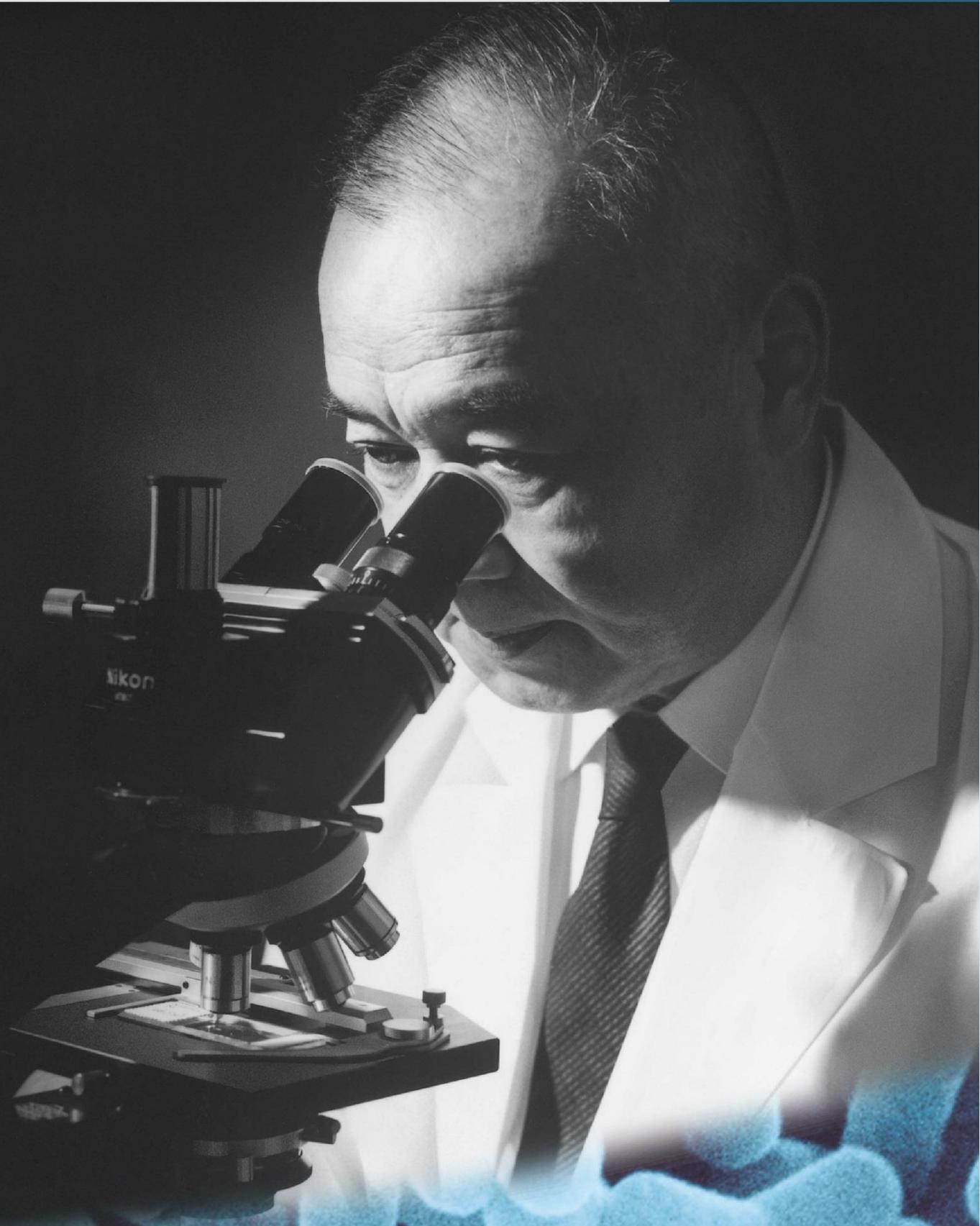


Lactobacillus casei strain Shirota (Yakult)

Research Update for Healthcare Professionals

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Lactobacillus casei strain Shirota (LcS) – Research Update

IMPROVEMENT IN INTESTINAL HEALTH

1. Intestinal microbiota profiles of healthy pre-school and school-age children and effects of probiotic supplementation.

Wang C *et al* 2015, *Ann Nutr Metab* 67:257-266.

Aim: This study aims to establish the baseline profile of intestinal microbiota in pre-school and school Japanese children and to investigate the effects of a probiotic on the microbiota.

Method: The intestinal microbiota was analyzed and the effect of daily consumption of probiotic (*Lactobacillus casei* strain Shirota (LcS)-fermented milk) on the intestinal microbiota and environment was studied before, during and after intervention.

Results: An open trial was performed on 23 children (14 boys, 9 girls; age 7.7 ± 2.4 years (mean \pm SD); BMI 19.6 ± 4.6). The composition of intestinal microbiota of healthy pre-school and school children resembled that of adults. During the probiotic intervention, levels of Bifidobacterium and Lactobacillus increased while those of pathogenic organisms like *Enterobacteriaceae*, *Staphylococcus* and *Clostridium perfringens* decreased significantly. A significant increase in fecal concentration of organic acids and a decrease in fecal pH was observed during the ingestion period. However, the pattern of fecal microbiota and intestinal environment was found to revert to the baseline level (i.e. before ingestion) within 6 months following cessation of probiotic intake.

Conclusions: Regular intake of an LcS-containing probiotic product may modify the intestinal microbiota composition and intestinal environment in pre-school and school children and maintain intestinal homeostasis.

2. Probiotic *Lactobacillus casei* Shirota improves kidney function, inflammation and bowel movements in hospitalized patients with acute gastroenteritis – A prospective study.

Akoglu B *et al* 2015, *J Functional Foods* 17:305-313.

Aim: The study was conducted to evaluate the role of the probiotic *Lactobacillus casei* Shirota (LcS) in improving kidney function, inflammation and bowel movement.

Method: 142 hospitalized patients with symptoms of acute gastroenteritis received 65 ml LcS fermented milk twice daily.

Results: Intervention with LcS resulted in a significant decrease in daily average (-5.42 vs. -4.40) and cumulative rate of bowel movements (-32.49 vs. -26.43) and improvement of the glomerular filtration rate (after 24 hours: 41.9 ± 2.8 vs. 25.9 ± 4.2 ml/min, $p < 0.01$). Furthermore, treatment with LcS resulted in a significant decrease of CRP on days five, six and seven. Leukocyte counts decreased in all groups, however on day three the effect was significantly higher in the LcS group receiving antibiotics. The administration of *L. casei* Shirota twice a day had positive effects on the reduction of bowel movements, improvement of kidney function and inflammation compared to the control group.

Conclusions: The study suggests that LcS administration might be considered in those patients with acute gastroenteritis who present with high inflammation markers and / or acute impaired kidney function.

GUT BRAIN AXIS

1. Probiotic *Lactobacillus casei* strain Shirota relieves stress-associated symptoms by modulating the gut-brain interaction in human and animal models.

Takada M *et al* 2016, *Neurogastroenterol Motil* 35(1):9-17.

Aim: The aim of this study was to examine the effects of *Lactobacillus casei* strain Shirota (LcS) on gut-brain interactions under stressful conditions.

Methods: Three double-blind, placebo-controlled trials were conducted to examine the effect of LcS on psychological and physiological stress response in healthy medical students under academic examination pressure. Subjects received LcS-fermented milk or placebo daily for 8 weeks prior to taking a National standardized examination. Subjective anxiety scores, salivary cortisol levels, and physical symptoms during the intervention were pooled and analyzed.

In the animal study, rats were given the feed with or without LcS for 2 weeks and then subjected to water avoidance stress (WAS). Plasma corticosterone concentration and the expression of cFos and corticotropin releasing factor (CRF) in the paraventricular nucleus (PVN) were measured immediately after WAS.

In an electrophysiological study, gastric vagal afferent nerve activity was monitored after intragastric administration of LcS to urethane-anesthetized rats.

Results: Academic stress-induced increases in salivary cortisol levels and the incidence of physical symptoms was significantly suppressed in the LcS group as compared to the placebo group. In rats pretreated with LcS, WAS-induced increase in plasma corticosterone was significantly suppressed, the number of CRF-expressing cells in the PVN was reduced. Intragastric administration of LcS stimulated gastric vagal afferent activity in a dose-dependent manner.

Conclusions: These findings suggest that LcS may prevent hypersecretion of cortisol and physical symptoms under stressful conditions, possibly through vagal afferent signaling to the brain and reduced stress reactivity in the PVN.

2. **Fermented milk containing *Lactobacillus casei* strain Shirota prevents the onset of physical symptoms in medical students under academic examination stress.**

Kato-Kataoka A *et al* 2015, *Benef Microbes* 1-12 [Epub ahead of print].

Aim: This pilot study investigated the effects of the probiotic *Lactobacillus casei* strain Shirota (LcS) on psychological and physical stress responses in medical students undertaking an authorized Nationwide examination for promotion.

Method: In a double-blind, placebo-controlled trial, 24 and 23 healthy medical students consumed a fermented milk containing LcS and a placebo milk, respectively, once a day for 8 weeks until the day before the examination. Psychological state, salivary cortisol, faecal serotonin and plasma L-tryptophan were analysed on 5 different sampling days (8 weeks before examination, 2 weeks before examination, 1 day before examination, immediately after examination and 2 weeks after the examination). Physical symptoms were also recorded in a diary by subjects during the intervention period for 8 weeks.

Results: In association with a significant elevation of anxiety at 1 day before the examination, salivary cortisol and plasma L-tryptophan levels were significantly increased in only the placebo group ($P<0.05$). Two weeks after the examination, the LcS group had significantly higher faecal serotonin levels ($P<0.05$) than the placebo group. Moreover, the rate of subjects experiencing common abdominal and cold symptoms and total number of days experiencing these physical symptoms per subject were significantly lower in the LcS group than in the placebo group during the pre-examination period at 5-6 weeks (each $P<0.05$) and 7-8 weeks (each $P<0.01$) during the intervention period.

Conclusions: The results suggest that daily consumption of fermented milk containing LcS may exert beneficial effect by preventing the onset of physical symptoms in healthy subjects exposed to stressful situations.

IMMUNE-MODULATION

1. **The effectiveness of *Lactobacillus* beverages in controlling infections among the residents of an aged care facility: A randomized placebo-controlled double-blind trial.**

Nagata S *et al* 2016, *Ann Nutr Metab* 68(1):51-59.

Aim: The study was conducted to evaluate the role of *Lactobacillus casei* strain Shirota (LcS) fermented milk in normalization of bowel movements and infection control of the elderly residents and staff in facilities for the elderly.

Method: A randomized placebo-controlled double-blind study was performed on elderly residents (average age, 85) and staff members (average age, 37) of facilities for the elderly. The participants randomly received either LcS-fermented milk or a placebo once daily for 6 months. Clinical data and enteric conditions were compared between the two groups.

Results: A significantly lower incidence of fever and improved bowel movement was seen in the LcS-fermented milk group (n=36) in comparison to the placebo group (n=36). The numbers of Bifidobacterium and Lactobacillus were higher ($p < 0.01$) whereas pathogenic organisms such as *Clostridium difficile* were significantly lower ($p < 0.05$), fecal acetic acid concentration and total acidity was higher in the LcS group.

A significant difference in the intestinal microbiota, fecal acetic acid, and pH was also observed between the LcS and placebo groups among the staff members.

Conclusions: The study concludes that the long-term consumption of LcS-fermented milk may be useful in decreasing the daily risk of infection and improving the quality of life among the residents and staff in facilities for the elderly.

2. Daily intake of fermented milk with *Lactobacillus casei* strain Shirota reduces the incidence and duration of upper respiratory tract infections in healthy middle-aged office workers.

Shida K *et al* 2015, *Eur J Nutr* Sep 29 [Epub ahead of print].

Aim: Although several studies have demonstrated the efficacy of probiotics for preventing upper respiratory tract infections (URTIs) in at-risk populations, including children and the elderly. Few studies have investigated the efficacy of probiotics in healthy adults living normal, everyday lives. Thus, this study evaluated the effect of *Lactobacillus casei* strain Shirota-fermented milk (LcS-FM) on the incidence of URTIs in healthy middle-aged office workers.

Method: In a randomized controlled trial, 96 male workers aged 30–49 years consumed LcS-FM containing 1.0×10^{11} LcS bacteria or control milk (CM) once daily for 12 weeks during the winter season. URTI episodes were evaluated by a physician via a questionnaire of URTI symptoms.

Results: The incidence of URTIs during the intervention period was significantly lower in the LcS-FM group as compared to the CM group (22.4 vs. 53.2 %, $P = 0.002$). The time to-event analysis showed that the LcS-FM group had a significantly higher URTI-free rate than the CM group over the test period (log-rank test: $\chi^2 11.25$, $P = 0.0008$). The cumulative number of URTI episodes and cumulative days with URTI symptoms per person was lower in the LcS-FM group, and the duration per episode was shorter.

Inhibition of both reductions in NK cell activity in peripheral blood mononuclear cells and increase in salivary cortisol levels was observed in the LcS-FM group.

Conclusions: The results suggest that the daily intake of fermented milk with LcS may reduce the risk of URTIs in healthy middle-aged office workers, probably through modulation of the immune system.

OTHERS

1. Intake of a fermented soymilk beverage containing moderate levels of isoflavone aglycones enhances bioavailability of isoflavones in healthy premenopausal Japanese women: a double-blind, placebo-controlled, single-dose, crossover trial.

Nagino T *et al* 2016, *Bioscience of Microbiota, Food and Health* 35(1):9-17.

Aim: This study investigates the bioavailability of serum isoflavones after the intake of soymilk fermented by *Lactobacillus casei* strain Shirota (LcS) containing 32.5% isoflavone aglycones (FSM) or placebo soymilk containing no isoflavone aglycones (SM).

Method: In a double blind, placebo-controlled, single-dose, crossover trial, 7 healthy premenopausal Japanese women (mean age: 35.3±11.0) consumed FSM or SM on day 1 and crossed over to the other soymilk after a 6-day washout period. Serum isoflavones in blood samples collected at 0, 1, 2, 3, 4 and 5 hr after intake were analyzed by liquid chromatography, coupled with tandem mass spectrometry.

Results: The area under the curve (AUC) values for the serum concentrations of genistein and total isoflavones was significantly higher, by about 1.4 fold, up to 5 hour after FSM intake as compared with SM intake (each $p < 0.05$), and that of daidzein tended to be higher after FSM intake. In addition, AUC analysis of total isoflavones for individual subjects revealed that 5 out of 7 subjects had higher AUC values after FSM intake compared with SM intake and that the 2 remaining subjects had similar AUC values. These 2 subjects had higher AUC values after SM intake (mean, 2502 ± 348) than those of the other subjects (mean, 1158 ± 269).

Conclusions: The results indicate that the bioavailability of isoflavones, especially genistein, is enhanced after the intake of FSM containing 32.5% isoflavone aglycones compared with intake of SM containing no isoflavone aglycones and that the enhancement is observed in healthy premenopausal Japanese women whose isoflavone absorption capacity is low after SM intake.