GUT MICROBES AND EXPLORING PROBIOTICS

Yakult's probiotics research investigates THE DIVERSE IMPACT OF GUT MICROBES on human health.

On the morning of 9 June 1904, the French press was abuzz with excitement about a scientific lecture given the day before by Russia-born microbiologist, Élie Metchnikoff. Four years later, he would be jointly awarded the Nobel Prize in Physiology or Medicine, along with Paul Ehrlich, for their pioneering research in immunology. But in 1904, the attention was all on yoghurt. Metchnikoff, who worked at the Pasteur Institute in Paris, suggested that the longevity of a rural Bulgarian community was linked to the live bacteria in a sour milk that reduced ageing-related effects caused by harmful bacteria in the gut.

"It is often said that Metchnikoff was the first advocate of probiotics in the early 20th century," says Toshihisa Ota, the science representative at Yakult Honsha's Public Relations Department. "Several decades later, Yakult's founder, Minoru Shirota, observed that lactic acid bacteria suppress harmful bacteria in the intestines. Since then, much has been published about the effects of probiotics on maintaining intestinal function, immune regulation, and on metabolic disorders and mental health."

Yakult's fermented milk product in the little bottle requires no introduction. Each bottle contains billions of beneficial bacteria belonging to a strain called *Lacticaseibacillus paracasei* strain Shirota (previously known as *Lactobacillus casei* strain Shirota, LcS). This strain arrives in the intestine alive, due to its resistance against digestive juices.

Early research suggests the consumption of certain live microorganisms could have health benefits by replacing harmful bacteria in the gut with beneficial bacteria. The Yakult Central Institute in Japan, established at its current location in Tokyo in 1967, has continued Shirota's research into this field of probiotics by investigating the functions and impacts of gut bacteria on human health.

THE HUMAN GUT CONTAINS AROUND 1,000 DIFFERENT SPECIES OF BACTERIA

For example, research is uncovering links between the immune reactions that drive inflammatory bowel diseases (IBD) and gut bacteria.

Yakult Central Institute researchers collaborating with colleagues in Japan, the US and Germany, demonstrated, in laboratory studies, how segmented filamentous bacteria, which are found in the intestines of a wide range of mammals, are involved in triggering intestinal immune cells called T helper 17 (Th17) cells.

Yakult researchers also found that a polysaccharide-peptidoglycan complex derived from the cell wall of LcS bacteria prevents the production of interleukin 6 by intestinal immune cells in the lab.

The impact of gut microbes on human health goes beyond their effects on the intestinal tract. An international research team reported in *Nature Neuroscience* that host microbiota made substantial contributions to microglia homeostasis in a germ-free mouse model. Microglia are brain macrophages responsible for gobbling up pathogens and dying cells, in addition to being important for brain functions.

And although much more research is needed, there are preliminary indications that probiotics could have impacts on mental health.

"Germ-free mice, which lack microbes in the whole body, show enhanced secretion of stress markers compared to normal mice when they are physically constrained," says Ota. "Since this finding, clinical observations have indicated that gut microbes affect brain function through a gut-brain axis in human. Dysbiosis, where there is a microbe imbalance, is observed in several disorders, like depression and autism. But the mechanisms involved are still unclear."

Yakult researchers and their collaborators are trying to understand the effects of beneficial gut bacteria. For example, they gave a small group of healthy medical students in Japan a daily dose of 100 ml of fermented milk that contains 100 billion LcS or a placebo in the run-up to an important exam and for a short time after. The LcS group showed signs of better sleep, prompting Yakult researchers to believe the LcS-drink could help maintain sleep quality during times of stress.

In a separate double blind, placebo-controlled trial, the researchers examined the effects of regular consumption of LcS-fermented milk on the gastrointestinal symptoms often experienced prior to important exams. The LcS group of medical exam students reported less increases in feelings of stress, a reduced total score of abdominal dysfunction, and showed more gut microbe diversity compared to the control group.

Yakult has even sent capsules of freeze-dried LcS into space. Their collaboration with the Japan Aerospace Exploration Agency aims to examine how LcS consumption affects gut microbiota and immune function in crew members of the International Space Station.

The human gut contains around 1,000 different species of bacteria. Yakult continues to use state-of-the-art technologies to uncover their roles in human health and to advance the science of probiotics.■

Yakult and Shirota-ism

Infectious diseases, like cholera and typhoid, were common in Japan when Minoru Shirota began studying medicine in 1921. His desire to help prevent these diseases led to a career in the emerging field of microbiology.

By 1930, Shirota had demonstrated that lactic acid bacteria were effective in suppressing harmful bacteria in the intestine. He successfully isolated and cultured a strain of these bacteria and, in 1935, produced beverages that can safely deliver the bacteria, called *Lacticaseibacillus paracasei* strain Shirota, to the gut without being killed by digestive juices.

Shirota founded Yakult based on his philosophy, dubbed Shirota-ism, which brings together preventive medicine, the concept of maintaining a healthy gut for a long life, and the importance of affordability. Since then the company has pioneered and supported probiotics research worldwide.

Jar fermenters at microbial culture testing stations at the Yakult Central Institute.

Lacticaseibacillus paracasei strain Shirota.

Microorganism culture test at the Yakult Central Institute.

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