Effects of *Pediococcus acidilactici* R037 on Serum Triglyceride Levels in Mice and Rats after Oral Administration

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**Summary** The biological effects of heat-killed *Pediococcus acidilactici* R037 (R037) were evaluated when orally administered in mice and rats. Oral R037 administration at a daily dose of 10 and 100 mg/kg for 3 wk dose-dependently reduced fasting and non-fasting serum triglyceride concentrations in KK-A\(^y\)/Tajcl mice, a model of type II diabetes, obesity, hypercholesterolemia, and hypertriglyceridemia. Serum levels of free fatty acids in the 100 mg/kg group tended to decrease (not statistically significant), and total cholesterol levels remained unchanged. Treatment with R037 resulted in a significant decrease in blood glucose (at 100 mg/kg) and liver weight (at 10 and 100 mg/kg), and a small body weight gain (at 100 mg/kg) as compared to those in control mice. In addition, oral R037 administration at 100, 200, and 400 mg/kg/d for 1 wk dose-dependently suppressed the increase in serum triglyceride levels in Wistar rats after oral fat loading. Moreover, intraduodenal injection of 120 mg of R037 in Wistar rats suppressed gastric vagal nerve activity (GVNA) indicating suppression of intestinal digestion and absorption of food, and suppression of appetite. The R037 injection potentiated epididymal white adipose tissue sympathetic nerve activity (WAT-SNA) and tended to potentiate pancreatic sympathetic nerve activity (PSNA), suggesting that R037 activated lipolysis. Taken together, these findings indicate that R037 lowers serum triglycerides, possibly through suppressing intestinal absorption and potentiating lipolytic pathways. R037 may be useful for primary prevention of coronary artery diseases in subjects with mild or borderline dyslipidemia in combination with lifestyle changes.

**Key Words** *Pediococcus acidilactici* R037, triglyceride, oral fat tolerance test, lipolytic stimulation, autonomic nerve

Dyslipidemia, including elevated low-density cholesterol (LDL) and reduced high-density cholesterol (HDL), is a well-established risk factor for coronary artery diseases (CAD) (1, 2). However, despite a dramatic reduction in mortality by prevention and treatment of cases of elevated LDL and reduced HDL in recent decades (3), cardiovascular diseases are still the major cause of death in developed countries (3). Recent epidemiological studies have identified non-fasting triglyceride (TG) concentration as a clinically significant risk factor for CAD (4). Notably, the Fenofibrate Intervention and Event Lowering in Diabetes (FIELD) study found that fenofibrate, which decreases serum triglyceride levels, reduced total cardiovascular events mainly by reducing the number of non-fatal myocardial infarctions and revascularizations in patients with type 2 diabetes (5). In addition, recent cohort studies demonstrated that elevated non-fasting triglyceride levels were associated with increased risk for CAD (6). Thus, approaches to reduce the postprandial serum triglyceride concentration may also reduce CAD risk (6).

For subjects with borderline or mild dyslipidemia, lifestyle improvements such as a better diet and daily exercise are recommended as part of the primary prevention strategy. However, it is rather difficult, in general, to resolve these problems by changing lifestyle alone, given the inherent difficulty and discipline required to make these changes. Thus, an easier and more practical method, such as an alternative remedy or food supplement, could be useful when combined with lifestyle changes.

Lactic acid bacteria are of interest in this regard. In general, these bacteria are known to have beneficial effects, as probiotics, for intestinal digestion, absorption, immunity, and anti-inflammation (7). In addition to these well-established effects, some of these bacteria have been demonstrated to affect lipid and glucose metabolism. When administered as living cells in animals, *Lactobacillus johnsonii* La1 (NCC533) and *Lactoba-
**MATERIALS AND METHODS**

**Preparation of R037 powder.** We used heat-killed R037 because this strain showed similar hypolipidemic activity to live cells (data not shown) and, in general, products based on killed microorganisms are relatively easy to handle during manufacturing processes and have a long shelf-life. R037 was cultured in de Man-Rogosa-Sharpe (MRS) broth (Oxoid Ltd., Basingstoke, UK) at 30°C for 18 h. The cells were collected by centrifugation, washed twice with sterile water, killed by heating, and lyophilized. The following studies were carried out using a powdered formulation consisting of lyophilized heat-killed R037 (2.0 × 10^{11} bacteria per gram).

**Animals.** Ten-week-old male KK-A'/TacJcl mice, a model of type II diabetes, obesity, hypercholesterolemia and hypertriglyceridemia (CLEA Japan, Inc., Tokyo, Japan) (14) were used in testing for hypolipidemic effect, and 8-wk-old male Wistar rats (Charles-River Japan Inc., Kanagawa, Japan) were used in oral fat tolerance tests and autonomic nerve activity measurement. The animals were housed in a temperature- and humidity-controlled facility (temperature 20–24°C and 35–75% humidity) maintained on a 12-h light/12-h dark cycle and given a standard laboratory rodent diet (CE-2; CLEA Japan, Inc.). The animal experiments were approved by the Animal Experiment Committee of Kaneka Corporation (Approval No., 2011-25) or the Institutional Animal Care and Use Committee of the ANBAS Corporation (Approval No., ANBAS00305).

**Test for hypolipidemic effect.** The KK-A'/TacJcl mice were divided into three groups and given single oral gavage doses of either the control (distilled water; 8 mice), R037 formulation (10 mg/kg; 6 mice), or R037 formulation (100 mg/kg; 6 mice) daily (except Sunday) for 3 wk. At the end of the study, blood samples were collected from the sub-abdominal aorta and analyzed to determine serum triglyceride (TG), free fatty acid (FFA), blood glucose, and total cholesterol (TC) concentrations. Serum TG (15), FFA (9), and glucose (16) were determined as described previously. Total cholesterol was measured using a Cholesterol E-test Wako kit (Wako Pure Chemical Industries, Ltd., Tokyo, Japan) according to the manufacturer’s directions.

**Oral fat tolerance test.** The Wistar rats were divided into 4 groups (6 animals per group): one group received oral distilled water and three groups received either oral R037 100 mg/kg, 200 mg/kg, or 400 mg/kg daily for 1 wk. After overnight fasting, rats received oral administration of water or R037, followed closely by 1 mL of a fat supplement oral emulsion consisting of corn oil and 0.2% Tween solution at a 1 : 1 ratio. To determine the serum TG concentration, blood samples were collected from the jugular vein 30 min before and 2, 3, 4, and 6 h after the administration of the emulsion. Area under the concentration–time curve (AUC) of serum TG was also calculated by the trapezoidal rule and compared between the R037-treated and control groups.

**Measurement of autonomic nerve activity.** Autonomic nerve activity was determined in Wistar rats under urethane (1 g/kg, IP) anesthesia, as described previously (15). Briefly, a polyethylene catheter was inserted into the duodenum under anesthesia for intraduodenal injection. The rats were then cannulated intratracheally, restrained in a stereotaxic apparatus, and maintained at 35±0.5°C. For recording efferent autonomic nerve activities, the distal ends of the gastric vagal nerve, epidiymal white adipose tissue sympathetic nerve, pancreatic sympathetic nerve, and hepatic sympathetic nerve were ligated and hooked up to a pair of silver wire electrodes after laparotomy. The recording electrodes were immersed in a pool of liquid paraffin oil or a mixture of warm petroleum jelly and liquid paraffin oil to prevent dehydration and for electrical insulation, respectively. Each rat was allowed to stabilize for 30–60 min after the recording electrodes were placed. Electrical changes in gastric vagal nerve activity (GVNA), white adipose tissue sympathetic nerve activity (WAT-SNA), pancreatic sympathetic nerve activity (PSNA), and hepatic sympathetic nerve activity (HSNA) were amplified, filtered, and monitored on an oscilloscope. The raw nerve activity was converted to standard pulses by a window discriminator. Data were obtained as described previously (17). Baseline measurements of GVNA, WAT-SNA, PSNA, and HSNA were made for 5 min before intraduodenal injection of 1 mL of R037 suspension prepared at 120 mg/mL in water, nearly corresponding to 400 mg/kg of body weight, or saline. After the injection, the electrical activity was recorded for 60 min. Each group contained 4 rats.

*cillus paracasei* ST11 (NCC2461) were shown to improve glucose tolerance, and reduce body weight and abdominal fat weight in rats, respectively (8, 9). It was also demonstrated that *L. johnsonii* LA1 reduced food intake in rats (10). These effects are thought to be produced by modifying sympathetic and parasympathetic nerve activity (8–10). Some lactobacillus strains have been demonstrated to have cholesterol-lowering effects in humans as well as other animals (11), and some strains of lactic acid bacteria are reported to suppress high-fat diet-induced hypertriglyceridemia in hamsters (12). However, this triglyceride-reducing activity of lactic acid bacteria has not yet been established in humans.

We screened the strain showing triglyceride-reducing activity from among hundreds of lactic acid bacteria. *Pediococcus acidilactici* R037 (R037) showed high triglyceride-reducing activity and was isolated from “Dahi,” a traditional fermented milk that has been consumed regularly for a long time in the southern part of east Asia in countries such as India, Bangladesh, and Pakistan and originated thousands of years ago in eastern Europe and western Asia (13). We found that R037 is capable of reducing both non-fasting and fasting serum triglyceride concentrations in mice and suppressing fat-induced hypertriglyceridemia in rats. To assess a possible mechanism underlying these effects, we evaluated the effects of R037 on the activity of sympathetic nerves that innervate the pancreas, white adipose tissue, and liver, and on the activity of the parasympathetic nerves that innervate the gastrointestinal tract.
Effects of \textit{Pediococcus acidilactici} R037 on Serum Triglyceride

### Statistical analysis.
GVNA, WAT-SNA, PSNA, and HSNA were measured during each 5-min period after R037 administration and analyzed by digital signal processing. All data are expressed as mean±SE. The Mann-Whitney U-test was used to compare basal levels in each group. Because of the inter-individual variability in the pre-administration state, percent change from the baseline was calculated from neural discharge data. In order to analyze the effect of R037 on GVNA, WAT-SNA, PSNA, and HSNA two-way repeated measures analysis of variance (ANOVA) with factors of time (12 data points from 5 to 60 min) and treatment (before and after treatment with R037 suspension or saline) were used. All other data including concentrations of TGs, FFAs, blood glucose, and TC as well as body weight, liver weight, and total food consumption are expressed as mean±SD. Dunnett’s test or Student’s t-test was used to evaluate group differences. A p value of <0.05 was considered as statistically significant.

### RESULTS

#### Effect of R037 on serum triglyceride levels in KK-A\(^{y}\)/TaJcl mice

To investigate the effect of repeated administration of R037 on non-fasting serum triglyceride levels, KK-A\(^{y}\)/TaJcl mice were fed a standard diet and received oral administration of R037 for 3 wk. As shown in Table 1, compared with non-treated control mice, the non-fasting serum TG levels were significantly lower at both low and high doses (10 and 100 mg/kg) of R037 (p<0.01 and p<0.001, respectively), as was liver weight (p<0.05 at both doses). Furthermore, blood glucose levels (p<0.05) were significantly lower at only the high dose of R037 administration. The differences in serum FFA levels and serum TC between the R037-treated groups and control group were not significant, although the difference in FFA levels for R037 administration at the high dose was nearly significant (p=0.052). The effect of repeated administration of R037 on body weight is shown in Fig. 1. R037 treatment tended to suppress body weight increases in mice, but the effect reached statistical significance only at day 10 and day 13 in the group treated with 100 mg/kg of R037. In addition, the change in body weight from baseline at the high dose of R037 tended to be smaller than that of the control.

#### Oral fat tolerance test

Serum TG levels increased following fat loading and reached a peak at 3 h after loading in the control group.

![Fig. 1. Changes in body weight during R037 administration for 20 d in KK-A\(^{y}\)/TaJcl mice. Data are expressed as mean±SD (n=6 or 8). *p<0.05 compared with control (Dunnett’s test).](image)

*Table 1. Effect of oral administration of R037 for 3 wk on physiological parameters in KK-A\(^{y}\)/TaJcl mice.*

|                          | Control (n=8) | R037 (10 mg/kg; n=6) | R037 (100 mg/kg; n=6) |
|--------------------------|--------------|----------------------|----------------------|
| Body weight at day 20 (g) | 46.5±1.8     | 44.7±1.5             | 43.2±2.4             |
| Body weight changes from baseline (g) | 4.0±2.1     | 2.8±0.6              | 2.1±1.2              |
| TG (mg/dL)               | 387.5±52.3   | 251.3±59.7**         | 188.1±79.8***        |
| FFA (mg/dL)              | 1.6±0.8      | 1.2±0.5              | 0.8±0.2              |
| Blood glucose (mg/dL)    | 529.1±40.0   | 499.3±62.1           | 390.5±135.4*         |
| TC (mg/dL)               | 128.8±20.4   | 125.7±8.3            | 120.3±25.6           |
| Liver weight (g)         | 3.1±0.3      | 2.7±0.2*             | 2.7±0.4*             |
| Total food consumption (g) | 149.6±16.3  | 148.7±9.4            | 137.1±15.8           |

Data are expressed as mean±SD (n=6 or 8). *p<0.05, **p<0.01, ***p<0.001 compared with control (Dunnett’s test). TG, serum triglyceride; FFA, free fatty acid; TC, total cholesterol.
and gradually decreased thereafter (Fig. 2). R037 treatment suppressed this increase in a dose-dependent manner, with suppression by 400 mg/kg R037 being statistically significant 3, 4, and 6 h ($p<0.05$, $<0.01$, respectively) after fat loading and suppression by 100 mg/kg R037 being statistically significant 4 and 6 h ($p<0.05$ at both points) after fat loading (Fig. 2). Area under the serum TG concentration–time curve (AUC) from time 0 to 6 h was suppressed in a dose-dependent manner with statistical significance for 400 mg/kg ($p<0.01$) but not for 100 mg/kg ($p>0.05$) or 200 mg/kg of R037 ($p=0.051$) (Fig. 3).

**Effect of R037 on the autonomic nervous system in Wistar rats**

**Effect on GVNA.** GVNA was suppressed in a time-dependent manner to 44.2±15.4% of its basal level 60 min after intraduodenal administration of 120 mg of R037, while the response by intraduodenal administration of saline remained unchanged from 5 min through 60 min after administration. There were significant between-group differences in the response of the GVNA ($p<0.0005$, $F=70.2$) (Fig. 4A).

**Effect on epididymal WAT-SNA.** The response of epididymal WAT-SNA was slightly increased to 121.3±14.8% by intraduodenal R037 treatment, while administration of saline showed responses between 98.3% at 15 min and 109.6% at 55 min of its basal level, indicating no effect. The between-group differences were significant ($p<0.001$, $F=12.5$) (Fig. 4B).

**Effect on PSNA.** The PSNA response (percent change from the baseline) 60 min after the administration of saline was 134.9±15.0%, while after the same period of time following R037 administration the PSNA response was 169.4±46.6%. The between-group difference was not significant, although a tendency toward potentiation by R037 compared to saline was observed ($0.05<p<0.1$, $F=3.68$) (Fig. 4C).

**Effect on HSNA.** Administration of 120 mg of R037 gradually decreased nerve activity to 93.4% of its basal level at 55 min after administration. Alternatively, the administration of saline showed a response between 97.9% (at 10 min) and 105.8% (at 40 min) of its basal level post-administration, indicating no effect. The difference between groups was statistically significant.
Effects of *Pediococcus acidilactici* R037 on Serum Triglyceride

**DISCUSSION**

The present study demonstrated that oral administration of heat-killed *P. acidilactici* R037 formulation reduced non-fasting as well as fasting blood TG levels in mice and suppressed TG elevation induced by high fat loading in rats.

The mechanism(s) involved in the suppression of TG elevation and serum TG-lowering effect of R037 may involve, at least in part, the inhibition of intestinal digestion and/or the absorption of lipids. This speculation is supported by the suppression of GVNA, which is known to suppress gastrointestinal functions (including digestion, absorption, and peristaltic motion), possibly leading to a reduction in appetite.

In addition, the R037-induced potentiation of WAT-SNA indicates a stimulation of lipolysis, e.g., metabolism of TGs into glycerol and fatty acids via stimulating beta 3-adrenergic receptors. This effect, in addition to the PSNA potentiation, also suggests an enhancement of lipid synthesis, which may suggest an enhancement of lipid synthesis, was observed. Its contribution to the TG-reducing effect of R037 is unclear.

R037 also showed a tendency for PSNA potentiation. PSNA potentiation predicts suppression of insulin secretion and stimulation of glucagon secretion, which in turn would lead to stimulation of lipolysis in adipose as well as liver tissue. Furthermore, the PSNA potentiation also predicts suppression in digestive enzyme secretion, including lipase, which in turn would lead to suppression of intestinal fat absorption. Because we used R037 washed with sterile water, killed by heating, and lyophilized, the R037 cells rather than their fermentation products may have responsible for the effects on intestinal digestion and/or absorption of lipids via affecting sympathetic nerve activity. However, further studies are needed to determine which cell components of R037 are responsible for these activities.

It has been reported that some strains of lactic acid bacteria have triglyceride-reducing activity. For example, *Lactobacillus plantarum* KY1032 and *Lactobacillus curvatus* HY7601 were shown to lower triglycerides in hypertriglyceridemic rats fed a high-fat diet by upregulating triglyceride-secretion-related gene expression in the liver (18). It was also reported that *Lactobacillus rhamnosus* GG had protective effects against dyslipidemia in high-fat diet-induced obese mice by upregulating hepatic CYP7A1, the rate-limiting enzyme in bile acid synthesis (19). However, there are no lactic acid bacteria with triglyceride-lowering activity through modulation of intestinal digestion and/or the absorption of lipids via affecting sympathetic nerve activity similarly to R037, although it was reported that *Lactobacillus paracasei* ST11 (NCC2461) attenuated high-fat-induced obesity in rats by affecting sympathetic nerve activities (9).

Collectively, these data may suggest that the R037 formulation not only suppresses intestinal fat absorption but also stimulates lipolysis by affecting autonomic

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Fig. 4. Effect of intraduodenal administration of R037 on the gastric vagal nerve activity (GVNA), white adipose tissue sympathetic nerve activity (WAT-SNA), pancreatic sympathetic nerve activity (PSNA), and hepatic sympathetic nerve activity (HSNA) in Wistar rats. Data are expressed as mean ± SE. The significance of the differences between values after administration of saline and R037 from 5–60 min was analyzed by two-way repeated measures ANOVA.
nerve transmission, both of which may have contributed to the observed TG-lowering effect.

Generally, many species of lactic acid bacteria are known to stimulate digestion/absorption and to increase appetite through enhancing GVNA (9, 10). In contrast, R037 may suppress intestinal fat digestion/absorption and appetite through suppressing GVNA, stimulating WAT-SNA, and possibly stimulating PSNA, as described above.

Recent cohort studies as well as meta-analysis have demonstrated that both fasting and non-fasting hypertriglyceremia are risk factors for cardiovascular diseases in Western as well as Asian Pacific populations (20–25). Given that oral administration of the R037 formulation was effective in reducing both fasting and non-fasting serum TG concentrations in rodents, R037 could be of clinical importance if its effects were similar in humans. Furthermore, given their long history of dietary use and safety, lactic acid bacteria may be particularly useful for preventing future cardiovascular diseases, either alone or in combination with lifestyle changes, in subjects with borderline or mild dyslipidemia. In addition to suppressing intestinal fat absorption and stimulating lipolysis, the R037 formulation may also suppress appetite, suggesting its potential usefulness as a dietary intervention in patients with lifestyle diseases as well as in the general population. Such possibilities remain to be studied in the future.

CONCLUSION

*P. acidilactici* R037 has TG-reducing activity in rodents, possibly through suppressing intestinal fat absorption. Autonomic control of lipolysis may also be involved in this effect. Since it may reduce appetite as well, this formulation may be useful in humans for primary prevention of CAD in subjects with borderline or mild dyslipidemia.

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**Animal rights**

All institutional and national guidelines for the care and use of laboratory animals were followed.

**Author contributions**

TU and AT contributed equally to this study.

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Effects of *Pediococcus acidilactici* R037 on Serum Triglyceride

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