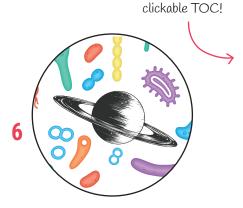
Natural Products Insider.

Probiotics and the microbiome

A *universe* of understanding continues to unfold







4

Viewpoint: Probiotics 3.0: The gut-brain axis

NPI Content Director **Todd Runestad** solves his daughter's common GI issues, and at the same time contextualizes the current innovation happening with probiotics—notably the numerous human studies that have shown improving gut bacteria composition through probiotic supplementation can improve mood, anxiety and cognition.



Guardians of the gut galaxy

Probiotics suppliers are working on an expansion of the universe of new research and new commercially available strains, writes **Lisa Schofield**. Collectively, their efforts illustrate a richly colored landscape of targeted applications to which consumers are increasingly drawn.



13

The state of innovation in the 'biotics' world

Todd Runestad culls a list of microbiomefocused ingredients that are pushing the envelope of progress, a list that includes some notable prebiotics, postbiotics and probiotic blends. 18

Probiotics in clinical practice: It's complicated

The microbiome and its relationship with human health turns out to be far more complex and nuanced than the simple stories we like to tell about it, explains **Erik Goldman**, and that subtlety can be difficult for medical professionals to convey to their inquisitive patients.



24

Microbiome: The root of wellness and the next frontier

With gut health continuing to become the center of consumers' wellness approach, shoppers are attracted to offerings with gut microbiome-supporting solutions. That means bringing new microbial strains into the fold with targeted attributes—including digestion, performance, sleep quality, balanced mood and more, describes ADM's Vaughn DuBow.

26

'Biotics,' more than a digestive health aid

SPINS' Haleigh Resetar reveals how consumers who formerly trolled the vitamin aisle for better digestive health can now find supportive products from snacks to beverages, with positioning touching on broader areas such as immunity, mood support and heart health.

Copyright © 2023 Informa Markets. All rights reserved. The publisher reserves the right to accept or reject any advertising or editorial material. Advertisers, and/or their agents, assume the responsibility for all content of published advertisements and assume responsibility for any claims against the publisher based on the advertisement. Editorial contributors assume responsibility for their published works and assume responsibility for any claims against the publisher based on the published work. Editorial content may not necessarily reflect the views of the publisher. Materials contained on this site may not be reproduced, modified, distributed, republished or hosted (either directly or by linking) without our prior written permission. You may not alter or remove any trademark, copyright or other notice from copies of content. You may, however, download material from the site (one machine readable copy and one print copy per page) for your personal, noncommercial use only. We reserve all rights in and title to all material downloaded. All items submitted to Natural Products Insider become the sole property of Informa Markets.



Don't miss the education session:

Synbiotics and the Evolving Market for Microbiome Ingredients

April 18 | 12-1pm





APRIL 18 & 19, 2023

Meadowlands Exposition Center Secaucus, NJ

supplysideeast.com

LEARN MORE

Probiotics 3.0 The gut-brain axis

y college-age daughter texted me recently. She has long suffered the typical gastrointestinal (GI) issues all too many women complain about: abdominal pain, gas, bloating, bowel movement issues.

"Dad?" she texted. "Should I be taking a prebiotic?"

Notable that Gen Z has skipped right past probiotics and now hears the siren song of prebiotic fibers—the lunchbox for probiotic bacteria—as a way toward better gut health.

Instead, I purchased for her Nature Made's Digestive Probiotics Advanced Dual Action Capsules. The supplement contains only two probiotics, but they are specific strains. One is the most-researched strain ever: Lactobacillus rhamnosus GG. known in the trade as LGG. The other: Bifidobacterium lactis HN109. One emblematic study found 1.8 billion CFUs (colonyforming units) of the HN109 strain reduced seven out of nine GI symptoms over 14 days, compared to two of nine in the placebo group.

The Nature Made product uses 2 billion CFUs. Great to see finished product brands using dosage levels that meet those found in clinical trials.

The report from my daughter: "Something is working. Like honestly helping soooo much."

Point for Dad. And point for probiotics' ability to support digestive health.

Probiotics 2.0 is the friendly bacteria's ability to support immune health—an estimated 70-80% of humans' immune cells are located in the digestive tract.

Probiotics 3.0 is the gut-brain axis. Several human studies have shown that improving gut bacteria composition through probiotic supplementation can improve mood, anxiety and cognition, with the likely mechanism of action being a reduction in neuroinflammation and influencing

neurotransmitter synthesis and release.

An emblematic 2019 double-blind, placebocontrolled study for three weeks found a fourstrain probiotic blend significantly improved mood, anger, fatigue and sleep quality. The strains were L. fermentum LF16, L. rhamnosus LR06, L. plantarum LP01 and B. longum BL04.

It's a truly fascinating story, how the body's gut and brain talk to each other. The gut influences mood, sleep, cognition and overall mental health, and it's the gut bacteria that do the talking.

Being that bacterial cells in the body outnumber regular human cells by a ratio of perhaps 10:1, it's clear that Probiotics 4.0-and more-are only needing scientific validation to demonstrate the vital role bacteria play in our health, and how probiotic supplementation can bring about health states far afield from probiotics 1.0 digestive upset.

For those of you attending the SupplySide East show, an educational session on Tuesday, April 18, will dig into this consumer-resonant and researchexpanding sector of biotics: "Synbiotics and the Evolving Market for Microbiome Ingredients."

See you there!

Todd Runestad CONTENT DIRECTOR

todd.runestad@informa.com

https://www.linkedin.com/in/toddrunestad





A PROBIOTIC BREAKTHROUGH

100% Pure ingredient 100 YEARS OF EFFICACY Science-based

100+ Clinical trials

1 St Organic Probiotic Yeast

A Classic Strain Revamped to Meet Modern Market Trends

Organic *S. boulardii* is a unique health solution offered in exclusivity by Lallemand. This innovative positioning for a classic probiotic creates new opportunities for consumers willing to make conscientious buying choices.

48%

of global consumers

are willing to spend more money for an organic product

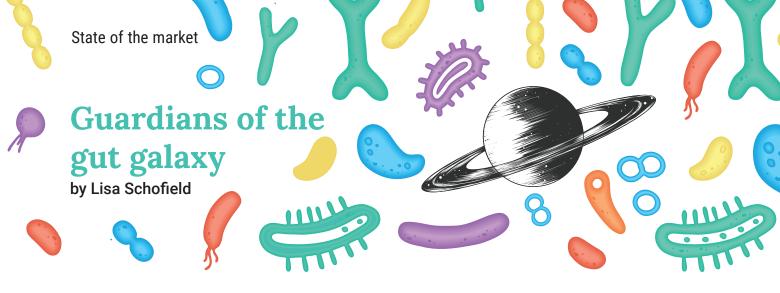
most of the time or all the time1

CONTACT US

sboulardiibylallemand.com / sboulardii@lallemand.com

¹FMCG GURUS, Country profi le survey, 25 countries, 25.000 consumers, 2021.





onsumers are now increasingly aware that probiotics have the potential to be good for them, their digestion and even possibly their immune health. On the B2B side, probiotic research development continues to link strains with new health areas and thus potential new product applications.

Innovative probiotic-containing products launched in 2023 and beyond should be welcomed by a growing number of consumers. According to the FMCG Gurus' report "Probiotics in 2021," the percentage of consumers worldwide who purchased probiotic products in a 12-month period grew by 8% in two years—from 51% in 2018 to 59% in 2020. As another way of looking at it, 6 in 10 consumers had used probiotics.

In a market survey of more than 1,000 consumers conducted in 2021 by KRC Research for Danone, 67% indicated they believed probiotics can play a role in helping with their overall health. This offers a flexible springboard for moving into condition-specific probiotic formulations.

For example, according to Bérengère Feuz, marketing director, Lallemand Health Solutions, a trending area for probiotics is metabolic health—with consumers showing a growing interest to include probiotics as part of a weight management strategy.

She pointed to an FMCG Gurus "Weight Management Strategies" report, which found that 30.1% of global consumers associated probiotics with weight management, and between February 2020 and February 2021, the online search volume for "weight management probiotics" increased by 41%.

"In recent years, many probiotic products in different health segments beyond the gut have been launched," observed Madempudi Ratna Sudha, Ph.D., managing director, Unique Biotech Ltd.

He noted additional segments include probiotics for sports nutrition, weight management and inflammation; target areas such as kidneys, respiratory function, liver, bone, mental, cardiovascular, oral and skin health; and populations including women, infants and children. Another area witnessing an upward surge and interest is probiotics in cosmetics.

The gut-brain axis and its relationship to mood is of interest to both consumers and brand marketers. Jordi Riera, chief business development manager, Kaneka Probiotics/Kaneka Americas Holding Inc., cited FMCG Gurus market research that identified one of the top 10 trends for 2023 as "Fuel my mood," into which several probiotic strains squarely fall.

Speaking of expanded opportunities, more than one physiological axis is now commonly acknowledged in the human body. According to Denis Alimonti, director of U.S. nutrition, Maypro, in

IN THIS ISSUE Table of contents p.2 Innovation nation p.13 Consumers p.26



The gut-bone axis refers to the communications between the gut microbiome and the skeletal system.

addition to the gut-brain axis, formulators should be mindful of the gut-bone and gut-skin axes, as well as the gut-vagina axis for women's health. (Maypro is the exclusive U.S. sales and marketing distributor for Fonterra's Nutiani strains.)

He explained, "The gut-bone axis refers to the communications between the gut microbiome and the skeletal system; growing evidence reveals that gut microbiota is a very important factor in bone turnover, including that of periodontal bone in dental health. The gut-skin axis involves a bidirectional relationship between the gut microbiome and skin-health regulated through inflammatory mediators and the immune system."

The increased understanding of the vaginal microbiome is spurring more manufacturers to focus on the potential benefits of probiotic consumption to improve the gut-vagina axis, Alimonti added. "The cross-talk between these two complex biological ecosystems has important effects on host physiological, immunological and metabolic homeostasis."

TARGETED PROBIOTIC RESEARCH

Probiotics suppliers are working on new research and new commercially available strains. Collectively, they illustrate a richly colored

landscape of targeted applications.
In reference to mood, a new
unpublished study led by probiotic
researcher Ralf Jaeger, Ph.D., showed that
a multistrain probiotic supplement improved

mood and sleep in 70 subjects consuming either placebo or probiotics for six weeks. Jaeger and his team also measured an increase in serotonin production in the gut. The supplement, Bifizen (from Probiotical/Ashland) contains 1 billion live cells each of *L. fermentum* LF16 (DSM 26956), *L. rhamnosus* LR06 (DSM 21981), *L. plantarum* LP01 (LMG P-21021) and *B. longum* 04 (DSM 23233).

Fonterra's omnibus survey conducted in May 2022 showed that 37% of respondents reported experiencing mood/stress concerns, the most commonly stated health concern, per Marshall Fong, senior global marketing manager for Fonterra.

A recent, 60-day unpublished study showed that consumers who supplemented with Fonterra's Nutiani HN001 strain experienced greater happiness, as assessed by the Oxford Happiness Questionnaire.

"We are currently validating those results in a larger randomized controlled trial, but the results add to those from two previous human trials demonstrating benefits of HN001 in mental wellness," Fong shared. These include a



CLINICAL TRIALS: PUTTING THE PROOF BACK IN HEALTH CLAIMS - ARTICLE

7

Dietary supplement "structure/function" claims have long been shrouded in uncertainty, limiting their utilization by companies hoping to validate and differentiate their products. Furthering the discussion, three industry experts take a hard look at the FTC's new "competent and reliable scientific evidence standard," which was expanded to emphasize the general rule that FTC expects companies to support health-related claims with high-quality, randomized controlled trials (RCTs).



randomized clinical <u>trial</u> on 423 women finding that those taking HN001 had 1/30 the risk of developing postnatal depression than those taking placebo, and a smaller randomized clinical <u>trial</u> on 33 people with prediabetes showing a significant improvement in mental wellness, as assessed by a Short Form 12 questionnaire.

SKIN-BIOTICS

Fong revealed that in early 2024, Fonterra is on track to introduce probiotic solutions for skin health, including new clinical evidence backing HN001 and a new strain with additional skinhealth benefits.

"The new science and strain will support claims related to dry, irritated skin as well as skin clarity," he shared. "This is the first stage of our efforts to capitalize on the growing understanding of the gut-skin axis to address increased consumer interest in attaining beauty from within."

Another skin-biotic, but with a twist, is offered by Sabinsa, which recently introduced LactoSporin, a postbiotic that is purified from the culture supernatant of the strain *Bacillus coagulans* MTCC 5856 (Lactospore) by a patented process. This ingredient has an INCI (International Nomenclature Cosmetic Ingredient) name—Bacillus Ferment Filtrate Extract—said Anurag Pande, Ph.D., Sabinsa's VP of scientific affairs.

In a <u>study</u>, LactoSporin was evaluated for its role in preserving skin integrity in cultured cells in vitro. It was found to be a powerful antioxidant, showing protection against ultraviolet (UV)-induced cellular damage, and it inhibited collagenase activity, "suggesting its potential use in preventing accelerated aging," Pande said.

The study also showed the ingredient inhibited the activity of the enzyme hyaluronidase, thereby preventing hyaluronic acid (HA) fragmentation, the major cause of skin moisture loss.

Additionally, he related, "increased expression of transforming growth factor-beta, and hyaluronan synthase in skin fibroblasts, suggests that LactoSporin could keep the skin moisturized and



maintain skin firmness." The study concluded the patented ingredient is a skin-protective postbiotic with the potential for wide application in cosmetic formulations.

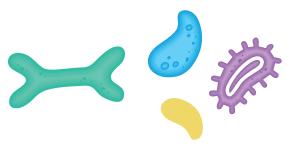
GI-RELATED STRAINS

A partnership between two probiotics suppliers has created a new symbiotic ingredient, Feuz reported. Lallemand Health Solutions and FrieslandCampina Ingredients launched PRO-Digest Health Shot, which combines 5 billion CFUs (colony-forming units) per serving of Lallemand's *B. lactis* Lafti B94 with 5 grams of FrieslandCampina's Biotis GOS (galactooligosaccharide) prebiotic.

Lafti B94 <u>supports</u> healthy microflora; reinforces gut barrier integrity; and helps with abdominal comfort, bloating and occasional constipation. Biotis GOS, a dairy-derived prebiotic, has been <u>shown</u> to influence the balance of the gut microbiota, producing beneficial effects on gut health, as well as improving gut discomfort, constipation and other GI-related issues.

According to Feuz, the partnership led to further combinations, namely PRO-Digest Bowel Support, which contains *L. paracasei* HA-196 and Biotis GOS, to improve quality of life in adults with irritable bowel syndrome (IBS)-like symptoms, helping with bowel frequency in occasional diarrhea and/or constipation. In 2022, Health Canada affirmed this study of 251 adults with different IBS subtypes via the claim that *L. paracasei* HA-196 helps support healthy bowel

State of the market



habits in adults with IBS, demonstrating efficacy in supporting quality of life with emotional well-being and social functioning.

SPORE-FORMING STRAINS

Other strains have shown viability in areas such as sports nutrition, respiratory support, stress and even facilitating the absorption of iron. For example, Unique Biotech's spore-forming strain *Bacillus coagulans* Unique IS-2 has been found to enhance the absorption of protein in resistance-trained males with a significant increase in branched chain amino acids by 33%, according to Sudha. "Moreover, there was an increase in lower body muscle power with a significant improvement in leg press and vertical jump power," she said.

In a recently completed study, Unique Biotech's spore-forming *Bacillus clausii* UBBC-07 was <u>shown</u> to enhance immunity in children as shown by a reduction in number of upper respiratory tract infections (URTIs).

In the mental health segment, Unique Biotech's multistrain probiotic formulation Cognisol (Bacillus coagulans Unique IS-2, Lactobacillus and Bifidobacterium sp.) was found to help reduce examination stress in students.

Another spore-forming probiotic is *Bacillus* subtilis DE111, from Deerland Probiotics & Enzymes (which was acquired by ADM in November 2021). According to Kristin Wilhoyte, global director of product marketing, the strain was recently shown in two separate studies from the same cohort to germinate in the small intestine after three hours post-consumption, and to act antagonistically toward intestinal and urinary tract pathogens, as well as to generate short-chain fatty acids (SCFAs) that support lower GI function.

Formulation trends **beyond** supplements



In the U.S., more than 1,700 SKUs feature probiotics across 18 dairy categories—ranging from yogurts to cheeses to milks, but largely in yogurts—proprietary Mintel data showed.

Marshall Fong, senior global marketing manager for Fonterra, noted that beyond dairy, he's seeing probiotics "pop up in a wider variety of formats, including energy drinks, juices, ice cream, sauces, spreads, chocolate, nutrition bars and infant formula."

Kyle Griffiths, VP sales and marketing at CSL, believes probiotic-enhanced foods and drinks "such as waters, smoothies, chocolates and ice creams" are viable alternatives to probiotic supplements.

Jordi Riera, chief business development manager, Kaneka Probiotics, concurred consumers and brands have shown an

increased interest in having probiotics appear in more diverse foods. "This interest, however, is challenged by the technical difficulty of keeping valuable probiotic strains stable and efficacious in the context of high heat and moisture environments involved in the food and beverage processing," he pointed out.

Some types of probiotics are up to that challenge—notably, spore formers. ADM/ Deerland's DE111 has been tested and shown to survive the stomach environment, as well as remain viable under a wide temperature and pH range. Kristin Wilhoyte, global director of product marketing, reported that in stability testing, DE111 experienced virtually no loss of colony forming units (CFUs) over 24 months when stored at room temperature (25 C and 77 F).

Probiotics have ventured into topicals, working with the skin microbiome. Griffiths observed an increase in "probiotic skin care products where they are being used for their potential to improve the appearance and health of the skin, such as reducing redness, promoting acne resolution and reducing the signs of aging."

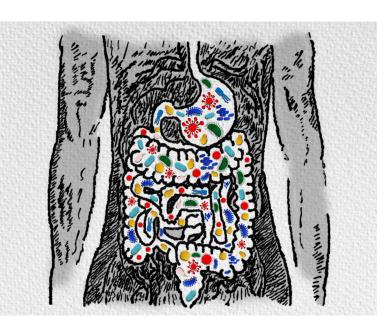
WIDE-RANGING HEALTH EFFECTS

In 2022, CSL USA Inc. (i.e., Cultures Supporting Life) published five clinical studies, according to Kyle Griffiths, VP sales and marketing.

One clinical <u>study</u> showed that Synbio (CSL's blend of two *Lactobacillus* strains) reduced the chronic inflammation generated by the aging process, sometime referred to as inflammaging. In another trial awaiting publication, Synbio revealed its capability to reduce bacterial vaginosis and to promote healthy vaginal eubiosis.

IMC510, a new strain from CSL, has been recently shown to support weight management. The first <u>study</u> was a proof of concept on a small sample of subjects, Griffiths noted. This was followed by a confirmation <u>study</u> on 40 people, where the ingredient demonstrated to support aspects of weight, waist circumference and body mass index (BMI), even when taken without a calorie-restricted diet.

CSL has partnered with ProbioEtna, a startup focused on microbiome solutions for women's health. A 2023 <u>study</u> on *Lactobacillus rhamnosus* CA 15 demonstrated superior ability in combatting bacterial vaginosis and vulvovaginal candidiasis, restoring a healthy vaginal microbiota after just 10 days of administration, according to Griffiths.



In a market survey of more than 1,000 consumers conducted in 2021 by KRC Research for Danone, 67% indicated they believed probiotics can play a role in helping with their overall health.

STRAINING SUPREME

Remember when probiotics always needed to be refrigerated and pretty much the only kind were simply labeled *Lactobacillus acidophilus*? Primarily, it all stopped at the species.

"The challenge for consumers has historically been that products don't list the strain, and in those cases, there's no way for them to know if the product has been scientifically shown to have a benefit," Fong commented.

In 2023, it is not enough to formulate simply with acidophilus because consumers are catching on and expecting specific strains. According to Pande, today, technologies such as polymerase chain reaction or 16SrRNA sequencing allow identification of the bacteria to strain levels, considered as a subtype of a species. Each strain possesses characteristic features or traits that differentiate them from other subtypes or strains. The benefits of one strain may not occur in another strain of the same species.

Fong believes strain development is critical for continued growth in probiotics. "Fonterra has several strain-development projects in place and plans to launch new strains later this year," he revealed.

CSL's internal R&D, in collaboration with universities and research centers, has engineered a platform to isolate, screen and identify specific strains with the compelling potential to bring



health benefits in a wide range of applications, Griffiths mentioned.

"It all starts with identifying the target mechanism of action that our ideal strains should have to exert the health benefit," he elaborated. "We then screen our genome bank to identify potential candidates and perform some initial in vitro assays to find those that can express the highest activity. We then move the candidates into a strain-development process to evaluate the ability to industrialize the strain at the highest quality, potency and stability. The last step is to use the new probiotic candidate in a clinical study to demonstrate its efficacy."

New strains are discovered and tested at a rapid clip. A new study illustrated how strains

are initially examined. The researchers started by screening 17 *Lactobacillus* strains based on their starch hydrolysis and glucoamylase activities; this number was whittled down to five (*L. fermentum* KGL4, *L. rhamnosus* RNS4, *L. fermentum* KGL2 and *L. rhamnosus* KGL3A). KGL2 and KGL3A demonstrated the strongest antioxidant capacity, according to the study authors, while KGL4 and KGL3A exhibited possible ability to adhere to the intestinal epithelium, as well as to potentially influence immune function.

As consumers worldwide just want to be healthy and enjoy their lives, probiotic products are being shown and validated to adequately serve as overall health and wellness guardians.



Lisa Schofield is a veteran writer and editor who got her start interviewing rock stars for national music magazines. She now writes and edits content for B2B media and suppliers in the natural health product industry. She has served as editor for Vitamin Retailer and Nutrition Industry Executive, and prior to that as associate editor for Whole Foods.



THE PREBIOTICS OPPORTUNITY HAS ARRIVED - VIDEO

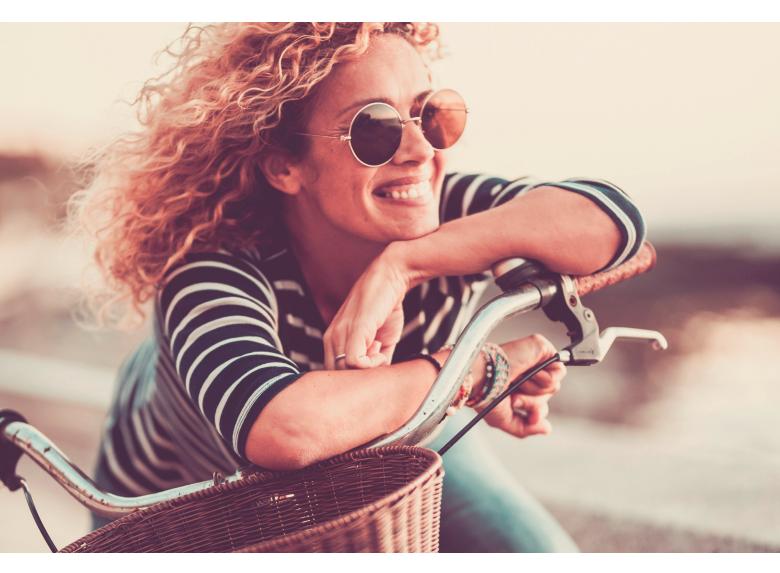
11

More than merely the lunchbox for probiotic bacteria, prebiotic fibers offer functionality as a stable binder for bars, a low-cal sweetener option for beverages, and a fiber source for all foods and beverages. Want proof that they have entered prime time?

WATCH







The Future Is Bright

PROBIOTIC SUPPORT FOR IMMUNE HEALTH

MuniSpore delivers support for the immune system starting in the gut, where about 70% of the immune system resides.

More than 20 studies have been performed to confirm the safety and efficacy of MuniSpore, the probiotic spore *Bacillus clausii* CSI08. This highly stable, science-backed strain has been shown to provide support for a healthy immune system by crowding out unwanted bacteria and providing antioxidant activity.





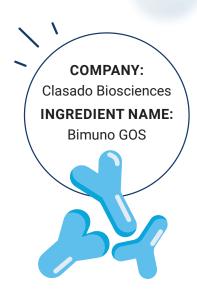


The state of innovation in the 'biotics' world

by Todd Runestad



PREBIOTICS



WHAT IT IS: Galactooligosaccharide (GOS) with 20 human clinicals on gut, immune support and cognitive health, including symptom relief of irritable bowel syndrome (IBS), inflammation biomarkers, increasing activity of natural killer (NK) cells and supporting the gut-brain axis.

EMBLEMATIC SCIENCE: An early <u>study</u>, from 2008, found Bimuno GOS was superior to a traditional GOS in increasing bifidobacterial species and at a lower dose. A 2015 double-blind, placebo-controlled, randomized <u>study</u> for 10 weeks using 5.5 g/d on 40 elderly subjects age 65-80 found positive influence on gut microbiota, immune parameters and metabonomics, suggesting use in positively affecting the microbiota and markers of immune function associated with aging.

INNOVATION: Targeted prebiotic with a proprietary composition of GOS has a unique blend of qualities that feeds and stimulates the growth of *Bifidobacteria*.

MARKET POTENTIAL: Considered GRAS (generally recognized as safe) for use beyond nutraceuticals: dairy goods, baked snack products and beverages.



WHAT IT IS: Tributyrin, the primary active ingredient, is GRAS as a food additive that, once cleaved in the body, releases butyrate—a key short-chain fatty acid (SCFA) that acts as a critical signaling molecule for improving gut health and effects on other organs via the gut-brain axis.

EMBLEMATIC SCIENCE: Early <u>clinicals</u> confirm ButyraGen's ability to increase blood levels of butyrate.

INNOVATION: This next-gen prebiotic is a direct butyrate generator independent of the underlying state of a person's microbiome. Produced with minimal fermentation means less gas and bloating. Works well with synergistic probiotics to further increase butyrate as a true synbiotic formulation.

MARKET POTENTIAL: The recent interest and increased awareness around the functionality and benefits of butyrate create an opportunity for brands to incorporate butyrate-generating ingredients across product lines.

IN THIS ISSUE Table of contents p.2 State of the market p.6 Sales channels p.18



WHAT IT IS: A dual-prebiotic fiber of inulin and xylooligosaccharides (XOS), along with magnesium, that promotes gut microbiome diversity—in particular *Bifidobacterium*—through both the distal and proximal colon.

EMBLEMATIC SCIENCE: The combination of 1 g XOS with 3 g inulin modulated both the intestinal environment and immune status, including attenuating the proinflammatory effects of a high-fat diet, while 5 g XOS alone showed only prebiotic properties (increased concentrations of bifidobacterium and butyrate).

INNOVATION: Working with U.K. leaders in the areas of the microbiome, nutrition and metabolism, Wellbiome holds three patents related to its formulation, manufacture and application.

MARKET POTENTIAL: At a suggested dosage of 5.1 g/d, it is targeted to: individuals over the age of 40 to maintain gut health, stressed individuals to improve microbiome resilience and recovery, and athletes or active individuals to be taken preor post-workout to help improve performance or prevent risk of injuries or illness.



WHAT IT IS: A kiwi fruit-based prebiotic containing the proteolytic enzyme actinidin that aids in protein digestion.

EMBLEMATIC SCIENCE: Green kiwifruit, which contains the enzyme actinidin, can provide enhanced upper-tract digestion, particularly gastric, of a variety of food proteins, particularly those in yogurt, cheese, fish and raw eggs.

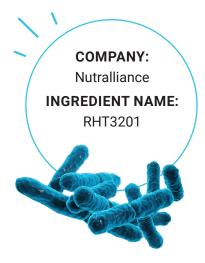
A follow-up double-blind, placebo-controlled study found finished products containing a green kiwifruit extract provided significant improvement for constipation and the symptoms of IBS, such as bloating, gas and abdominal pain.

INNOVATION: A gentle water extraction technique avoids the use of synthetic solvents, while standardization of both enzyme content and soluble fiber helps formulators with accurate dosing levels.

MARKET POTENTIAL: With the growing use of protein powder supplements, complex vegan meats and dairy/alt-dairy proteins, a need exists to address healthy digestion and breakdown of those complex proteins.

2

POSTBIOTICS

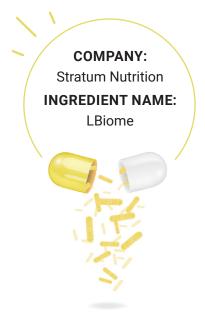


WHAT IT IS: Scientifically and clinically validated postbiotic ingredient with an anti-allergy effect that has a new dietary ingredient (NDI) filing and Korean FDA functional ingredient approval.

EMBLEMATIC SCIENCE: An optimal heat-treated temperature was established on *L. rhamnosus* IDCC 3291 isolated from Korean infants fed breast milk, then the bacterial cells enumerated for maximum effect, with positive results seen in a <u>12-week study</u> of children ages 1-12 with moderate atopic dermatitis. The randomized, double-blind, placebo-controlled study found no differences in safety parameters between the two groups.

INNOVATION: Standardized postbiotic ingredient made with patented technology and certified under various regulatory agencies, including FDA and KFDA.

MARKET POTENTIAL: Useful in supplements, beverages and foods, RHT3201's certifications—along with the completed and ongoing research—shows the company's continued efforts to bring to the market a high-quality product, keeping in mind the needs of the market and consumer base.



WHAT IT IS: A postbiotic ingredient standardized to 60 billion heat-treated inanimate cells of human-derived *Limosilactobacillus fermentum* and *Lactobacillus delbrueckii* per gram, while also containing all products and metabolites of fermentation.

EMBLEMATIC SCIENCE: Adhering as soon as it is in contact with the gut lining enables fast efficacy, which has been validated in 40 published studies on mechanisms and efficacy, including 12 human clinicals demonstrating digestive support in <u>adult</u> and <u>pediatric</u> populations, in particular to help "slow the go."

INNOVATION: Discovered in the early 1900s in France, LBiome was ahead of its time, with decades of international use before the word "postbiotic" was even a recognized scientific term.

MARKET POTENTIAL: Consumers want the digestive benefits of probiotics but are gravitating toward delivery formats that are unfriendly to viable organisms. Suitable for most chews, gummies, ready-to-drink (RTD) liquids, powders, bars, confections and most other functional foods and delivery formats—with a benign taste profile.

2

PROBIOTIC BLENDS



WHAT IT IS: *B. animalis* subsp. *lactis* CECT 8145 and its heat-treated counterpart BPL1 HT with particular efficacy for weight management applications.

EMBLEMATIC SCIENCE: A <u>study</u> showed impact on visceral fat reduction, a healthy waist circumference and metabolic health pathways.

INNOVATION: Its postbiotic form is capable of nearly limitless formulation applications because of the BPL1 strain's innate robustness, and formulators don't have to make adaptations for live colony-forming units (CFUs) as compared to traditional probiotics.

MARKET POTENTIAL: Because it undergoes a heat-treated process and contains nonviable microorganisms, it can withstand harsh formulation environments like high heat in baked goods and snacks or pasteurization in dairy products or energy drinks.



WHAT IT IS: A patent-pending probiotic complex designed for the support of the immune system, composed of *L. plantarum* PBS067, *L. acidophilus* PBS066 and *B. lactis* BLO50, safe for nutraceutical applications.

EMBLEMATIC SCIENCE: A four-week, double-blind, placebo-controlled study—with an additional four-week follow-up—of 50 healthy adults <u>showed</u> increased antioxidant capacity, enhanced antimicrobial peptides and greater production of B vitamins for normal immune system support. Supplemented group experienced half the incidence and persistence of symptoms around respiratory, gastrointestinal (GI) and musculoskeletal seasonal illnesses, which continued through the follow-up period.

INNOVATION: SynBalance screens its library of property probiotic strains through different in vitro assays in order to select the best-performing ones for a specific field of interest, and then tests them in clinical trials.

MARKET POTENTIAL: The ingredient feeds nicely into today's "healthy living" goals, with an emphasis on a proactive and preventive approach to well-being. ◆





Documented. Perfected. Trusted.

THE ONE AND ONLY BB-12®

The quality, potency, and documented health benefits of Chr. Hansen's BB-12® are key to deliver what you and your consumers expect.

Leveraging more than 145 years of expertise, Chr. Hansen has pioneered probiotics for decades and has been perfecting the production and distribution of BB-12 $^{\circ}$ since first discovering the strain.

Ensure that your consumers always experience the expected health benefits by choosing Chr. Hansen's BB-12®.





Probiotics in clinical practice: It's complicated

by Erik Goldman

robiotics and the microbiome ... it used to be so simple.

There were "good bugs"—friendly flora that created a gastrointestinal (GI) environment conducive to robust digestion, regular bowel movements and overall health. There were "bad bugs," microorganisms that disrupted the gut, causing all sorts of unpleasant symptoms.

And there were probiotics—good bugs in a pill or capsule. Take some of those, tip the scales in favor of the friendlies, and health and longevity is yours ... just like those happy Eastern European villagers in the old yogurt commercial.

It was a wonderful, easy-to-communicate, good-versus-evil narrative, and it caught on with the public. Suddenly, the microbiome—an arcane little province of microbiology—became Facebook fodder, as millions worldwide began bantering about concepts like "the second brain" and "dysbiosis."

Alas, like so many other aspects of life, the microbiome and its relationship with human health turns out to be far more complex and nuanced than the simple stories we like to tell about it.

For medical professionals, this has created a significant challenge. Patients come in asking simplistic questions, like, "Doc, should I take a probiotic?" and, "Which is the best probiotic for me?" But the sheer volume of probiotics now available, and the vast variety of strains,



has made these questions difficult to answer in simple sentences.

Microbiome research has exploded over the last 20 years, and it has shown that gut microbes—and there are lots of them—can influence an astonishing range of human functions: appetite, sleep cycles, glucose metabolism, hormone regulation, immunity and mood, just to name a few.

Dan Merenstein, M.D., professor of family medicine at Georgetown University and director of the school's research programs in family medicine, has headed 10 probiotic studies since 2006. He's witnessed the gradual mainstreaming of probiotics, and also the increasing complexity of the story.

Merenstein said evidence exists that many common disorders—including asthma, atopy, diabetes, obesity, colon cancer, ulcerative colitis, irritable bowel syndrome (IBS), rheumatoid arthritis (RA) and various liver diseases—are associated with changes in the gut microbiome. Compared with healthy people, those with these diseases show distinct alterations in their gut flora.

What's less clear is whether the relationship between microbiome changes and disease is causal, and whether probiotic treatments would have meaningful clinical impact.

"It's possible that people with ulcerative colitis get the disease and then their microbiome

IN THIS ISSUE Table of contents p.2 Innovation nation p.13 Formulations p.24



Probiotics are not drugs, suppressing or amplifying a particular biological function. Rather, they are changeagents that cause shifts in the microbial ecosystem.

changes, or it's possible that the microbiome changes and then they get the disease. We haven't figured that out—yet," Merenstein stated. "But there's a lot of interest in this because if we can change people's microbiomes, we could potentially treat things like ulcerative colitis or obesity."

One of the interesting things about microorganisms is that the same bug can have multiple effects on humans. For example, in the context of antibiotic-associated diarrhea—one of the most common conditions for which people take probiotics—a strain of *Bifidobacterium* (*B. lactis* HN019) can reduce bowel movement frequency, thus mitigating diarrhea. Yet in the context of constipation, that same bug may actually increase bowel movement frequency.

From a pharmaceutical
perspective, where a drug has
a discrete and one-directional
mechanism of action, this seems
paradoxical. But it makes sense if one keeps
in mind that probiotics are not drugs, suppressing
or amplifying a particular biological function.
Rather, they are change-agents that cause shifts
in the microbial ecosystem.

"Probiotics tend to normalize things," added Arthur Ouwehand, Ph.D., adjunct professor of microbiology at the University of Turku, Finland, and one of the world's experts on probiotics and their impact on human health. He is a member of the scientific advisory team for HOWARU, a line of proprietary probiotic strains from International Flavors & Fragrances (IFF).

"It's about balancing back to a normal state," Ouwehand explained. "Probiotics are not like drugs that push only in one direction: A laxative is always a laxative. It always pushes in the same direction whether necessary or not. But probiotics push toward the middle, toward balance."

'WHAT PROBIOTIC SHOULD I TAKE?'

The honest answer to the question, "What probiotic should I take?" is, "It depends on what outcome you're hoping to reach." And that means practitioners need to understand the unique biological activities of various species

and strains. That's no easy task, given the ongoing deluge of new research.

The rapidly evolving sciences of genomics and metabolomics have given microbiologists tools to characterize specific probiotic organisms and their bioactive metabolites down to the molecular level. The challenge is in translating these bewildering details into practical, clinical recommendations.

Further complicating the picture is the fact that "the microbiome" is not a single entity confined to the gut, but a network of interrelated ecosystems all over the body. There's a microbiome on the skin, in the mouth, the lungs, the conjunctiva of the eyes, the biliary tract, the mammary glands, and the genitourinary tract. These invisible worlds interact directly and indirectly with each other, and with all the major human organ systems.

Take, for example, the relationship between the gut and the vaginal microbiota. These two ecosystems are distinct and unique. One main difference between them is that in the gut, high microbial diversity is a sign of health, while in the vagina, it means something's wrong. But the two ecosystems are interconnected. They interact directly and indirectly, and both can profoundly impact a woman's well-being.

Dysbiosis in the gut, the vagina or both is associated with a wide range of disorders. Bacterial vaginosis and vulvovaginal candidiasis are the most obvious ones, but microbiome changes have also been linked to infertility, fallopian tube inflammation, elevated risk of papillomavirus and HIV infection, premature rupture of membranes, failure of in vitro fertilization, cervical dysplasia, depression, anxiety and gestational diabetes.

And guess what? These microbial ecosystems change over a lifetime. As much as commensal microbes influence human physiology, they are also influenced by dietary, environmental, hormonal and lifestyle factors. In and of itself, aging alters microbial ecosystems.

Timothy "Ted" Dinan, Ph.D., and John Cryan, Ph.D., of the APC Microbiome Institute, University College Cork, Ireland, one of the world's leading microbiome research centers, noted the gut microbiota tends to change as people age—and usually for the worse. Aging is associated with "a narrowing in microbial diversity," and especially a decline in friendly bacteria that correlates with declining health status.

Age-associated microbial changes are <u>implicated</u> in declines of innate immunity, muscle mass and cognitive function.

For example, University of Helsinki researchers analyzed the microbiota of 72 elders with Parkinson's disease, compared with 72 matched controls. They found marked reductions in *Prevotellaceae* species in the Parkinson's patients. A correlation also was shown between elevated levels of *Enterobacteriaceae* and severity of postural instability and impaired gait.

Again, it is not yet clear whether that relationship is causal. But the available data do suggest that, at least for neuropsychiatric disorders, treatments targeting the gut ecosystem (microbiota transplantation, antibiotics, probiotics) could play a therapeutic role.

Hot off the presses!

We cover probiotics day in, day out.

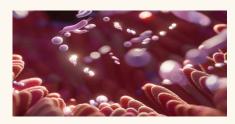
Click a story below to see enhanced coverage of these topics.



BIOTICS EXPAND THROUGH STORES

Dec. 13, 2022

Market research reveals consumers keen on a healthy microbiome.



PREBIOTICS AND FERMENTATION

Jan. 13, 2023

Ferming helps build—and support—digestive ingredients.



PROBIOTIC STRAINS 101

Jan 16, 2023

Formulators can innovate by matching pro's and pre's.



HOLISTIC AGING FROM THE INSIDE OUT

Jan. 23, 2023

20

Probiotics can play the healthy aging game, too.

COMPLICATING FACTORS WITH PATIENTS

The vision of effectively treating debilitating diseases with something as simple as probiotic supplements is tantalizing. But all too often, when probiotics are subjected to clinical trials, the outcomes are far more modest and equivocal than the observational, epidemiologic and animal studies led us to expect. In actual clinical practice, the impact of probiotic supplementation can be highly variable.

Many reasons are behind this. A big one is strain specificity. The biological activity of a particular organism is highly strain specific. For example, a particular strain of *Latobacillus reuteri* (*L. reuteri* DSM1793) is able to quell lipopolysaccharide-induced inflammation in small intestinal epithelial cells. But other strains of *L. reuteri* don't have this effect, Merenstein explained.

The *L. rhamnosus* GG strain can <u>stimulate</u> production of anti-inflammatory cytokines and reduce pro-inflammatory signals. But not all *L. rhamnosus* strains can do this. "One strain's evidence is not evidence of another strain's efficacy," Merenstein asserted.

This means that when choosing probiotics, practitioners and their patients really need to pay attention to the strains used in formulations to ensure they are actually the ones backed by solid clinical data. The problem is many commercially available products do not display strain-specific information on their labels. (Not to mention the difficulty in communicating actual evidence-based results in a supplements regulatory structure that allows only structure/function claims.)

Merenstein noted 42 of 93 (45%) off-the-shelf products he looked at did not provide strain designations, lamenting, "It's impossible to know what's in the product or what evidence exists for it."

Another complicating factor is the complex interrelationship between diet and microbiome. According to gastroenterologist Kenneth Brown, people who habitually eat a lot of refined carbs, trans fats, sugar and highly



You cannot simply probiotic your way out of conditions you Burger King'd your way into.



processed foods will have a very different gut ecosystem than people who eat healthy plant-rich diets. The microbiome adapts to what someone is eating.

A former antibiotic drug researcher, Brown shifted into natural products several years ago with the launch of Atrantil, a combination of three botanicals—quebracho colorado, horse chestnut and peppermint—which can mitigate production of methane gas in the small intestine. Recently, Brown partnered with Microbiome Labs on a new formulation that combines that company's sporebased probiotics with Atrantil.

Based on observing his own patients, Brown said people often fail to get full benefits from probiotics because they don't make the dietary changes that create a conducive environment for friendly gut bugs. Likewise, people who make radical dietary changes often get frustrated because their digestive systems—conditioned by

years of fast food—are not able to break down and fully assimilate the healthy fibrous stuff they're now eating.

"You need to change their microbiome and their diet together. It's not an either-or. You can't just change one and not the other," Brown suggested.

In other words, you cannot simply probiotic your way out of conditions you Burger King'd your way into.

IDENTIFIABLE REASONS FOR RECOMMENDING PROBIOTICS

ANTIBIOTICS: In the clinical setting, one of the strongest indications for probiotics is to reduce the side effects of antibiotic drugs, especially diarrhea. But this begs important practical questions: If antibiotics cause GI disturbance by killing "friendly" bugs, won't they also kill off the probiotics? Can probiotics and antibiotics be taken simultaneously, or should they be taken at different times of the day?

Ouwehand, who has studied these questions in depth, said it is a good general rule to allow a few hours' time between antibiotic and probiotic doses. But several studies have shown that they can be taken concurrently, with little risk that the drug will obliterate the probiotics. That's because most antibiotics are highly targeted in the types of microbes they can kill. Even the so-called broad-spectrum ones don't kill everything.

Plus, antibiotics kill only metabolically active microbes. Most probiotics used in supplements are freeze-dried, so they're metabolically dormant when ingested, and need time to resuscitate. Therefore, they're unlikely to be damaged by an antibiotic drug.

IMMUNITY: Should everyone routinely take probiotics for immune system support?

Merenstein said there's reason to believe they should. "They've (probiotics) been shown to decrease sick days associated with GI and respiratory (infectious) illnesses.

He and his colleagues reviewed 17 randomized clinical trials, looking at the role of probiotics in preventing acute respiratory tract infections, acute lower digestive tract infections, or acute otitis media. They found that among infants and children, there was a 29% decrease in the likelihood of needing an antibiotic prescription in the probiotic-treated versus the control groups. When they narrowed their analysis to the five studies with the lowest risk of bias, they found a 54% decrease in antibiotic prescriptions for these three common infections.

VALUE: The Georgetown group also used data from two well-executed meta-analyses looking at trends in respiratory infections to <u>estimate</u> the potential cost-savings if probiotics were used more widely. Their model showed if Americans routinely took probiotics for immune system support, it would result in an estimated cost-savings of \$3.73 billion to \$4.6 billion in total health care costs annually, and avert upward of 19 million sick days just from respiratory infections alone.

"The data are there for probiotics," Merenstein said. But he stressed that while metanalyses are excellent for detecting general trends, they seldom give the sort of species- or strain-specific information that clinicians really need.

Medical understanding of probiotics and the microbiome is already vastly more complex than it was 20 years ago, and that trend is likely to continue as research expands. Clinicians working in the field say we're still far from reaching the full potential benefits that probiotics promise, but things are moving in the right direction.

















Erik L. Goldman is founding editor of Holistic Primary Care-News for Health & Healing, a medical publication serving 60,000 health care professionals. He has also written and edited medical textbooks, monographs, and a wide range of print and digital medical education media. You might catch him on late-night walks around his beloved New York City.



Passion for probiotic performance

Creating effective, documented and reliable probiotics that benefit your consumer's health

At Probi®, our passion for science and people has transformed us into pioneers. We are driven to challenge the status quo in a never-ending search for innovative ways to improve human health.

That's why our dedicated teams of experts are involved from the study design throughout the manufacturing process, providing effective probiotics that are clinically proven to support health and wellbeing.

Contact us or read more about our focus on clinical studies, reliable solutions, and what we can offer at www.probi.com.

Probi[®]

Microbiome: The root of wellness and the next frontier

by Vaughn DuBow



lobally, 58% of consumers perceive a connection between the function of the bacteria in the gut to wider aspects of well-being, per proprietary ADM Outside Voice research. As they seek greater control over their personal health, consumers are looking for gut microbiome-supporting solutions and offerings to meet individual health and wellness goals.

With gut health continuing to become the center of consumers' wellness approach, shoppers are attracted to offerings with gut microbiome-supporting solutions, including prebiotics, probiotics and postbiotics. Bringing new microbial strains into the fold with targeted attributes—including digestion, performance, sleep quality, balanced mood and more—can further elevate personalized offerings.

Convenience, choice and variety are key attributes to encourage consistency in adding

specialized nutrition to everyday routines. Health and wellness brands have an opportunity to combine various functional ingredients such as fiber, "biotics," protein, botanicals, and vitamins and minerals into one food, beverage or supplement to help target multiple wellness attributes in a single offering.

The gut microbiome is and will continue to be an important aspect of health and wellness, having captured the attention of both the scientific community and the general public in recent years with exciting discoveries that may support specific needs as we enter the next frontier of wellness support. When combined, these emerging trends and developments in the microbiome space have created widespread global consumer interest, as well as a market ripe with opportunity and high growth potential for ingredient suppliers and CPG brands.

For an <u>expanded version</u> of this story on natural products in sider.com, click the link.



Vaughn DuBow is the global director of marketing, microbiome solutions, at ADM, where he drives demand and innovation for ADM's wide variety of cutting-edge microbiome solutions. DuBow came to ADM with over 15 years of experience, with his most recent role as the global manager of sports nutrition ingredients at Lonza. He also has an MBA from Western Governors University

IN THIS ISSUE Table of contents p.2 Sales channels p.18 Consumers p.26

Kaneka PROBIOTICS



Real Probiotic Solutions for Specific Health Targets



BABY COLIC



INTENSIVE G.I.



CARDIO HEALTH



WOMEN HEALTH



IMMUNE HEALTH



LIVER HEALTH



BRAIN HEALTH



GUM HEALTH



SKIN HEALTH



I WEIGHT MANAGMENT

Quality Standards



Patented products



Clinically-tested and safe



Naturally-ocurring



Allergen-free



Shelf stable



No modified genetically



Generally recognized as Safe (FDA) and/or Natural Product Number (Health Canada)

Kaneka Americas Holding, Inc. | Probiotics Division

Contact Us! | sales@kanekaprobiotics.com | kanekaprobiotics.com

'Biotics,' more than a digestive health aid

by Haleigh Resetar

hether consumers are scrolling through a shopping app or strolling through the aisles at their local grocery store, products packed with probiotics and prebiotics are lining the shelves.

Traditionally, "biotics" have been found in the vitamins and supplements section and were tailored to those looking for support in their efforts to "aid their gut" or better their digestive health. Now, however, they can be found in products from snacks to beverages, with positioning touching on broader areas such as immunity, mood support and heart health.

THE ORIGINAL - PROBIOTICS

Probiotics were the starter bacteria for many shoppers and consumers looking at improving their digestive health because of their availability in stores and their notability in the industry. Over the last three years, probiotics have continued to grow in popularity, with an increasing interest in prioritizing microbiome health. The most popular departments for these -biotics are vitamins, supplements and refrigerated.

In the VMS (vitamins, minerals and supplements) category, probiotics accounted for more than \$1 billion in revenue year over year (YOY); and in the refrigerated department, products with probiotics have surpassed \$6.4 billion in revenue (SPINS Natural Enhanced + MULO channels powered by IRI). Growth in both departments can be expected because of traditional probiotic supplements and the natural probiotics in dairy products such as yogurt, but other categories have been integrating these



bacteria with overwhelming success in more unexpected ways.

Incorporating functional ingredients into beverages has been one of the hottest trends in both the conventional and natural product industries, and probiotic sodas are no exception. Probiotic soda has grown significantly over the last three years, culminating in \$4.6 million in revenue and 41.8% in dollar growth. Many consumers have been consuming these bubbly concoctions as an alternative to kombucha because they offer flavors that rival their favorite traditional soda brands, including cola and cherry vanilla.

The idea of making snacks both tasty and healthy is not new, but the types of ingredients being added to these products is changing every day as brands innovate within the category to come up with ways to make even the most unsuspecting snack nourishing. Crackers and crispbreads are one of these product areas that are growing when it comes to probiotic products, with 20.1% growth and \$2.4 million in revenue. In addition to having probiotics, many of these brands will also sport other attributes that consumers are looking for such as being grainfree or keto-friendly.

Apart from products with added probiotics, options naturally containing probiotics are piquing consumer interest. For instance, kimchi has grown 19.8% in dollar growth with \$42.4

IN THIS ISSUE Table of contents p.2 Formulations p.24 Sales channels p.18

11

million in total revenue, as shoppers broaden their palates with international flavors and seek out products with natural probiotics. Sauerkraut is another fermented food consumers are adding into their routine with 88% growth and \$55.56 million in revenue.

NEWCOMERS - PREBIOTICS

While prebiotics aren't necessarily "new," their presence in grocery stores and their recognition by consumers was not nearly as pronounced as their probiotic counterparts until more recently. Prebiotics have become very popular in the pet channel, growing at 6.5% with \$1.58 billion in revenue, specifically rising in pet food. This goes along with the trend of consumers wanting to provide their pets with quality products that follow their own personal priorities.

Similar to probiotics, soda has been a huge market, with prebiotic sodas growing at 233% and \$79.9 million in revenue. Snacking is also a popular market for prebiotics, with granola and snack bars bearing the most growth at 15.8% and \$544.2 million in revenue. Shoppers are wanting an easy way to integrate functional ingredients into their everyday life while simultaneously replacing their less healthy products with wellness-focused ones.

WORKING TOGETHER

Probiotics and prebiotics can often both be found in products (known in the industry as

"synbiotics"), working together

Snacking is also a popular market for prebiotics, with granola and snack bars bearing the most growth at 15.8% and \$544.2 million in revenue.



to help consumers with their designated health concerns. Products containing synbiotics have grown 2.3% with \$1.3 billion in total revenue. The fastest-growing departments include frozen at 88%, refrigerated at 22.9% and grocery at 11%. While VMS is still an important department for these ingredients and is positively growing at 8%, consumers are looking for products that serve more than one purpose.

In 2023, we expect to see beneficial bacteria maintain popularity—particularly growing outside of the VMS space—and we will continue to watch for innovation in other departments.



Haleigh Resetar is a West Virginia native and graduate of West Virginia University with degrees in journalism and integrated marketing communications. As a member of the SPINS marketing team, she manages the social media profiles for SPINS and ClearCut Analytics accounts, contributes content to the company blog, and acts as the primary contact for media data requests.

Natural Products <u>Insider</u>.

Contact us here

Natural Products Insider leads CPG brands from ideation through manufacturing, supporting the development of innovative, healthy and compliant products in the dietary supplement, functional food and beverage, and sports nutrition industries. As an official content provider for SupplySide, Natural Products Insider connects ingredient buyers and suppliers with executives across the health and nutrition marketplace.

