**Lactococcus lactis** Strain Plasma Improves Subjective Physical State and Presenteeism: A Randomized, Open-Label Crossover Study among Healthy Office Workers

Takeshi Kokubo¹, Shimpei Wakai², Daisuke Fujiwara³, Osamu Kanauchi¹, Kenta Jounai³, Hisahiro Ichikawa⁴, Mihoko Takuma⁴, Yoshihisa Kanaya⁵, and Ryoei Shiraoaka⁶,⁷

¹Research Laboratories for Health Science and Food Technologies, Kirin Holdings Co., Ltd., Yokohama 236-0004, Japan
²Health Science Department, Kirin Holdings Co., Ltd., Tokyo 164-0001, Japan
³Koiwai Dairy Products Co., Ltd., Tokyo 164-0001, Japan
⁴Good Conditioning Division, Yahoo Japan Corporation, Tokyo 102-8282, Japan
⁵CAPS, Inc., Tokyo 106-0032, Japan
⁶Medical Corporation NYS, Tokyo 150-0033, Japan

**ABSTRACT:** Maintaining employees’ presenteeism is a major issue in the workplace. Simple and convenient methods to improve presenteeism are required. We investigated whether administering the lactic acid bacteria *Lactococcus lactis* strain Plasma (LC-Plasma) can improve the performance and physical condition of office workers. Subjects were randomly assigned to one of two groups: 1) an intake period (consumption of LC-Plasma-containing yogurt beverage) followed by a non-intake period, or 2) a non-intake period followed by an intake period. Each period lasted 4 weeks and there was a 4-week washout period between each. Assessment was conducted using the World Health Organization Health and Work Performance Questionnaire (HPQ), the Profile of Mood States (POMS) questionnaire and physical condition questionnaires. A total of 153 subjects were analyzed. Absolute presenteeism (as assessed by the HPQ) and vigor (as assessed by POMS) were significantly higher in the intake period than the non-intake period. The subject’s physical health (as assessed by typical common cold symptoms, physical condition, sneezing or runny noses, coughing or sore throats, and lassitude) was also superior during the LC-Plasma intake period. Our results suggest that intake of LC-Plasma for 4 weeks improves work performance through reducing the risk of infection.

**Keywords:** *Lactococcus lactis* strain Plasma, presenteeism, vigor, work performance

**INTRODUCTION**

Absence from the workplace due to sickness is a global public health problem. Specifically, infectious diseases, such as the common cold and influenza, are of major concern, especially in winter. In addition to absence from work, decreased work performance owing to health problems has a profound effect in the workplace. The impact of presenteeism on work performance is greater than that of absenteeism. Presenteeism is defined as an employee being physically present at work but with reduced performance due to illness or another medical condition; absenteeism is defined as absence from work (Hemp, 2004). Studies have shown the socioeconomic cost of presenteeism is much higher than the direct cost of absenteeism and medical care (Parsonage, 2007; Nagata et al., 2018). The cost of absenteeism is readily apparent whereas with the cost of presenteeism is difficult to assess. From an industrial health perspective, the cost of presenteeism is a major issue and needs to be addressed. A previous study has been reported that short rests or physical exercise may improve presenteeism (Justesen et al., 2017; Michishita et al., 2017). However, these methods largely depend on the motivation of workers and may not be easily sustained over the long-term. Accordingly, more simple and convenient solutions are required.

*Lactococcus lactis* strain Plasma (LC-Plasma) is a synonym for *Lactococcus lactis* subsp. *lactis* JCM 5805. LC-Plasma is a cocci-shaped lactic acid bacterium; it is occasionally used to make cheese and yoghurt and is registered as the type strain of *Lactococcus lactis*. In previous studies, LC-Plasma were identified when screening strains of lac-
tic acid bacteria that activate plasmacytoid dendritic cells (pDCs) and induce type I and type III interferons (Jounai et al., 2012). pDCs play an important role in initiating adaptive immune responses, including antigen presentation and anti-viral infection (Siegal et al., 1999; Cervantes-Barragan et al., 2012). Oral administration of LC-Plasma has been found to activate mucosal pDCs (Jounai et al., 2012) and prevent respiratory (Jounai et al., 2015), mucosal (Jounai et al., 2018), and systemic viral infections (Suzuki et al., 2019). LC-Plasma reportedly stimulates human pDCs to reduce flu-like symptoms, such as runny noses and sore throats (Sugimura et al., 2013; Sugimura et al., 2015). LC-Plasma has also been reported to reduce accumulation of fatigue during consecutive high-intensity-exercise sessions in male athletes (Komano et al., 2018).

We therefore formulated the following hypothesis: daily LC-Plasma intake may reduce the risk of seasonal health problems of office workers through activating immune responses. Furthermore, the positive effects of LC-Plasma for office workers may lead to improved work performance and decreased presenteeism. To determine the effects of LC-Plasma on work performance and physical conditions in winter, we performed a randomized and open-label crossover study of healthy office workers.

### MATERIALS AND METHODS

#### Subjects

Subjects were healthy volunteers 20~65 years of age working in the Tokyo head office of Yahoo Japan Corporation. Included subjects did not regularly take medications, did not have a history of serious illness (e.g., diabetes, liver disease, kidney disease, and heart disease), and were not allergic to dairy products. Before the start of the trial, all subjects signed an informed consent form after receiving proper explanation of the purpose, methods, and expected adverse events of the study. The study received approval from the Ethics Committee of Shiba Palace Clinic (IRB No. 139676, Tokyo, Japan) and was conducted in accordance with the ethical principles of the Declaration of Helsinki.

#### Test samples

Yogurt beverages containing LC-Plasma were prepared by Koiwai Dairy Products Co., Ltd. (Tokyo, Japan). The beverage contained milk, powdered skimmed milk, granulated sugar, milk peptides, and water. Subjects consumed one cup of the beverage daily, which weighed 115 g and contained approximately $1 \times 10^{11}$ colony-forming units of LC-Plasma. The dose of LC-Plasma was the same as that used in previous studies (Sugimura et al., 2015; Shibata et al., 2016; Fujii et al., 2017; Komano et al., 2018). The nutritional composition of the beverage was as follows: 71 kcal, 3.4 g protein, 1.6 g lipid, 10.8 g carbohydrate, 44 mg sodium, and 117 mg calcium. Test beverages were refrigerated until consumption.

#### Study design

This was a randomized and open-label crossover comparative study, conducted from November 2017 to February 2018. As this was a preliminary study, we followed an open-label study design with less burden to subjects. The study comprised of three periods: first period (4 weeks); washout period (4 weeks); and second period (4 weeks). We randomly allocated subjects to two groups (A or B), matched by age and sex. Subjects in group A were asked to consume the test samples during the first period but not during the second period. Subjects in group B were asked to consume the test samples during the second period but not during the first period. Thus, over the whole study period, every participant had both a test sample intake period (LC-Plasma period) and non-intake period (control period). The experimental design is shown in Fig. 1.

Daily during the first and second periods, subjects recorded test sample intake, work attendance, and incidence of sickness in a diary, and completed a questionnaire about their physical condition. Subjects additionally completed the World Health Organization Health and Work Performance Questionnaire (HPQ) and Profile of Mood States (POMS) questionnaire at the end of the first and second periods. Subjects were instructed to maintain their daily habits (e.g., for diet, exercise, and sleep) and avoid foods containing lactic acid bacteria as much as possible.

This study was registered at the University Hospital Medical Information Network Clinical Trial Registry as UMIN000029950.

#### Subject characteristics

The consolidated standards of reporting trials flow diagram for this study is shown in Fig. 2. The study volunteers were recruited from October to November 2017. After providing informed consent, 226 subjects were randomized and allocated to groups A and B. During the study period, no participants were lost to follow-up. Owing to a low frequency of test sample intake or poor work attendance in the first and second periods, we excluded 33 subjects in group A and 40 subjects in group B from the analysis. Accordingly, 153 participants were included in the analysis. There were no significant differences in the baseline characteristics of subjects in groups A and B (Table 1).

#### Questionnaires

We used the Japanese version of the HPQ to assess the
Fig. 1. Experimental design. Subjects were allocated to either the *Lactococcus lactis* strain Plasma (LC-Plasma) intake or non-intake groups (period 1). After a 4-week washout period, the subjects’ entered the second period. Subjects who were previously in the intake period had a period of non-intake, and subjects previously in the non-intake period had a period of LC-Plasma intake. Every day during the first and second periods subjects kept a diary. Subjects completed the World Health Organization Health and Work Performance Questionnaire (HPQ) and Profile of Mood States (POMS) at the end of each period.

Table 1. Characteristics of the subjects analyzed in the efficacy group

|                      | Group A | Group B | 𝑃-value |
|----------------------|---------|---------|---------|
| Number of subjects   | 80      | 73      | −       |
| Age (years)          | 36.2±9.2| 36.4±9.0| 0.85    |
| Gender (% male/% female) | 58.8/41.2| 57.5/42.5| 0.88    |

Values are mean±SD. Statistical comparisons were carried out using the Student’s 𝑡-test for age and chi-square test for gender.

The POMS test (brief version, Japanese) comprises of 30 questions and uses a five-point Likert scale to assess current mood state. The test has the following subscales: tension-anxiety, depression-dejection, anger-hostility, vigor, fatigue, and confusion (McNair et al., 1981). Except for vigor, a low POMS score indicates a better state of mood.
To assess the incidence and severity of typical common cold symptoms, participants reported their physical condition every day during the first and second periods. The daily questionnaires addressed their physical condition and symptoms such as sneezing or runny noses, coughing or sore throats, feverishness, and lassitude. We assessed those symptoms for consistency with previous reports (Shibata et al., 2016; Fujii et al., 2017; Komano et al., 2018). The severity of each symptom was scored based on a five-point Likert scale, with low scores indicating a better state.

Study outcomes
The primary efficacy outcome measure was work performance, as evaluated with the HPQ score. The secondary outcome measures were the POMS score and the results of the physical condition questionnaire.

Statistical analyses
All values were expressed as mean±standard deviation (SD). We compared the HPQ and POMS questionnaire scores between the control and LC-Plasma periods using a two-tailed Wilcoxon signed-rank test. We compared the cumulative numbers of incident days for each symptom using a chi-square test. We performed all statistical analyses using the Excel Toukei software program (Social Survey Research Information, Tokyo, Japan). We considered a P-value of <0.05 as statistically significant.

RESULTS

HPQ
To evaluate the influence of LC-Plasma administration on work performance, subjects completed the HPQ at the end of the intervention period. Absolute presenteeism was significantly higher in the LC-Plasma period than in the control period (P=0.04; Table 2). We did not observe any differences between the two periods in terms of the other scores, absolute absenteeism, relative absenteeism, and relative presenteeism.

POMS
We evaluated the subject’s states of mood by POMS tests. The POMS test score for vigor was significantly higher in the LC-Plasma period than in the control period (P=0.02; Table 3). There were no significant differences for the other scores.

Physical condition
Table 4 shows the frequency of the occurrence of the specified physical symptoms. The frequency of incident days for abnormal physical condition (P<0.01), sneezing or runny nose (P=0.04), coughing or sore throat (P<0.01), and lassitude (P=0.01) were significantly lower in the LC-Plasma period than in the control period. There were no significant differences in the frequency of incident days for subjects feeling feverish (P=0.35) between the two groups.

Table 2. World Health Organization Health and Work Performance Questionnaire scores for absolute presenteeism improved during the Lactococcus lactis strain Plasma (LC-Plasma) periods

|                          | Control period | LC-Plasma period | P-value |
|--------------------------|----------------|-----------------|---------|
| Absolute absenteeism     | −4.11±22.47    | −4.79±26.78     | 0.90    |
| Relative absenteeism     | −0.04±0.15     | −0.04±0.17      | 0.95    |
| Absolute presenteeism    | 57.29±15.68    | 60.14±14.39     | 0.04*   |
| Relative presenteeism    | 1.00±0.26      | 1.02±0.24       | 0.30    |

Values are mean±SD.
*P<0.05.
Statistical comparisons were carried out using Wilcoxon signed-rank tests.
Effect size was calculated by Cohen’s D as 0.19.

Table 3. Profile of Mood States scores for vigor improved during the Lactococcus lactis strain Plasma (LC-Plasma) periods

|                | Control period | LC-Plasma period | P-value |
|----------------|----------------|-----------------|---------|
| Tension-anxiety| 47.11±9.99     | 46.61±11.21     | 0.61    |
| Depression-dejection | 48.87±9.91     | 49.09±10.53     | 0.56    |
| Anger-hostility | 46.92±10.63    | 47.37±11.37     | 0.76    |
| Vigor           | 40.73±8.86     | 42.35±9.70      | 0.02*   |
| Fatigue         | 51.20±1.00     | 50.41±10.42     | 0.24    |
| Confusion       | 52.81±10.03    | 52.61±10.72     | 0.66    |

Values are mean±SD.
*P<0.05.
Statistical comparisons were carried out using Wilcoxon signed-rank tests.
Effect size was calculated by Cohen’s D as 0.17.
**DISCUSSION**

It has previously been reported that LC-Plasma may up-regulate the anti-viral immune system by activating pDCs and, subsequently, interferon alpha (Jounai et al., 2012). In addition, oral administration of LC-Plasma has been shown to lower the incidence of influenza and common cold-like symptoms in many clinical studies (Sugimura et al., 2015; Shibata et al., 2016; Fujii et al., 2017; Komano et al., 2018). In the present investigation, we used a randomized open-label crossover approach to determine whether regular LC-Plasma administration may improve the work performance of office employees in winter. Absolute presenteeism (assessed by the HPQ) and vigor (assessed by the POMS test) were significantly higher in the LC-Plasma period than in the control period. The incidence of typical common cold symptoms was also superior in the LC-Plasma period. Our results indicate that intake of LC-Plasma can enhance work performance with respect to sickness in winter.

The HPQ, our primary efficacy outcome measure, was developed and has been validated by the WHO to assess subjective work performance (Kessler et al., 2003). Using the HPQ, responses are classified into relative and absolute values for both absenteeism and presenteeism. Reducing poor productivity in the workplace by reducing presenteeism is a major issue in occupational health. In a previous study, the cost of presenteeism was shown to account for about 70% of the total economic burden of employee health; by contrast, direct cost (such as medical and pharmacy expenses) account for about 20% (Edington and Burton, 2003). In the present study, intake of LC-Plasma for 1 month significantly increased the absolute presenteeism score. This is the first investigation to report improvement in presenteeism by food or food ingredient supplementation. LC-Plasma also improved the physical condition of the study participants; thus, the effect of LC-Plasma on work performance appears to derive from up-regulation of the immune system following the onset of sickness.

We also confirmed that the vigor score (determined by POMS) improved with LC-Plasma intake. Vigor is characterized as high levels of mental energy and mental resilience, and the willingness to undertake effort at work (Schaufeli et al., 2002). Work performance depends on both the physiological and psychological state of the employee. Accordingly, the improvement in vigor as a result of LC-Plasma intake is consistent with the results from the work performance scores.

Most typical common cold symptoms were significantly lower during the LC-Plasma period. Our results are consistent with those of previous clinical studies (Shibata et al., 2016; Fujii et al., 2017; Komano et al., 2018). The immunoprotective effect of LC-Plasma on physical condition was more conspicuous.

There are some limitations with our analysis, which may have affected the results. The study population was small and the investigation was only conducted upon office employees at a single workplace. Thus, it is unclear whether our findings might also apply to employees engaged in other areas, such as physical labor. Furthermore, this study adopted an open-label design with subjective

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**Table 4.** The cumulative number of incident days of typical common cold symptoms were improved during the *Lactococcus lactis* strain Plasma (LC-Plasma) period

|                | 1      | 2      | 3      | 4      | 5      | P-value |
|----------------|--------|--------|--------|--------|--------|---------|
| **Physical condition**<sup>1)</sup> |         |        |        |        |        |         |
| Control period  | 660    | 1,050  | 1,728  | 344    | 43     | <0.01** |
| LC-Plasma period| 724    | 1,207  | 1,597  | 290    | 40     |         |
| **Sneeze or running nose**<sup>2)</sup> |         |        |        |        |        |         |
| Control period  | 2,217  | 1,185  | 319    | 91     | 13     | 0.04*   |
| LC-Plasma period| 2,156  | 1,318  | 296    | 75     | 13     |         |
| **Cough or sore throat**<sup>3)</sup> |         |        |        |        |        |         |
| Control period  | 2,735  | 751    | 252    | 75     | 12     | <0.01** |
| LC-Plasma period| 2,773  | 839    | 184    | 55     | 7      |         |
| **Feverishness**<sup>4)</sup> |         |        |        |        |        |         |
| Control period  | 3,318  | 337    | 134    | 27     | 9      | 0.35    |
| LC-Plasma period| 3,318  | 382    | 123    | 30     | 5      |         |
| **Lassitude**<sup>5)</sup> |         |        |        |        |        |         |
| Control period  | 1,976  | 1,077  | 478    | 245    | 49     | 0.01*   |
| LC-Plasma period| 2,076  | 1,063  | 497    | 184    | 38     |         |

Values are mean±SD.  
*P<0.05 and **P<0.01.  
Statistical comparisons were carried out using chi-square tests.

<sup>1)</sup>1, very good; 2, good; 3, normal; 4, bad; 5, very bad.

<sup>2)</sup>1, normal; 2, slight; 3, mild; 4, moderate; 5, severe.

<sup>3)</sup>1, normal; 2, slight; 3, mild; 4, moderate; 5, severe.
outcomes. As subjects knew whether they were in the LC-Plasma or control period, the results may have been influenced by the placebo effect. Objective outcomes were not evaluated in this study even though the effect of LC-Plasma on biochemical immune parameters have been reported in previous studies. We instructed subjects to keep to their normal lifestyle within the test period, but we could not eliminate the influence of confounding factors. More extensive studies with a double-blind study design, using test samples of capsules of dried LC-Plasma powder or placebo beverages, are necessary to confirm our findings.

In conclusion, we found that intake of LC-Plasma for 4 weeks improved work performance and the physical condition of healthy office employees. More extensive studies of LC-Plasma are required. However, this strain of lactic acid bacteria appears to be beneficial as a functional food for improving the work performance of office employees with respect to risk of infection.

AUTHOR DISCLOSURE STATEMENT

Author RS is an industrial doctor of Yahoo. Koiwai Dairy Products is an affiliate of Kirin. This study was funded by Kirin and Yahoo. The authors declare no other conflicts of interest associated with this paper.

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