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Gut Microbiome Probiotics & Good Health

The Evidence Gets Stronger

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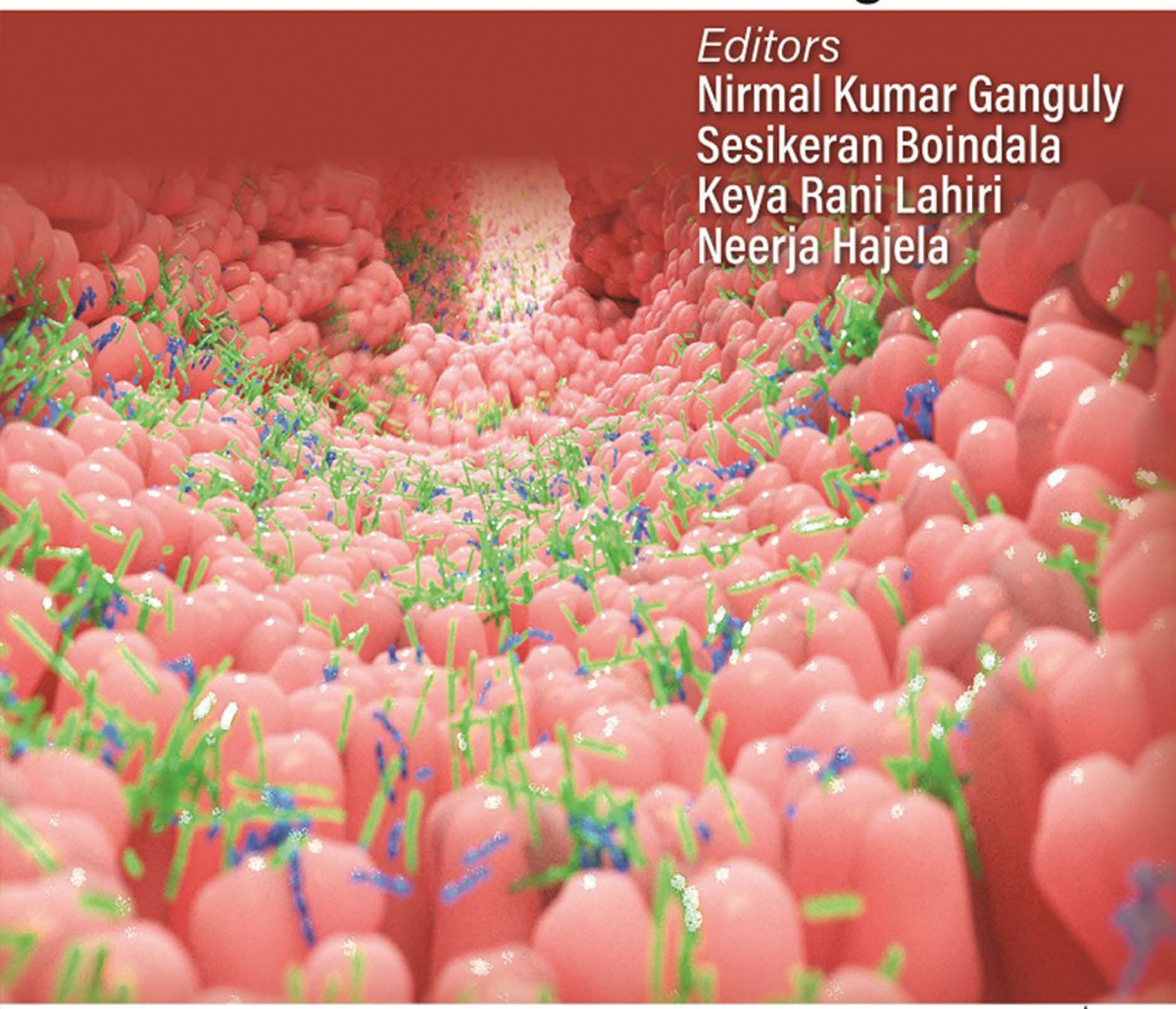

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CHAPTER 6

Effect of *Lacticaseibacillus paracasei* Strain Shirota Intake on the Stability of Gut Microbiota in the Elderly

Ryuta Amamoto

INTRODUCTION

Japan has the world's largest proportion of elderly residents: nearly 30% of the country's population is 65 years or older.[1] Therefore, developing innovative strategies to improve the health of the elderly in preparation for the coming super-aging society is one of the most important issues in Japan. The composition of the human gut microbiota is associated with various disorders and diseases, such as sarcopenia,[2] frailty,[3,4] and diabetes.[5] Thus, a favorable gut microbiota contributes to maintaining good health and to preventing and treating disease, especially in the elderly.

Since 2000, my colleagues and I have conducted an epidemiological study in the community of Nakanojo Town, Gunma Prefecture, Japan (the Nakanojo Study).[6,7] In 2015, we began collecting data regarding the composition of participants' gut microbiota and their consumption of fermented milk products, including those containing *Lacticaseibacillus paracasei* strain Shirota (LcS; previously known as *Lactobacillus casei* strain Shirota). These data demonstrated reduced risks of hypertension[8] and infrequent bowel movements[9] among elderly participants who habitually consumed fermented milk products containing LcS.

Population-based studies have shown that the gut microbiota in human adults is fairly stable, e.g., most predominant bacterial species flourish in the human gut for many years (Fu et al., 2019; Mehta et al., 2018),[10,11] and intraindividual (within-person) microbial variations are smaller than interindividual (between-person) differences.[10-12] However, few studies have examined variations in the gut microbiota between persons in detail, and little is known about the incidence, causes, and remedies for human microbial instability or about the association between personal lifestyle and the temporal stability of gut microbiota. Likewise, the effects of regular consumption of probiotics, including LcS products, on the stability of human gut microbiota is unknown. To address these questions, we used long-term data collected during the Nakanojo Study to explore variations of the gut microbiota in individual subjects over time and to identify relationships between the consumption of probiotics and changes in microbiota composition.

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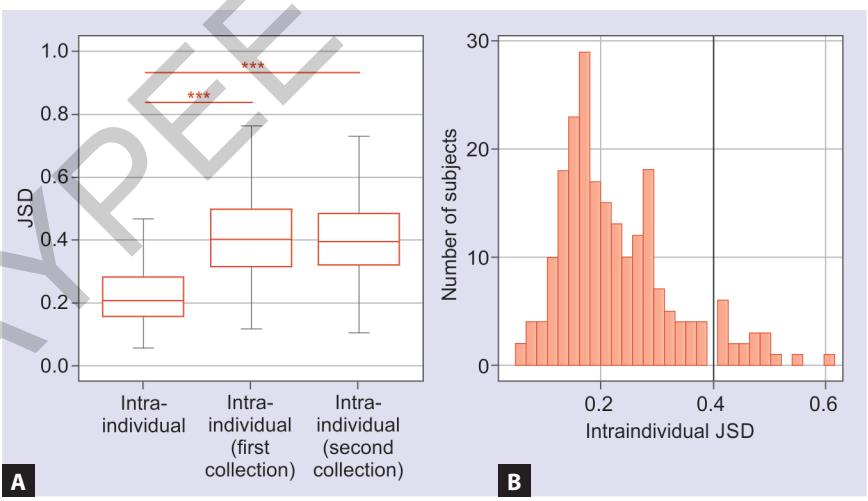
VARIATIONS IN THE GUT MICROBIOTA WITHIN AND BETWEEN SUBJECTS

To assess the temporal variability of gut microbiota among elderly Japanese people, my colleagues and I selected 218 elderly (age, 66–91 years) participants of the Nakanojo Study, who provided fecal samples annually for at least 2 consecutive years.[13] We used Jensen–Shannon distance (JSD) metrics,[14] which are generally used in enterotypes classification of the human gut microbiome,[15] to assess annual intraindividual and interindividual differences in the composition of the gut microbiota. Higher JSD values indicate greater differences.

First, we compared intraindividual variations and interindividual differences in the gut microbiota over time and identified participants who experienced large temporal variations in their gut microbiota. The JSD values for intraindividual differences in gut microbial composition over the year [median (minimum–maximum), 0.205 (0.056–0.606)] were significantly smaller than those for interindividual differences [first annual sample, 0.401 (0.117–0.763); second sample, 0.395 (0.104–0.763)] **(Fig. 1A)**. These results suggested that in Japanese elderly people the gut microbiota is stable overall, thus supporting other population-based observations.[10-12] However, the intraindividual JSD values of approximately 9% (19 of 218) of the subjects were equal to or higher than the median interindividual JSD (0.4) **(Fig. 1B)**. In other words, these 19 subjects experienced a substantial change—one



Figs. 1A and B: Intraindividual variation and interindividual differences in gut microbial composition, quantified according to Jensen–Shannon distance (JSD): (A) Comparison of intraindividual JSD value with interindividual values. ***$p < 0.001$ (Steel's test); (B) Distribution of intraindividual variation among the 218 subjects. The black line indicates the median interindividual JSD (approximately 0.4).

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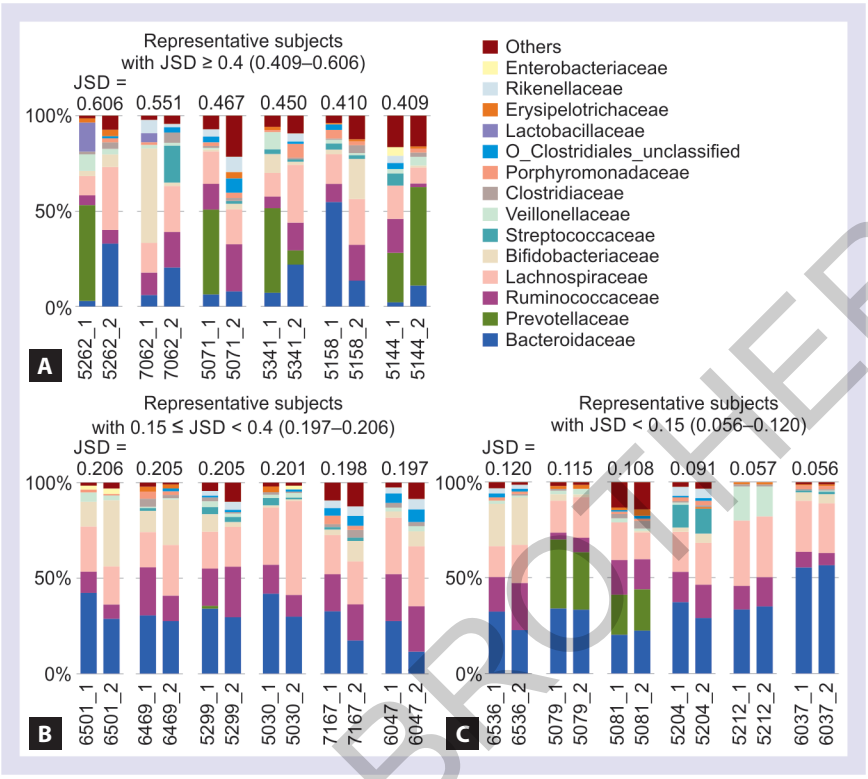

Figs. 2A to C: Changes in the predominant gut microbial composition at the family level between the first and second annual samples. Subjects were classified into three groups according to their intraindividual Jensen–Shannon distance (JSD): (A) JSD ≥0.4 (large variation); (B) 0.15 ≤ JSD <0.4 (moderate), or (C) JSD <0.15 (little variation in their gut microbiota between the 2 years); data for 6 representative subjects are shown for each JSD group.

equivalent to the interindividual difference—in their gut microbiota over 1 year. In addition, the noted changes in microbiota composition in the 19 subjects with JSD ≥0.4 were accompanied by the replacement of the predominant bacteria at the family level over the same 1 year period **(Fig. 2A)**. In contrast, the composition of the predominant bacterial community was maintained in the remaining subjects, whose intraindividual JSD was <0.4, with only modest **(Fig. 2B)** or scant change in the respective abundance of the component bacterial families **(Fig. 2C)**.

To investigate the persistence of the temporal variability in gut microbiota, we selected the 135 subjects who provided fecal samples for 3 consecutive years from the 218 total subjects. We then analyzed the correlation between the intraindividual JSDs for the first and second annual fecal samples (JSD1st–2nd) and between those for the second and third samples (JSD2nd–3rd).

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We noted that JSD1st–2nd was strongly and significantly correlated with JSD2nd–3rd (r = 0.57, $p < 0.001$). These results suggest that among elderly Japanese people, the stability of the gut microbiota composition in the elderly persists, and those who experience major changes in their gut microbiota are likely to have such changes subsequently.

CHARACTERISTICS OF SUBJECTS WITH JENSEN–SHANNON DISTANCE <0.4 COMPARED WITH ≥0.4

To gain insight into possible underlying causes for variation in intestinal microbial communities, we compared the baseline characteristics of subjects whose gut microbiota varied markedly (JSD ≥0.4 group) with those with relatively stable microbiota (JSD <0.4 group) **(Table 1)**. The percentages of current smokers and of those taking antibiotics were significantly higher among participants with highly variable gut microbiota than for those with more stable bacterial communities (current smokers, 15.8% versus 3.5%; recent antibiotic use, 10.5% versus 0.5%, respectively). However, of the 19 subjects only 2 were antibiotic takers and only 3 were current smokers, suggesting limited contribution of these features to the substantial changes in gut microbiota in this participant subgroup. Many other factors, including the intake of dietary fiber and the frequency of defecation, also influence the gut microbiota,[16,17] but nutrient intake and stool frequency were similar between the two participant groups with different JSDs. In contrast, participants with highly variable gut microbiota consumed fermented milk products containing LcS much less frequently than did subjects with more stable gut microbial communities; specifically, the intake frequency of these products over the previous 10 years for the former group was about one-third that of the latter. This result suggested that elderly participants who consumed LcS less frequently had larger changes in their gut microbiota than did their counterparts with less variability. Therefore, our next step was to investigate the effect of LcS on the stability of the gut microbiota in more detail.

RELATIONSHIPS BETWEEN THE FREQUENCY OF CONSUMPTION OF FERMENTED MILK PRODUCTS AND TEMPORAL VARIATIONS IN GUT MICROBIOTA

To investigate whether consumption of LcS exerts beneficial effects on the gut microbiota, my colleagues and I investigated the relationship between the frequency of fermented milk products consumption and the variation in the gut microbiota of our 218 participants over a 1-year period. The intraindividual JSD of gut microbial composition of subjects who consumed LcS-containing products ≥3 days per week during the preceding 10 years [median (minimum–maximum), 0.185 (0.057–0.494)] was significantly lower

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TABLE 1: Characteristics of subjects with Jensen–Shannon distance (JSD) < 0.4 or ≥ 0.4.

	< 0.4		*≥ 0.4*	
	n	***Mean ± SD***	***n***	***Mean ± SD***
Anthropometric parameters				
Age (years)	199	75.5 ± 6.2	19	74.1 ± 6.4
Sex (male/female, %)	199	45.7/54.3	19	42.1/57.9
Body mass index (kg/m^2)	199	22.6 ± 3.1	19	22.7 ± 3.6
Defecation status				
Defecation frequency (days/week)	199	6.1 ± 1.5	19	6.1 ± 1.7
Bristol stool form scale score	199	4.0 ± 0.9	19	4.0 ± 1.0
Current smoking and drinking habits				
Alcohol consumer (number [%])	199	7 [3.5]	19	3 [15.8] *
Smoker (number [%])	199	76 [38.2]	19	10 [52.6]
Medication status				
Antibiotics (number [%])	199	1 [0.5]	19	2 [10.5] *
Gastric acid–lowering medicines (number [%])	199	44 [22.1]	19	4 [21.1]
Frequency of consumption of LcS-fermented milk products				
Past 1 month (days/week)	199	3.37 ± 2.91	19	1.84 ± 2.43 *
Past 5 years (days/week)	199	2.35 ± 2.39	19	1.42 ± 2.27
Past 10 years (days/week)	199	1.82 ± 2.18	19	0.63 ± 1.67 *
Nutrient intake				
Energy (kcal/day)	188	2180 ± 604	18	2212 ± 543
Protein (g/day)	188	81.5 ± 24.7	18	84.4 ± 25.1
Lipid (g/day)	188	73.8 ± 28.0	18	72.9 ± 20.8
Carbohydrate (g/day)	188	283 ± 73	18	290 ± 69
Dietary fiber (g/day)	188	17.6 ± 5.3	18	19.2 ± 7.3
Saturated fatty acid (g/day)	188	22.6 ± 8.9	18	22.1 ± 7.1
Monounsaturated fatty acid (g/day)	188	24.5 ± 10.0	18	24.6 ± 6.6
Polyunsaturated fatty acid (g/day)	188	15.6 ± 5.9	18	16.4 ± 5.5
Cholesterol (mg/day)	188	371 ± 127	18	360 ± 111
Sodium (mg/day)	188	4737 ± 1795	18	5025 ± 2640
Potassium (mg/day)	188	3015 ± 963	18	3183 ± 1138
Calcium (mg/day)	188	803 ± 264	18	807 ± 309
Magnesium (mg/day)	188	316 ± 96	18	336 ± 119
Iron (mg/day)	188	9.91 ± 3.50	18	10.2 ± 3.7
Vitamin C (mg/day)	188	129 ± 51	18	135 ± 57

Intergroup differences in the ratios of male/female, smoker/nonsmoker, alcohol consumer/nonconsumer, and medicated/nonmedicated were assessed by using chi-square tests. Independent differences in each of the other variables between groups were assessed via analyses of covariance, after adjustment of data on age for sex and the others for age and sex. *P < 0.05 versus JSD < 0.4.

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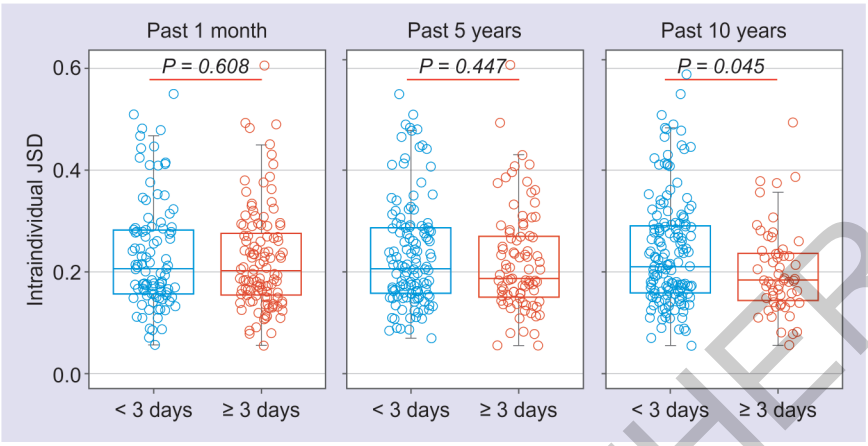

Fig. 3: Intraindividual Jensen–Shannon distance (JSD) in subjects consuming fermented milk products containing *Lacticaseibacillus paracasei* strain Shirota (LcS) <3 or ≥3 days/week during the previous 1 month, 5 years, and 10 years. Independent differences in JSD between groups were assessed by analyses of covariance, after data were adjusted for age, sex, body mass index, smoking status, and alcohol intake.

than that of the subjects who consumed LcS-containing products <3 days per week [0.211 (0.056–0.606), $p = 0.045$] **(Fig. 3)**. In addition, the percentage of participants with an intraindividual JSD ≥0.4 was 11.3% (18/160) in <3 days/week group but only 1.7% (1/58) in ≥3 days/week group; this 9% difference between the two groups was statistically significant ($p = 0.029$, Fisher's exact test). In regard to the preceding 1-month and 5-year periods, the intraindividual JSD values and the incidence of pronounced variation in the gut microbiota in ≥3 days/week group tended to be lower than those for the <3 days/week group, albeit nonsignificantly **(Fig. 3)**. These results suggest that the habitual consumption of probiotics may stabilize the gut microbiota of elderly Japanese people.

POSSIBLE MECHANISMS OF THE MICROBIOTA STABILIZATION BY LcS

The LcS has a high tolerance to gastric and bile acids[18] so it reaches the intestine alive,[19,20] which suggests that production of organic acids such as lactic acid is increased[21] and intestinal pH is decreased. In addition, LcS promotes a favorable balance of gut microbiota both by increasing the abundance of beneficial bacteria such as bifidobacteria and lactobacilli and by decreasing the abundance of harmful bacteria.[19,22] Together, these LcS-induced benefits regarding the component organisms and improvements in the intestinal environment may contribute directly to the stability of the composition of

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gut microbiota, consistent with the stabilization of gut microbiota among the participants of this study who consumed LcS-containing fermented milk products ≥3 days/week.

Furthermore, LcS exerts protective effects against infection,[22,23] thus potentially reducing the frequency of medication use and consequently stabilizing the gut microbiota. Although the use of antibiotics and gastric acid–lowering medicines was similar between the <3 and ≥3 days/week groups, the intraindividual JSDs remained lower in the ≥3 days/week group after analyses were adjusted for these treatments. Thus, the intake of antibiotics or gastric acid–lowering medicines does not appear to greatly influence the relationship between the frequency of consumption of LcS and the stability of microbiota.

Other factors such as stress suppression may be involved in the stabilization of gut microbiota by LcS, as LcS has been reported to suppress naturalistic stresses.[24,25] Moreover, LcS has several immunoregulatory effects, including enhancement of natural killer cell activity[26] and maintenance of salivary immunoglobulin A (IgA) levels.[27] Recent reports have suggested that gut microbiota is regulated by host IgA,[28] such that the effects of LcS on humoral immunity may promote stabilization of gut microbiota. Further studies are needed to clarify the mechanism of the increased stability of microbiota composition among our subjects who habitually consumed fermented milk products containing LcS.

SUMMARY AND FUTURE PERSPECTIVES

A gut microbiota that remains compositionally stable potentially contributes to maintaining good health and to preventing and treating disease, especially in the elderly. Our data suggest that about 10% of our elderly Japanese participants experienced a substantial compositional change in the predominant gut microbiota during a year. In addition, those who had pronounced variation in their gut microbiota were likely to have subsequent microbiota changes. These results suggest that the individual stability of gut microbiota is continuously maintained and is regulated by lifestyle habits. Moreover, our study showed that habitual consumption of probiotics, particularly LcS, may stabilize the elderly's gut microbiota.

In the future, we plan to clarify the relationship between changes in the microbiota and health status. Several studies have reported that changes in the gut microbiota are associated with disease onset and increased frailty.[3,4] Furthermore, instability in the gut microbiota increases the risk of exacerbation in human inflammatory bowel disease,[29] cognitive decline in a mouse model,[30] and complications and mortality in COVID-19.[31] Therefore, minimizing changes in the composition of the gut microbiota may be beneficial. We hope to conduct a long-term follow-up study to

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clarify the relationship with health status, such as requiring nursing care and mortality. Elucidating the mechanism through which the consumption of probiotics stabilizes the gut microbiota and how this stabilization affects the health of the elderly may provide hints for the maintenance of a healthy, long-lived society.

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Salient Features

- Importance of the adaptive immune system of the human body and its disruption in severe coronavirus disease of 2019 (COVID-19) infection.
- Potential use of Mouse Immunoglobulin A (IgA) antibody for development of a drug for gut microbial regulation.
- Role of Lactic Acid Bacteria (LAB) in boosting immune response by stimulation of IgA and IgG production as well as Th1 cell stimulation.
- Fermentation of camel and goat milk produces antimicrobial bioactive peptides that have potential clinical benefits as antihypertensives or antioxidants.
- Short-chain fatty acids and biomolecules help in the survival of ingested *Lacticaseibacillus paracasei* (formerly *Lactobacillus casei*) strain Shirota and *Bifidobacterium brevis* in the ileal mucosa.
- A novel emerging concept of battling *Helicobacter pylori*, a silent predator, with probiotics.
- *Lacticaseibacillus paracasei* strain Shirota plays an important role in stabilizing the gut microbial community of the elderly.
- The gut-brain axis—probiotics help in improving sleep quality.
- Probiotics and psychobiotics play an important role in bolstering the performance of athletes.

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