京都大学
KYOTO UNIVERSITY

"For Ever Brighter Smiles"
MORINAGA MILK

May 30, 2024

No. 1 company in the world for articles on *Bifidobacterium* resident in humans[*1]

Morinaga Milk and Kyoto University have confirmed that Human-Residential Bifidobacteria (HRB) can convert indole, a uremic toxin precursor, into indole-3-lactic acid (ILA) which is beneficial to the body

Published in Scientific Journal "*Gut Microbes*"

Morinaga Milk Industry Co., Ltd. has conducted fundamental research for many years on *Bifidobacterium*, particularly those that naturally reside in the human gut (Human-Residential Bifidobacteria (HRB)) and believed to provide various health benefits. In conjunction with Kyoto University, we have established an industry–academia joint course called the "Research Course on HRB"[*2] and the results have been utilized in the development of ingredients used in our products and in benefitting human health. Recently, the research conducted in this industry–academia joint course led to the discovery that certain HRB, including Morinaga Milk's HRB strains can convert a toxic substance precursor into a beneficial substance. The research results were published on May 5, 2024, in the scientific journal "*Gut Microbes*" [*3].

1. Research background

Indole, a compound produced by some intestinal bacteria, is metabolized by the liver and converted into indoxyl sulfate, a typical uremic toxin. If kidney function is normal, indole is excreted in urine. However, it has been found that low kidney function can lead to decreased urine volumes and accumulation in the blood, and as a result, indole and indoxyl sulfate contribute to the progression of kidney dysfunction. As part of research investigating the beneficial effects of HRB, including Morinaga Milk's HRB strains, on the intestinal environment, verification was carried out on whether indole concentration in the gut could be lowered, as well as the associated mechanisms.

2. Study details and results

(1) HRB can lower the concentration of indole produced by *Escherichia coli* (*E. coli*) bacteria

E. coli, known to produce indole, was cultured, after which the culture supernatant was mixed with various HRB strains, and cultured again. Bifidobacterial strains, including Morinaga Milk's HRB strains, that are capable of significantly reducing the concentration of indole produced by *E. coli* were discovered (Fig. 1).

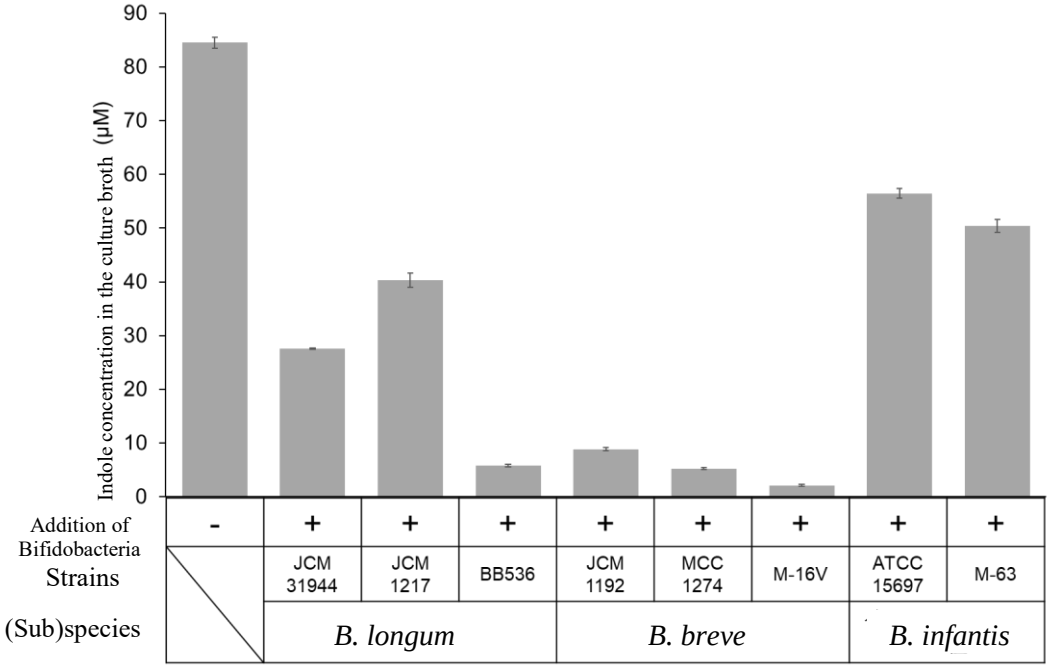

Figure 1. The indole concentration lowering effect of HRB

(2) HRB converts indole to tryptophan (Trp) and indole-3-lactic acid (ILA)

Next, in order to investigate how *Bifidobacterium* reduces the concentration of indole, stable isotope-labeled indole was added to the medium and HRB was cultured, whereupon it was discovered that it had been converted into tryptophan (Trp; a type of essential amino acid) and indole-3-lactic acid (ILA), which has been reported to improve brain function and strengthen the immune system (Fig. 2).

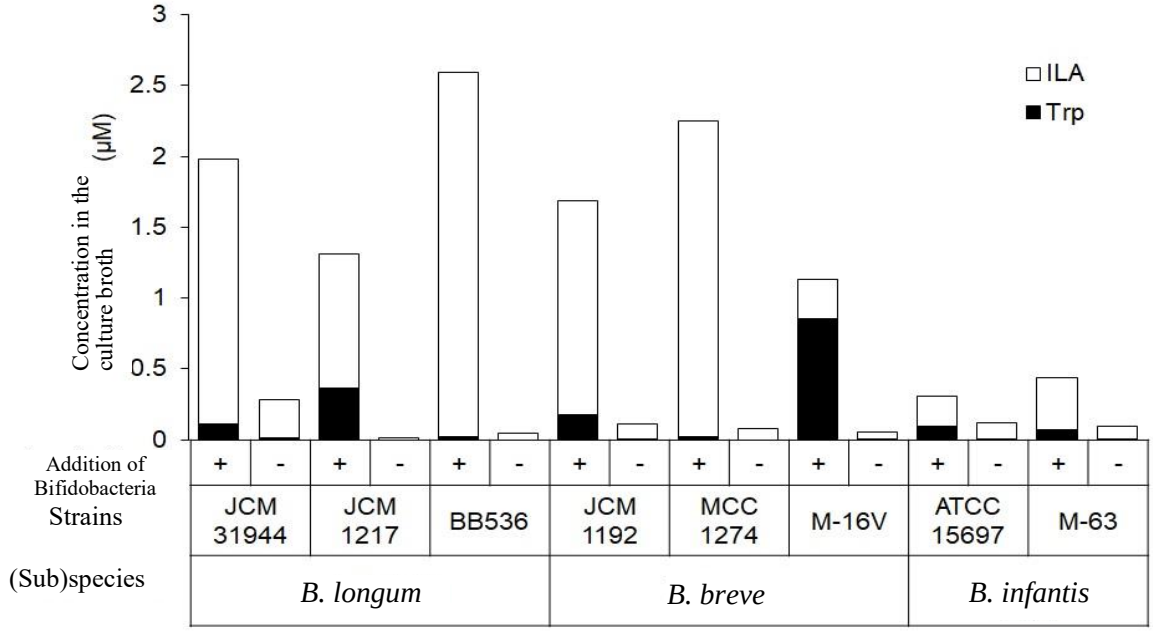

Figure 2. The substances produced by *Bifidobacterium* in the conversion of indole

(3) A metabolic pathway that converts indole into indole-3-lactic acid (ILA) via tryptophan (Trp) was discovered

We predicted the metabolic pathway of bifidobacteria in converting indole into beneficial substances (Trp and ILA), and made an assumption of the genes involved in metabolism. We prepared HRB with a deficit of the genes (*trpB*, *aldh*) that encoded the enzyme tryptophan synthase β subunit (TrpB) responsible for converting indole into Trp as well as the enzyme aromatic lactate dehydrogenases (ALDH) responsible for converting Trp to ILA, and we conducted an experiment as in Fig. 2. As a result, in *trpB*-deficient strains, Trp and ILA were hardly produced, and in *aldh*-deficient strains, Trp had accumulated, and therefore it was found that both genes were important in this metabolism process (Fig. 3).

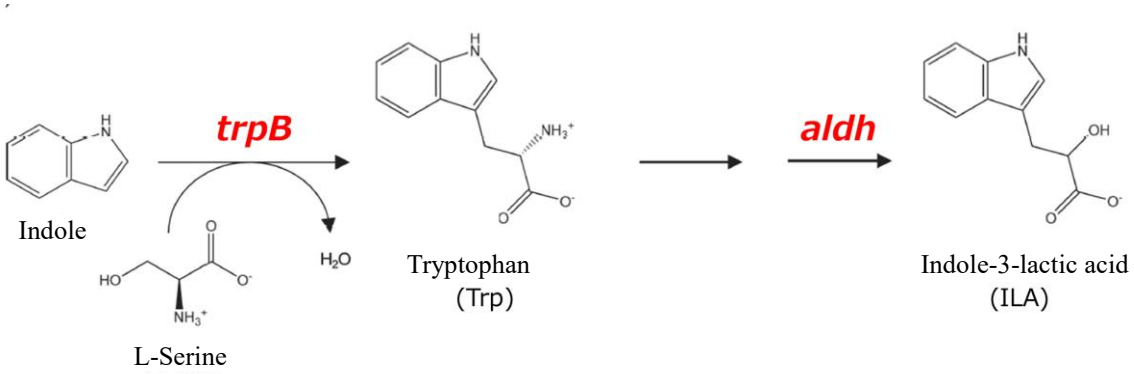

Figure 3. The metabolic pathway of converting indole into indole-3-lactic acid and the responsible genes

(4) HRB species are the only intestinal bacteria possess both of these important genes

Finally, in order to investigate what kind of intestinal bacteria possess the two genes important for converting indole, we carried out analysis on 11,943 high-quality genomes of intestinal bacteria registered in the U.S. National Center for Biotechnology Information (NCBI) database. As a result, it was found that only 95 bacterial strains possess both genes of *trpB* and *aldh*, and all of them were recognized as the HRB species.

From the above results, it was shown that HRB, including Morinaga Milk's HRB strains, could convert the toxin precursor indole into the beneficial ILA within the body, and that it could potentially protect our health (Fig. 4). Morinaga Milk will continue to work toward communicating correct information and providing superior ingredients to contribute to human health.

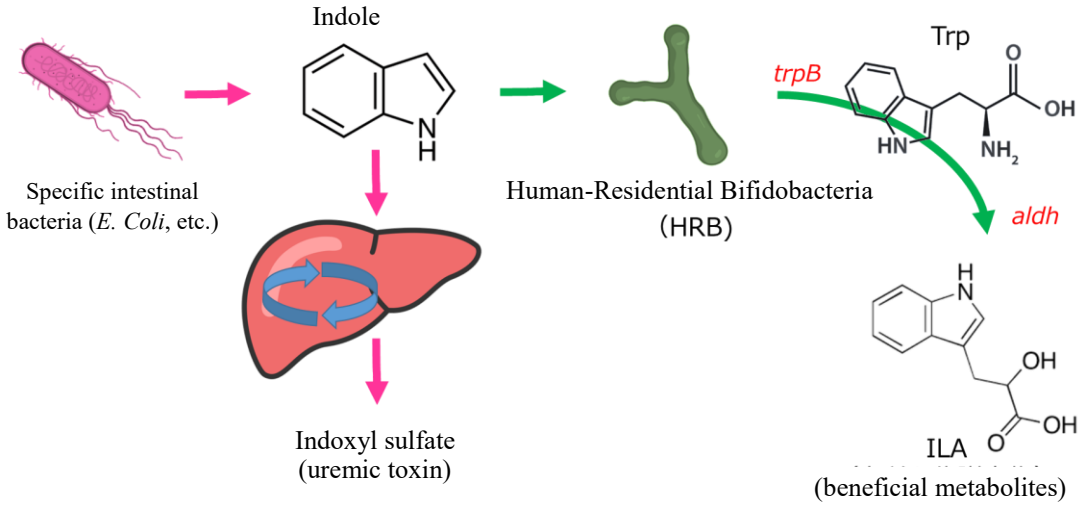

Figure 4. Summary of the Research

*1 According to investigations by KnowledgeWire, as of January 2024. (No. 1 in the world for corporation-submitted numbers of research articles on PubMed and the Ichushi WEB database (JAMAS))

*2 From October 1, 2020, Morinaga Milk established an industry–academia joint course in conjunction with Kyoto University, named the "Research Course on Human Residential *Bifidobacterium* (HRB)," in order to accelerate efforts toward understanding the mechanisms of symbiosis of Bifidobacteria living in the human gut (HRB) and the human host, as well as understanding the molecular mechanisms (mechanisms of action) of the health benefits of probiotic materials closely involved with human health, and various research findings have been published.
URL: https://www.morinagamilk.co.jp/release/newsentry-3489.html

*3 Cheng Chung Yong, Takuma Sakurai, Hiroki Kaneko, Ayako Horigome, Eri Mitsuyama, Aruto Nakajima, Toshihiko Katoh, Mikiyasu Sakanaka, Takaaki Abe, Jin-Zhong Xiao, Miyuki Tanaka, Toshitaka Odamaki, and Takane Katayama. Human gut-associated Bifidobacterium species salvage exogenous indole, a uremic toxin precursor, to synthesize indole-3-lactic acid via tryptophan. Gut Microbes 05 May 2024
URL:http://dx.doi.org/10.1080/19490976.2024.2347728