important gut health is, and they'll all agree; digestive health is fundamental to overall health and wellness.

Popularity among consumers and the prevalence of gut disorders globally offer business opportunities for manufacturers looking to provide effective products in this space. The obvious place to start is the global probiotic market; data from the International Probiotics Association (IPA) shows the probiotics market is expected to continue growing year-on-year, reaching over €39 billion by 2020! The article on page 5 offers insight to the industry globally, and investigates the markets in 25 countries around the world for a full overview of probiotics in 2018.

While there's plenty of business opportunity here, producing high-quality probiotics is technically challenging. Kyle O'Brien walks us through manufacturing quality probiotics from strain to solution on page 13.

There's more to digestive health than probiotics, with several botanical extracts showing promise. Artichoke, ginger, curcumin and *Boswellia serrata* have all shown efficacy in helping improve symptoms of various gut complaints, and all four are covered in depth in the article from Antonella Riva on page 14.

Finally, an exciting new area of research is glycoscience, as covered by Sergio Pumarola on page 20. Originally seen solely as a source of energy for cells, functional sugars now represent an innovative area of research for the sector.

Consumer interest and further research into healthy microbiomes mean we can expect commercial opportunities to continue to boom. The next step is making digestive health solutions accessible to mass market, with functional food and beverages and dietary supplements leading the way. I'm looking forward to the future of this market and am enjoying seeing innovation in action as manufacturers step up.

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SCIENCE IS OUR NATURE

Probiotics Market Insights: What to Watch in 2018

by George Paraskevakos and Elisa Fernandez

The probiotics market continues to experience unprecedented year over year growth. Industry analysts at Euromonitor International assessed the entire probiotics market in 2017 at €36 billion[1], up from €29.6 billion in 2012. That number is predicted to reach over €39 billion by 2020, as usage expands globally.

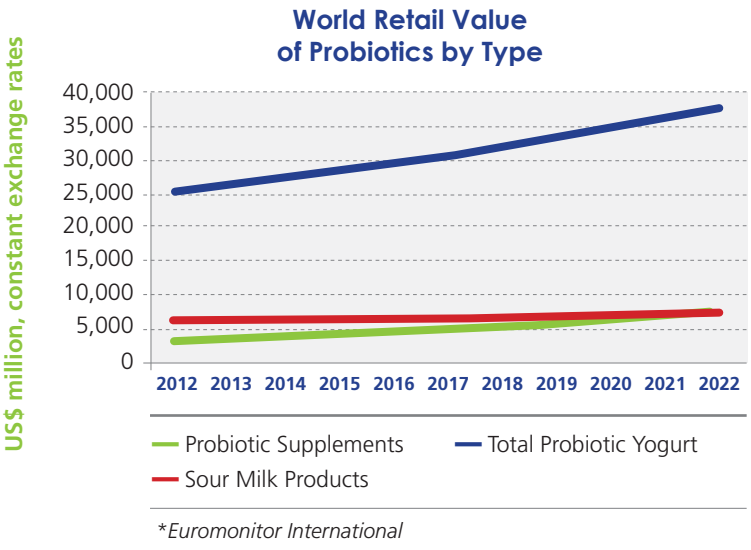
Three sectors dominate the landscape

Of the entire global retail market, yogurt and sour milk products represent 88 percent of all consumption. Supplements fill in the remainder.

- 73 percent consumed as dairy-based yogurt products, which is similar to that in 2012.
- 15 percent as sour milk products, down 2 percent from 2012
- 12 percent as supplements, up from 9 percent in 2012

Market Overview - Probiotics

Forecasted Growth to 2022



**Euromonitor International*

7.1 billion
US$ retail value of global probiotic supplements in 2022

40%
Probiotic supplement growth from 2017 to 2022

22%
Total probiotic yogurt growth from 2017 to 2022

While contributing a much smaller portion of the market, supplements are experiencing phenomenal growth. Expected growth comparisons through 2022:

- Dairy-based yogurt products should see 22 percent growth
- Supplements are expected to grow 40 percent

Also worth noting is the rising popularity of kefir in the United States may be cannibalising sales of probiotic yogurt.

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Probiotic supplements are the big story

Probiotic supplement sales are soaring, with retail sales surpassing €4 billion in 2017. According to Euromonitor International, global probiotic supplement value is predicted to reach €6 billion in 2022. Projected growth for probiotic supplements from 2007 through 2022 is 283.6 percent, outpacing other ingredients including proteins, calcium and fish oils.

Probiotics in digestive disorders

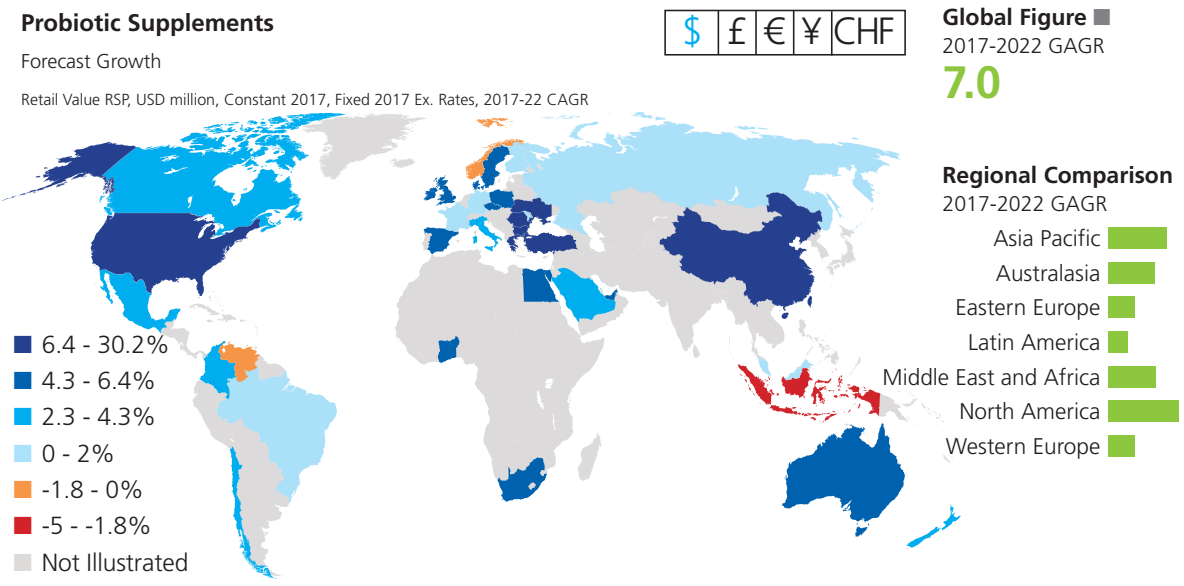
Digestive disorders continue to be a prime target for probiotic supplements. In the ten-year period 2012 through 2022, use of probiotic supplements as digestive remedies is expected to more than double worldwide. Compare this to antacid sales, which are expected to rise only 14.9 percent as opposed to probiotics at 114.3 percent. In fact, probiotics surpassed antacid use for gut problems in 2016. Other remedies including proton pump inhibitors, H2 blockers, and anti-diarrheals will rise, but with a much smaller share of the market. Lastly, irritable bowel syndrome (IBS) medications will see an expected drop of 11.3 percent. Of note is that ageing populations are driving this sector.

Probiotic use beyond the gut

As probiotic research expands utility beyond digestion, supplement use is finding application in many other need states. For example, global growth in use for immune health has shot up 48 percent in the five-year period of 2012 through 2017. Women's health usage is also seeing strong growth; consumption rose 52 percent in the same period. Another hot sector is that offered by the recent research on the gut-brain axis. Probiotic sales in the mood and psychological realm grew by 28 percent in the five-year period mentioned. Expect continued growth as labs across the world contribute convincing evidence for the use of probiotics outside the digestive system.

Market Overview - Probiotics

Global Probiotic Supplement Growth



**Euromonitor International*

Probiotic use compared to other supplements

While probiotic supplement use is growing phenomenally, it has ample room to grow. Other categories of supplements in the health space surpass probiotic use. Multivitamins, calcium and vitamin C find two to three times the users as probiotics in one sample surveyed. Also, usages rates of vitamin D and omega-3 fish oils exceed that of probiotics. It will be interesting to revisit the comparisons in a few years.

Probiotic use by age

All age segments are using more probiotic supplements. In the two-year span from 2015 through 2017, consumers aged 30 to 44 years showed the highest percentage increase in probiotic use followed by the 45 to 59 years group. Interestingly, vitamin C and omegas showed reductions in use, although they still outshone probiotics in absolute use.

Drivers of growth

Awareness

Higher consumer awareness of the benefits of probiotics is leading to a significant growth in the sales of supplements. Growth is being driven by increased awareness across global platforms, driven by technology and especially social media. In addition, public health programs and traditional media are increasingly reporting on the role of probiotics in fighting disease and disorders.

While probiotic supplement use is growing phenomenally, it has ample room to grow.

Broadened capability

Since 2007, stronger clinical studies, scientific-based evidence of benefits of probiotics and a deeper understanding of the human microbiota have produced an explosion of support for probiotic usage. Probiotics are no longer consigned to digestive health categories in the practitioner's toolbox. Large research studies, most notably the NIH Human Microbiome Project, have spurred discovery that the microbiota is integral to the immune system, metabolic systems, and respiratory system, and may prevent and/or treat many chronic diseases and disorders. This remarkable expansion of duties or rather 'discovered capabilities' will be a force behind increased adoption of their applications.

Demographics

Ageing populations across many continents are also drivers for increased consumption. As people age, health needs escalate and interest in health generally increases as well. Nevertheless, probiotic usage is rising among all age groups.

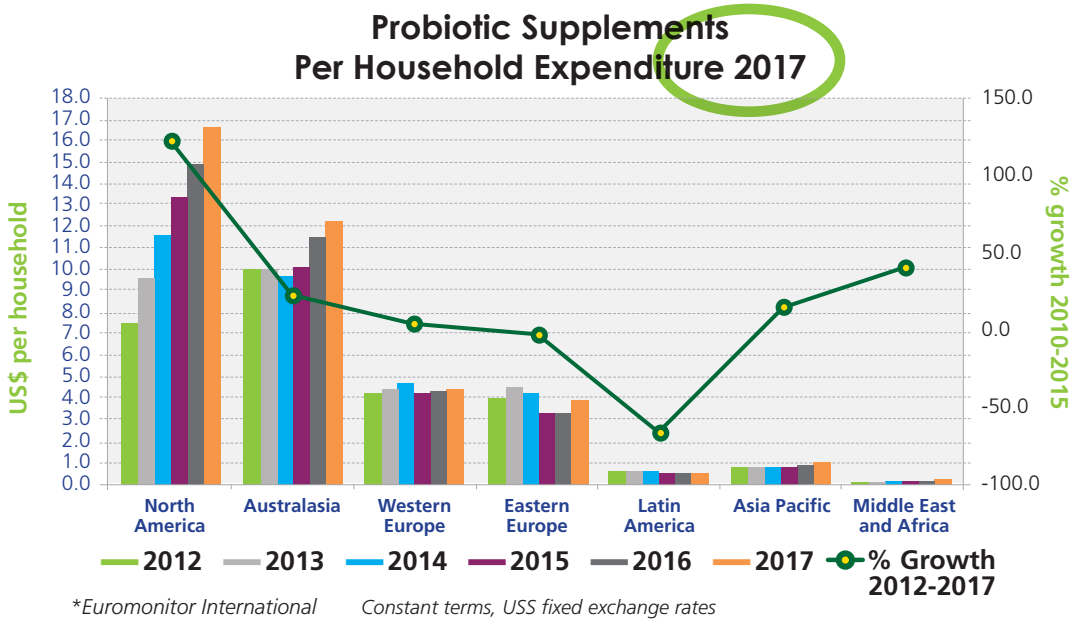
Dwindling healthcare resources

Soaring healthcare costs are directing more attention to prevention across the sphere of health care. Probiotics are increasingly part of the strategy for both prevention and treatment for consumers and health practitioners.

In 2002, the certification of active live cultures in yogurt propelled the market toward a classification of yogurt as a probiotic product. This led to important innovation in the consumer retail environment with many new launches and therapeutic specialization.

Per Household Spend in Each Region

Probiotic Supplements — 2017 Data



*Euromonitor International *Constant terms, US$ fixed exchange rates*

Global glimpses of probiotic use

North America

North America led the world in household expenditure in 2015, spending €11 on probiotic supplements. That number breached €13.5 per household by 2017. Absolute growth from 2015 to 2020 is forecast to be €905 million. This translates to 9.8 percent compound annual growth rate (CAGR)[2] for the five-year period.

United States

Consumers are searching for ways to improve diets and reduce unhealthy foods and beverages; the trend is driving increased sales of probiotics foods and supplements. Total retail value in the United States exceeded €1.4 billion according to analysts.

Canada

A pioneer in the space, Health Canada was one of the first regulators to introduce a probiotic monograph, with IPA's support and a pre-approval approach to introducing probiotic products to market. This is a much smaller aging population than the United States which, coupled with unhealthy diets and stressful lifestyles, has helped boost sales of probiotics and fibre-rich foods. Probiotic supplements could address constipation and increase regularity.

Western Europe

Absolute growth from 2015 to 2020 is estimated to be €94 million. This translates to 2.5 percent CAGR for the five-year period.

Finland

While not as brisk as in past years, product launches in established brands continued. Some were innovative, but most were extensions of popular brands.

France

Market data put the probiotic supplement group in the number two spot in value capitalisation in 2015 within dietary supplements in France. One product which claimed to be important for health of the immune system proved especially popular. Thus, the ageing population will be a big factor in the growth of probiotic usage, say market analysts.

Germany

Probiotic foods and supplements saw strong growth in 2015, driven by positive media attention and growth in the ageing population. New products with emphasis on long-acting and viability broadened the market demand. Probiotic supplement sales grew 1 percent in 2015.

Italy

Wellness through natural health products is a growing interest in Italy. Industry sources report that physicians are increasingly recommending dietary supplements along with traditional prescription medicine for minor health problems. Probiotics have long had a favoured place as a prescription alongside antibiotic therapy in this country. Italy also has a probiotic guideline in place which resembles that of Health Canada.

Sweden

Probiotics in the form of supplements and packaged foods with added probiotics are being marketing strongly to Swedish consumers. Sales of both categories are rising. Food with either intrinsic or added probiotic value has proven increasingly popular in Sweden. Growth in awareness of the microbial impact on health is driving the market.

United Kingdom

Foods and beverages with probiotic fortification continued to gain market share in 2015. The pediatric subset market continues to grow. Sources believe a strong market may exist for dietary supplements combining probiotics and protein, as both components are spurring widening interest.

CIS countries

Absolute growth from 2015 to 2020 is estimated to be €69.7 million. This translates to 4.2 percent CAGR for the five year period.

Belarus

Advertising as well as public health initiatives promote the use of dietary supplements in the goal of reducing disease and disorders. Probiotic advice takes a back seat to initiatives on reducing consumption of cigarettes and alcohol.

Russia

Probiotic supplements are becoming increasingly popular as traditional diets—rich in yogurt and other fermented foods—are replaced by processed, packaged foods as well as fast foods from retailers. Probiotic supplements claimed 28 percent value share of the dietary supplement category in 2015. Probiotic supplements are advised by the medical community in conjunction with antibiotics, an obligatory practice not as common in western cultures. In addition,

probiotic supplements are routinely suggested for digestive complaints. Both adults and children are included in the protocol. Prebiotics including inulin are often included with the probiotic supplement.

Uzbekistan

Increased consumer awareness campaigns are boosting sales of probiotic supplements according to market data.

Oceania

Absolute growth from 2015 to 2020 is estimated to be €6.7 million. This translates to 1.8 percent CAGR for the five year period.

New Zealand

Probiotic supplement sales grew at a fast pace in 2015: 10 percent growth in addition to being the second highest performer in non-herbal/traditional dietary supplements market category. Probiotics using delivery systems that did not require refrigeration experienced a strong introduction.

Australia

The population is generally aware of factors fueling good health and the lifestyle ingredients which sustain it. An aging population will spur use of probiotic supplements.

Latin America

In LATAM the absolute growth from 2015 to 2020 is estimated to be €7.4 million. This translates to 1.6 percent CAGR for the five-year period.

Mexico

Probiotic supplements were increasingly popular in 2015. Analysts believe a stressful lifestyle has led to more stomach ailments and gastritis for which probiotics are seen as a solution. On the retail level, sales of probiotic supplements increased by 11 percent in 2015.

Brazil

Brazil is currently going through a regulatory framework revision, whereby IPA has commented on the process. The previous published strain list is being revisited, taking into consideration all the updated science and technology that has transpired in the last decade. The new guidelines promise to be more in-line with current frameworks globally.

Argentina

Argentina, where regulations already exist, is in the process of taking on the harmonisation work at the Codex level as a lead country, with IPA's support. The FAO/WHO definition is a well-respected reference for the sector but would need to consider all the advancements in technology which have happened in the last 10 years. The ultimate goal is the establishment of eligibility criteria to ensure consistent application at national and international levels by Codex member countries; available to promote human health and well-being.

Asia Pacific

Asia dominates the all sources probiotic market by a large degree. Absolute growth from 2015 to 2020 is estimated to be €73.5 million. This translates to 2.8 percent CAGR for the five-year period. Rising disposable incomes will increase demand.

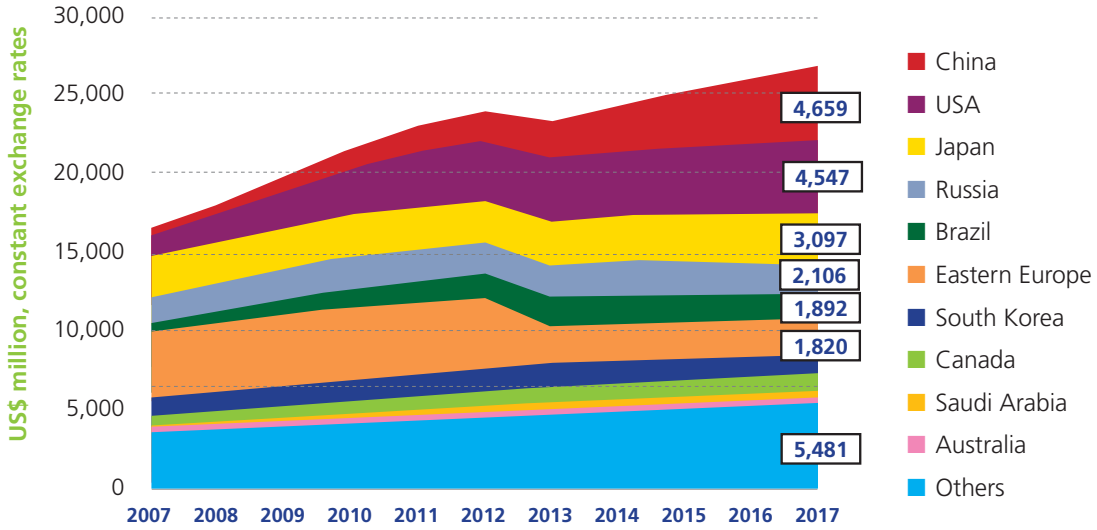
China

The digestive wellness platform with both pre- and probiotics has exploded in China.

Market Overview - Probiotics

Digestive Wellness Platform Explosion in China

Digestive Health Positioned Pro/Pre Biotic Yogurt, Leading Markets, 2007-2017



**Euromonitor International*

South Korea

Consumers are buying more yogurt; devices to make yogurt at home are selling at an even faster clip. Consumption of yogurt in South Korea is rivalling that of milk.

Indonesia

Fermented milk and yogurt products are competing with digestive remedies in this market. When probiotics are included in their marketing claims, products are shown to be more popular.

Malaysia

The probiotic supplement market here grew 17 percent in 2015. Consumers with busy lifestyles consumed probiotic supplements to maintain digestive health.

Pakistan

Medical practitioners educate consumers about dietary supplements including probiotics.

Middle East & Africa

The Middle East and Africa represent small markets with plenty of room to grow. Indeed, the Middle East and Africa are the biggest untapped markets. Absolute growth from 2015 to 2020 is estimated to be €47 million. This translates to 17.7 percent CAGR for the five year period.

Egypt

Supplements may gain traction with middle and upper class Egyptians. Some analysts expect probiotic supplements will dominate the vitamin and mineral category in coming years. Meanwhile, a young population and poor incomes will impede a broad market demand for probiotic supplements.

Israel

The 7 percent surge in dietary supplement sales in 2015 followed a 6 percent rise the prior year. Probiotic supplement sales appear to be the biggest factor in growth. Widespread awareness of benefits of probiotics, particularly for babies suffering with colic, was raised due to media coverage in the country.

South Africa

An emphasis on prevention rather than treatment is moving the South African dietary supplements market. Combination supplements which are viewed as more economical are popular.

United Arab Emirates (UAE)

Consumers are becoming more aware of how diet impacts health. Healthcare professionals, industry and advertising campaigns are raising awareness and driving sales of probiotic foods and supplements. Analysts report that consumers are more receptive to foods beyond the standards. Probiotics fit in this category. With high per capita income for the most part in the UAE, sales in the probiotic category should continue on a positive trajectory.

Final thoughts

Market analysts predict a robust growth market for probiotics in the years to come. Supplements are expected to lead the charge by a wide margin. Broadening awareness by the consumer because of advertising and public health campaigns is driving increased consumption across the global market. In addition, evidence-based research is expanding the array of diseases and disorders which respond to probiotics in either a preventive or therapeutic capacity. All of these market drivers point to increased probiotic applications worldwide.

i Listed monetary values are in USD$ currency, fixed exchange rate

ii The compound annual growth rate (CAGR) measures growth over multiple time periods. It is the growth rate that spans from the initial investment value to the ending investment value if one assumes that the investment has been compounding over the time period.

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Manufacturing Quality Probiotics from Strain to Solution

By Kyle O'Brien

Producing high-quality probiotics is technically challenging. From fermentation to finished product, every step must be carefully controlled to maintain viability and, ultimately, deliver a health benefit to the consumer.

The complexity of the fermentation process creates the possibility for quality problems to appear if very tight controls are not in place. During fermentation, the first step of the probiotic production process, tiny quantities of live microorganisms are put in conditions tailored to support their multiplication. Establishing favourable conditions for growth of the bacteria enables companies to turn a vial of a given strain into a bioreactor full of the microorganism ready for the downstream processing steps of concentration, stabilisation and the important process of freeze-drying to extremely low water activity levels.

However, conditions that are favourable for growth of the desired bacteria may also aid the multiplication of a host of other undesirable microorganisms. An unintended microorganism that appears in the probiotic medium or process can thrive, increasing its own population while outcompeting the desired strain. This undesirable event can lead to a finished culture that fails purity testing in addition to creating large expenses in both product scrap and lost production time.

The fragility of fermentation poses other challenges, too. Changes to process controls can affect the growth of the targeted microorganisms, leading to batch-to-batch variation and inconsistent performance of finished products.

To achieve consistent, high-quality output, probiotic production facilities must control and monitor each step of the process, from ensuring the purity of the starting strain, through amplification and scale-up, onto the finished, freeze-dried culture.

The probiotic segment has seen continuous growth due in part to ever-advancing scientific research as well as a consumer desire to live a healthier lifestyle. The growth of this segment has resulted in an increase in the number of companies entering the probiotic space without a clear understanding of the production challenges that exist.

Newcomers unaware of the experience, equipment and process controls needed for optimal probiotic creation have the potential to produce inferior products. Marketing such substandard probiotics runs the risk of running afoul of regulatory agencies and failing to deliver a health benefit to the consumer. This has the potential to cause a negative impact on the entire industry.

Recognizing the need to improve awareness and raise quality across the board, UAS Labs is working with fellow members of the International Probiotics Association to create finished goods manufacturing guidelines. These guidelines will help new entrants understand what it takes to bring probiotics to market, thereby encouraging them to commit the time, capital and expertise needed to meet probiotic standards for quality and enable the industry to continue to experience healthy growth.

Kyle O'Brien is marketing coordinator at UAS Labs.

IN THIS ISSUE Market Insights **p.5** Natural Products for Digestive Health **p.15** Table of Contents **p.2**

Digestive Health:
Natural Products as Effective Help for Modern Life's Big Challenge

By Antonella Riva

It's well known that taking care of digestive health is essential to maintaining good overall health, as the digestive system is a complex part of the body, assigned to retain nutrients and to eliminate waste. Furthermore, improving and maintaining so-called 'gut health' is becoming increasingly important: in fact, what we introduce into our body may influence not only the body itself but also the mind, and thus poor digestion may affect energy, mood, pain and allergies.

In modern life—due to unhealthy dietary habits, stressful lifestyles, and increasing elderly populations—the incidence of chronic conditions, and digestive and gastrointestinal disorders has grown worldwide. Sometimes, they present as mild discomfort and the risk lies in ignoring or underestimating them, starting a dangerous journey towards those sly mechanisms of low-grade chronic inflammation: several scientific studies have demonstrated its role in the onset of many chronic conditions such as cardiometabolic and gut diseases. Related to this, a substantial amount of evidence suggests many foods, nutrients and non-nutrient food components are able to modulate inflammation both acutely and chronically.[I]

The most common digestive condition is Functional Dyspepsia (FD), a series of chronic or recurrent pains or discomfort in the upper abdomen. Symptoms are frequently correlated to meals and may include abdominal pain, bloating, early satiety, fullness, belching and nausea, and its prevalence has been noted to vary between 11 percent and 29.2 percent of the adult population.[II] Functional Dyspepsia is not life threatening and has not been shown to be associated with any increase in mortality. However, its impact on people's quality of life and its burden on healthcare services has been proven to be considerable.[III]

In this scenario, pushed by awareness of the key role of dietary habits—'We are what we eat', said the German philosopher Ludwig Feuerbach—people try to change their lifestyle, turning to healthier foods, becoming more and more keen to improve the consumption of healthy nutrients, and also looking for natural approaches in different aspects of their life. In the specific gut area, consumer interest for remedies that improve digestive and gastrointestinal health registered double-digit growth in recent years, and is expected to grow further in the years to come. In fact, symptoms of Functional Dyspepsia are usually treated with conventional drugs, but as many of them demonstrate a limited efficacy, it is not surprising up to 50 percent of subjects suffering from this condition seek out alternative therapies. To this end, several botanical supplements are being studied and reveal enormous potential.

IN THIS ISSUE Manufacturing Quality Probiotics **p.14** Functional Sugars **p.20** Table of Contents **p.2**

The basics of quality

Plants represent a rich source of new active principles and botanical extracts are used in different markets, including health foods and supplements. Quality and rigorous standardisation of the botanical extract are essential to guarantee the necessary safety and efficacy profile. Furthermore, there is a growing need among consumers for scientifically-supported information around health foods and supplements, as they want to make informed choices, avoiding products that are too processed or whose origins are uncertain. They are now more demanding of products backed up by transparent composition, obtained from production chains and processes carried out in full accordance to best practices and consistent with traditional dietary uses.

Quality certifications have become basics for the main players in the market and the real difference comprises scientific literature supporting a botanical extract: for extracts intended to be used in health foods, pre-clinical and clinical studies should be designed according to internationally recognised standard procedures and published in peer-reviewed scientific journals.

This is the basic quality approach ingredient suppliers should guarantee to their customers, and, conversely, what companies should be asking their raw material suppliers to provide every time they consider adopting an ingredient for a new formula.

Taking care of gastrointestinal health, naturally

The efficacy of artichoke and ginger in functional digestive discomforts was confirmed in a randomised, double-blind placebo-controlled clinical study conducted on 126 subjects. Those who received 120mg of the active principles (100mg artichoke extract and 20mg ginger extract) twice a day before meals showed statistically significant (+34 percent) symptom relief compared to the placebo group over a short-term 14-day treatment and the efficacy was maintained until the 28th day of supplementation. Furthermore, 86.2 percent of the treated subjects reported the amelioration of Functional Dyspepsia, with a marked reduction of intensity (63.1 percent) compared with the placebo group (24.6%).[IV]

Gut diseases and gastrointestinal conditions have been demonstrated to be linked with silent chronic inflammation, one of the big challenges of our time. Humans need help in ensuring that a natural inflammatory response does not turn into low-level chronic inflammation throughout their life. In fact, according to the World Health Organization, over one third of the 57 million deaths each year worldwide are provoked by chronic diseases and 90 percent of these diseases have an inflammatory origin. As a result, understanding and controlling inflammation has become a central goal of modern clinical investigation. With specific regard to the gastrointestinal system, for example, there is a large body of scientific literature supporting the increase exercise-heat stress has on gastrointestinal damage and risk of exertional heatstroke. This happens because during prolonged endurance exercise, blood flow is mainly diverted towards skeletal muscle and skin. A recent double-blind placebo-controlled human study conducted independently by a team of American researchers at the High Point University (NC) shows that short-term dietary curcumin phytosome -based supplementation may be helpful in the maintenance of the gastrointestinal barrier integrity and physiological strain responses during exertional heat stress.[VI]

Focusing on gut health benefits, this study examined an acute supplementation regimen, where participants ingested five tablets (500mg each) of curcumin or placebo for three days prior to exertional heat stress (EHS). This dosing strategy was selected with reference to those used in two recent clinical studies, which demonstrated the positive effects of curcumin on healthy inflammatory responses to endurance cycling[VII] and on delayed onset muscle soreness.[VIII] There were two major findings in this study: first, dietary curcumin supplementation may reduce the rise in core temperature (Tc), mean body temperature (Tb), heart rate (HR) and Physiological Strain Index (PSI) during exertional heat stress; second, these changes are accompanied by maintenance in gastrointestinal barrier integrity and associated cytokine responses, as indicated by the lower circulating concentrations of Intestinal Fatty Acid Binding Protein (I- FABP) post-exercise in subjects supplemented with curcumin (58 percent vs 87 percent in the placebo group, p =0.002). This study was the first to examine curcumin for potential benefits on system-level physiology responses during exertional heat stress; these data suggest that short-term curcumin phytosome supplementation may help to lower EHS risk in non-heat acclimated individuals.

The liver is one of the most important accessory digestive gland which detoxifies various metabolites, synthesises proteins, and produces biochemicals necessary for digestion. Curcumin showed proven benefits also in the most common chronic liver disorder in Western countries (Non-Alcoholic Fatty Liver Disease), which affects 30 percent of the general adult population, and up to 60-70 percent in diabetic and obese patients. NAFLD carries a significant burden for the public health system: in a five-year population-based follow-up, the presence of people affected by NAFLD increased overall healthcare costs by 26 percent after controlling for comorbidities, and is projected to be the leading cause of liver transplantation by 2020. In a recent randomised double blind placebo controlled study that looked at the efficacy and safety of curcumin supplementation in fatty liver disorders, curcumin was able to improve liver health after just 8 weeks of supplementation reducing serum lipids and uric acid concentrations in patients with NAFLD.[IX, X]

Among the botanical supplements able to help in managing inflammation is *Boswellia serrata* gum resin, which has long been used in Indian and Chinese medicine for the treatment of arthritis, respiratory tract inflammation, diarrhoea and liver disorders.[XI] Modern pharmacological research has identified the active principles of the gum resin in boswellic acids—a series of unique pentacyclic triterpenoids.

The clinical efficacy of *Boswellia serrata* is supported by seven clinical studies showing improvement in inflammation-driven chronic conditions that include neuropathic pain (cervical and lumbar radiculopathies, lateral epicondylitis, tendinopathies) - associated also with a significant reduction of paracetamol use after seven days; reduction (up to 42 percent) of corticosteroid use in the management of asthma; and reduction of pain and oedema associated with intense exercise in rugby players.[XII, XIII, XIV, XV, XVI]

Notably, two recent clinical trials showed the great potential of *Boswellia serrata* in gut health XVII, XVIII. In particular, the reduction of discomfort in supportive care for ulcerative colitis patients in remission was observed.[XVII] All tested parameters improved significantly after treatment; mild, diffuse intestinal pain and cramps decreased in intensity and frequency in the treatment group compared with the control group and compared with baseline (P<0.05).

During the four weeks, the episodes of diarrhoea, evacuations with blood/mucus, and number of bowel movements decreased in the treatment group compared with baseline and compared with the control group ($P<0.05$). Notably, the levels of calprotectin in the stool reflected these clinical health benefits.

A second clinical study[XVIII] showed relief of IBS symptoms, namely abdominal pain, altered bowel movements, meteorism, and cramps. Irritable Bowel Syndrome (IBS) is a chronic, relapsing, gastrointestinal disorder in which abdominal pain or discomfort is associated with defecation or change in bowel habits. It affects 10-20 percent of the adult population and is often unrecognised or untreated. Considering the chronic nature of this disorder, IBS has a strong negative impact on subjects' work and social life. All IBS symptoms investigated improved during the period with *Boswellia serrata* with any IBS symptoms significantly decreasing, from 58 percent to 12.5 percent. Consistently, the number of subjects who needed medical attention significantly decreased to 4.1 percent.

Beyond bioavailability: bioabsorption

Edible plants are a paramount source of precious substances able to help in maintaining overall wellbeing, but many of them are poorly absorbed by the human body. This was a big challenge for researchers and producers.

Biomimetics is the science that studies nature and natural phenomena to understand the principles of underlying mechanisms, to obtain ideas from nature, imitating its design and processes to apply concepts that may benefit science, engineering, and medicine, to solving human problems. The concept can be explained as 'innovation inspired by nature', with many botanical dietary supplements representing these origins.

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Functional Sugars: The Nutritional Revolution

By Sergio Pumarola

Glycoscience and functional sugars are at the forefront of nutrition research as 'glyco' structures appear to play an important role in organisms. Originally seen solely as a source of energy for cells with a structural component, the study of these structures now represents one of the most innovative areas in science and may contribute to solving some of society's most prominent problems.

The classical function of carbohydrates in nutrition is related to the empirical and generic 'fibre' concept which contains very different components. One of the relevant ones involves improving or delaying the release and absorption of nutrients, usually changing the viscosity of food or the intestinal bolus but also changing the catalytic efficiencies of digestive enzymes. The other relevant component is the selective beneficial effect on microbiota.

With the development of glycoscience, there is the increasing understanding that specific carbohydrates can improve health and prevent disease, with a molecular-defined mechanism. Carbohydrates are ubiquitous in cells; they can be found on all cell surfaces, in the cytosol and nucleus of eukaryotes, and within the extracellular matrix. Complex carbohydrates monosaccharides or oligosaccharides attached to cells or other molecules (including DNA)—are involved in aspects as diverse as cell synthesis, structure, and cell to cell interactions, and play critical roles in development and disease.

While functional sugars in nutrition have great potential, they should not be considered a magical tool to confuse the population with false promises. The understanding of a healthy diet will need to go hand in hand with dialogues with regulatory bodies, education, public information, and marketing.

Beta-glucans are an example of multi-functional sugars. These natural glucose polysaccharides are found in many food sources including oats and other cereals, yeast and mushrooms, and have been shown to be beneficial for various areas of health. Beta-glucans have been shown to have cholesterol lowering properties and therefore can play an important role in reducing the risk of coronary heart disease. In 1991, the US Food and Drug Administration (FDA) approved a health claim for this effect and recommended a minimum of 3g of beta-glucans per day. Since then, studies have shown increased consumption of beta-glucans leads to a corresponding decrease in the risk of coronary heart disease. Beta-glucans from specific sources have also been found to have a beneficial impact on the immune system; they can bind to white blood cells and activate them leading to an increased natural immune defense against pathogens.

Promoting a healthy gut microflora is now understood to be important for infant and adult health and healthy ageing, as well as helping prevent allergies, infection, immune disease and chronic disease. Carbohydrate polymers can have a beneficial effect on human gut microbiota, and the oligosaccharides in breastmilk can help to improve long-term health. The prebiotic effect of 'fibres' are now linked to better-defined carbohydrates such as galacto-oligosaccharides (GOS) from bovine lactose and fructo-oligosaccharides (FOS) from plant inulins, which support the growth of the gastrointestinal microflora, changing its composition or activity, helping to improve wellbeing and health.

Examples of relevant functional sugars by the main nutritional function claimed:

Sugar release control/viscosity:

Rare sugars: L-arabinose, D-tagatose, D-psicose, D-allulose

Disaccharides: Isomaltulose, trehalose

Polyols: Erythritol

Polysaccharides: Polydextrose

Resistant starch

Fibres: Cellulose, hemicelulose, lignans

Soluble fibre: beta-glucan, glucomannan, exo-polysaccharides

Gut health/immunity:

Inulin: FOS, GOS, XOS, MOS

Oligosaccharides

Beta-glucan

Sugar release control/Low digestibility CH/Viscosity:

Rare sugars: L-arabinose, D-tagatose, D-psicose, D-allulose

Disaccharides: Isomaltulose, trehalose

Polyols: Erythritol

Polysaccharides: Polydextrose

Resistant starch

Fibres: Cellulose, hemicelulose, lignans

Soluble fibre: beta-glucan, glucomannan, exo-polysaccharides

Microbiota – Gut health - Immunity:

Inulin: FOS, GOS, XOS, MOS

Oligosaccharides

Beta-glucan

There are fewer than one dozen monosaccharides that are commonly occurring constituents of glycoconjugates in higher organisms that, once formed, can be chemically modified in various ways—for example, by acylation, sulfation or phosphorylation. Beyond the limited amount of components, the complexity of glycans comes from the branchings and variations in the connection points which are a very special feature of sugars—in contrast to nucleic acids and proteins that combine exclusively to form linear structures. Glucose, therefore, with six connection points can form (theoretically) twelve different dimers—and nearly all occur in nature—on the other hand, only one dinucleotide or dipeptide build up from one kind of monomer can exist. The combinatorics calculations over 6 to 7 sugar monomers are exponential and readily surpass manageable orders of magnitude, compared to proteins or nucleic acids, and provide the cell with an enormous arsenal of very specific signals for enabling it to communicate with its environment.

The complexity of the present glycan structures cannot be understood without the study of its origins, and the close relationship existing between proteins and sugars. Glycans are as old as—or older than—nucleic acids and proteins and it is generally accepted by scientists that the origin of glycans is closely linked to the origin of life and its evolution. Dr. Jun Hirabayashi from the Research Center for Glycoscience, National Institute of Advanced Industrial Science and Technology (AIST), describes in detail the origin of glycans, which are assumed to have been first synthesised in the form of simple homo-polysaccharides (amylose, cellulose, etc.), and are understood to have evolved into more complex hetero-polysaccharides. This evolution is assumed to have triggered the advent of proteins ('lectins') related to the 'recognition system of glycans' that recognises each structure, identifies molecules, introduces biological signaling and facilitates infections. The enormous diversity of glycoconjugates are assumed to have evolved from the continuous interaction between the different synthesis systems of glycans (glycosyltransferases and sugar-nucleotide syntheses), and the recognition systems of glycans which specifically recognise and identify glycans derived thereof (lectins, cytokines and antibodies against glycans, etc.). Synthesis and recognition systems of glycans depend on each other and are still considered to be undergoing coevolution.

But complexity is not the main obstacle to overcome in this market. Carbohydrates are substantially more difficult to synthesise and characterise compared with nucleic acids and proteins. The structural analysis of carbohydrates is still very expensive and has not been extended to the industry. We are in the dawn of being able to analyse the structure of complex sugars. It is necessary a technological revolution as was happening with genome research—reducing dramatically the costs of analysis—to be able to involve industry in this novel revolution of functional sugars, based on chirality, structural complexity and control on sugar-protein interactions.

Carbohydrates are one of the most important components in many foods but the relevant information we have is low. We get information on the approximate amount and size of the carbohydrates present in food and also if they are more or less digestible. Current technologies, including high-performance liquid chromatography, are adept at separating polysaccharides that differ in the number or type of sugars, but current technologies are not as successful at separating isomeric structures.

There are different examples of functionalities of carbohydrates that clearly need to avoid confusing consumers. For example, the traditional concept of fibre based only on digestibility has been challenged on the view that some fibres are more beneficial to the microbiota than others. The present chemical methods of analysis are not able to determine the activity differences. Companies are introducing a myriad of different fibers based on empirical analysis on relevant activity, promising consumers a guarantee of processing and sourcing in similar conditions with the hope that the activity of new batches will be maintained. The same situation happens with other complex functional sugars from natural sources. They are difficult to analyse—mainly the isomeric structures—and then it is very difficult to establish a dose-response effect to show a real health benefit to consumers—as is generally required by the regulatory authorities.

Reviewing recent regulatory approvals, it is difficult to deny the relevance of the 'glyco' substances in food innovation, as far as they represent much more than 25 percent of all Novel Food proposals approved in the European market since 2000.

The approval of trehalose in 2001 represents the first Novel Food approval related to functional sugars. Its relevant market success developing a low glycemic index market has led to further novel proposals in the next years, with isomaltulose and tagatose both in 2005. A large number of companies have been involved in this attractive market that was amenable to premium prices, for direct alternatives to sucrose.

A second group of substances in this area can be grouped around the general concept of fibres. An interesting market related to scientific backed proposals claiming health benefits related to soluble or insoluble fibers exists to compete with natural sourced food ingredients. Examples in this group were the approvals of medicago extract (2009) or wheat bran (in 2011). This group includes more technological focused substances such cyclodextrin (alfa in 2008, and gamma in 2010), dextran (2001), guar gum (2010) or methyl-cellulose (2013), although gums and cellulose are also involved in the fibre market.

One very specific application that has received the recognition of the regulatory bodies is related to supply of 'glyco' nutrients to improve resistance to cartilage, as is the case of glucosamine salts, roaster comb extract (2013) or chondroitin sulphate with a preliminary experience of use in pharma but just approved in 2017 as a Novel Food.

The frontier between food and pharma is becoming thinner. Today, the progression of science and technology has enabled a clearer understanding of the cross-kingdom communication system with the gut. The gut is now considered a sensory organ that detects messages in the food, processes the information, and then either reacts directly or transmits signals to distal organs. Gut microbiota modulation and the relationship with the immune system have attracted much attention in previous years and sugars in nature are a preferred type of molecules in cell-to-cell communication.

In 2011, the European regulatory bodies accepted the following as Novel Foods: standardised glucans from different food sources including chitin, baker's yeast or fungus, with all focusing on immune-stimulation. This positive evaluation has contributed to investments in the range of applications and novel processes in obtaining these glucans.

The increasing activity in functional sugars is opening new areas of business development, and the deeper understanding of the novel available functional 'glyco' structures from nature will continue guiding the functional food and nutritional industries to this new Promised Land.

Sergio Pumarola is an open innovation consultant.

Takeaways for Your Business

Harnessing the microbiome has long been considered the next frontier in human health but despite innovative solutions in recent years, the full potential of this sector is yet to be realised. Probiotics and prebiotics are among the most promising approaches for gut health but many botanical extracts and natural ingredients show potential in alleviating symptoms of various gut disorders. The digestive health trend continues to boom in mainstream media across the board, with the New Nutrition Business Report 2017 naming 'Digestive Wellness 2.0' as one of the key trends driving food, nutrition and health. It's clear digestive health is entering a new era thanks to new technologies and greater understanding of the effects gut health has on overall health.

Probiotics is an increasingly recognised term among consumers, as promotion of their digestive health benefits has been widespread and prolific. They have migrated from traditional foods into supplements and are now a high-demand ingredient for functional foods and beverages. Data suggests increasing health concerns are expected to play an important role in boosting growth over the next few years, while rising disposable income and increasing standards of living are expected to benefit the overall market. At the same time, the effectiveness of probiotics in improving gut-related disorders will likely drive global demand in an ageing society.

Human milk oligosaccharides are a specific carbohydrate where the potential to change the composition of the infant gut microbiome is well-documented. It is predicted that the use of oligosaccharides in infant formula will help build the most appropriate microbiome for infants, setting the foundation for the best start in life. In China, infant formula is projected to be a key growth driver of the probiotics market through 2023, and research projects infant formula with probiotics will claim a market share of 76 percent, worth €18.7 billion globally by 2024. Asia-Pacific represents the greatest market opportunity for probiotics in infant formula and probiotics in general, with this market expecting sales of €16.4 billion by 2020.

A second market with emerging potential is women's digestive health; gut health issues are a top concern among female consumers, with increased awareness that women's gastrointestinal systems and hormones require a different approach—for example, women are five times more likely than men to develop irritable bowel syndrome (IBS). As such, women are looking for added functionality to support their gut health; protein powders with added probiotics to aid digestion, and tailored dietary supplements are likely to thrive among female consumers.

Ingredients such as magnesium, omega-3s, curcumin and botanical extracts such as artichoke, ginger and *Boswellia serrata* require increased consumer education to compete with the probiotic space and should be targeted at consumers looking for help alleviating symptoms. The obvious competitor here is the pharmaceutical industry, but products with science-backed health claims and proof of efficacy will make ground quickly.

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