

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

Takeshi Kokubo<sup>1</sup>, Shimpei Wakai<sup>2</sup>, Daisuke Fujiwara<sup>2</sup>, Osamu Kanauchi<sup>1</sup>, Kenta Jounai<sup>3</sup>, Hisahiro Ichikawa<sup>4</sup>, Mihoko Takuma<sup>4</sup>, Yoshihisa Kanaya<sup>5</sup>, and Ryohei Shiraoka<sup>5,6</sup>

<sup>1</sup>Research Laboratories for Health Science and Food Technologies, Kirin Holdings Co., Ltd., Yokohama 236-0004, Japan

<sup>2</sup>Health Science Department, Kirin Holdings Co., Ltd., Tokyo 164-0001, Japan

<sup>3</sup>Koiwai Dairy Products Co., Ltd., Tokyo 164-0001, Japan

<sup>4</sup>Good Conditioning Division, Yahoo Japan Corporation, Tokyo 102-8282, Japan

<sup>5</sup>CAPS, Inc., Tokyo 106-0032, Japan

<sup>6</sup>Medical 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-

Received 9 December 2019; Accepted 2 April 2020; Published online 30 June 2020

Correspondence to Takeshi Kokubo, Tel: +81-90-1450-3577, E-mail: Takeshi\_Kokubo@kirin.co.jp

Copyright © 2020 by The Korean Society of Food Science and Nutrition. All rights Reserved.

© This is an Open Access article distributed under the terms of the Creative Commons Attribution Non-Commercial License (<http://creativecommons.org/licenses/by-nc/4.0>) which permits unrestricted non-commercial use, distribution, and reproduction in any medium, provided the original work is properly cited.

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.

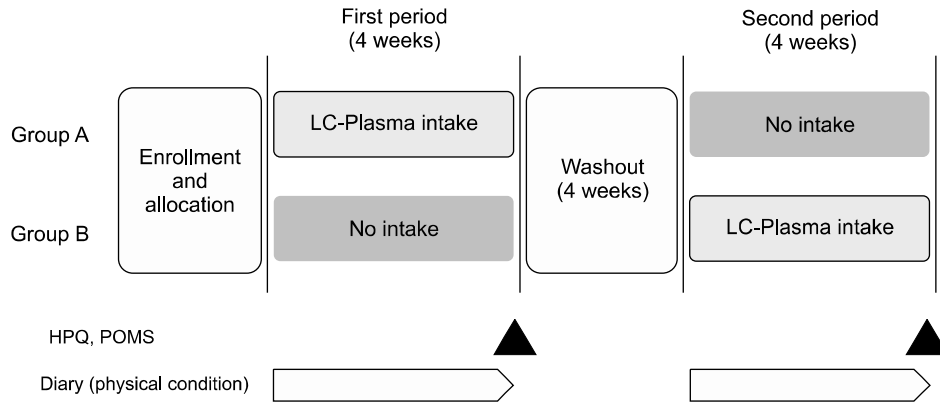
This study was registered at the University Hospital Medical Information Network Clinical Trial Registry as UMIN000029950.

### Subject characteristics

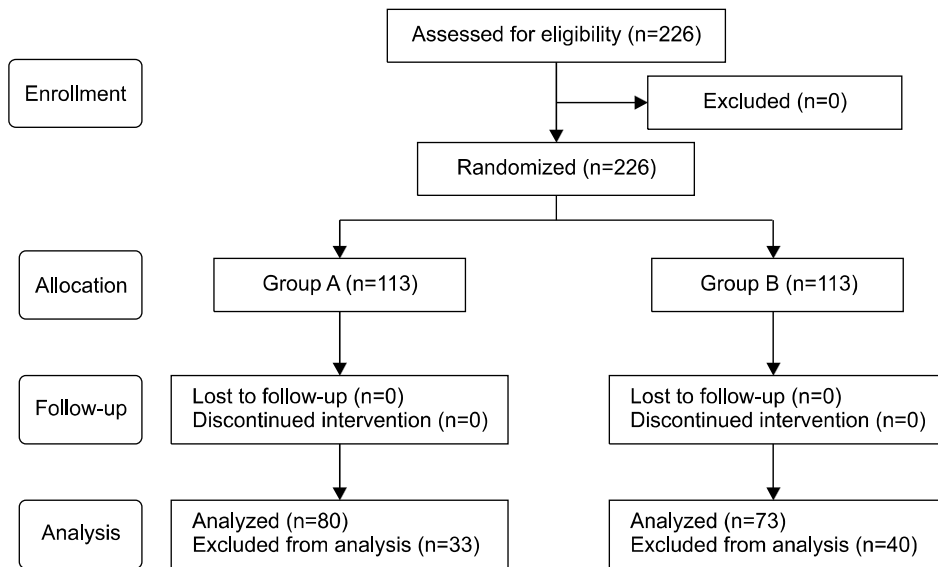
The consolidated standards of reporting trials flow diagram for this study is shown in Fig. 2. The study volunteers were recruited from October to November 2017. After providing informed content, 226 subjects were randomized and allocated to groups A and B. During the study period, no participants were 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.



**Fig. 2.** Consolidated standards of reporting trials flow diagram. The subject volunteers were randomized to two groups prior to the start of the study. Subjects who did not meet the inclusion criteria were excluded from the analysis.

**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.

effect of the intervention on the subject's workplace performance (Kessler et al., 2003). We assessed four factors: relative and absolute absenteeism, and relative and absolute presenteeism based on the HPQ. Absenteeism is an indicator of absence from work. Absolute absenteeism is calculated by subtracting actual work hours from expected work hours. Relative absenteeism is the percentage of absolute absenteeism hours out of the expected

work hours. If the person works more than expected, the value is negative. Presenteeism is defined as reduced performance at work due to illness or medical conditions. Respondents assessed their personal job performance and the job performance other workers in similar roles, using the eleven-point Likert scale. Absolute presenteeism is actual job performance, relative presenteeism is a ratio of actual job performance compared with the job performance of other workers in similar roles. Higher absenteeism scores indicate greater absence; higher presenteeism scores indicate greater work performance.

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	<i>P</i> -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	<i>P</i> -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.

**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>2)</sup>						
Control period	2,735	751	252	75	12	<0.01**
LC-Plasma period	2,773	839	184	55	7	
Feverishness <sup>2)</sup>						
Control period	3,318	337	134	27	9	0.35
LC-Plasma period	3,318	382	123	30	5	
Lassitude <sup>2)</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.

## 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 immuno-protective 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

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.

---

## REFERENCES

- Cervantes-Barragan L, Lewis KL, Firner S, Thiel V, Hugues S, Reith W, et al. Plasmacytoid dendritic cells control T-cell response to chronic viral infection. *Proc Natl Acad Sci USA*. 2012. 109:3012-3017.
- Edington DW, Burton WN. Health and productivity. In: McCunney RJ, Rountree PP, Barbanel CS, Borak JB, Bunn WB, Harber P, et al., editors. *A Practical Approach to Occupational and Environmental Medicine*. 3rd ed. Lippincott Williams & Wilkins, Philadelphia, PA, USA. 2003. p 140-152.
- Fujii T, Jounai K, Horie A, Takahashi H, Suzuki H, Ohshio K, et al. Effects of heat-killed *Lactococcus lactis* subsp. *lactis* JCM 5805 on mucosal and systemic immune parameters, and antiviral reactions to influenza virus in healthy adults; a randomized controlled double-blind study. *J Funct Foods*. 2017. 35:513-521.
- Hemp P. Presenteeism: at work-but out of it. *Harv Bus Rev*. 2004. 82:49-58, 155.
- Jounai K, Ikado K, Sugimura T, Ano Y, Braun J, Fujiwara D. Spherical lactic acid bacteria activate plasmacytoid dendritic cells immunomodulatory function via TLR9-dependent crosstalk with myeloid dendritic cells. *PLoS One*. 2012. 7:e32588. <https://doi.org/10.1371/journal.pone.0032588>
- Jounai K, Sugimura T, Morita Y, Ohshio K, Fujiwara D. Administration of *Lactococcus lactis* strain Plasma induces maturation of plasmacytoid dendritic cells and protection from rotavirus infection in suckling mice. *Int Immunopharmacol*. 2018. 56:205-211.
- Jounai K, Sugimura T, Ohshio K, Fujiwara D. Oral administration of *Lactococcus lactis* subsp. *lactis* JCM5805 enhances lung immune response resulting in protection from murine parainfluenza virus infection. *PLoS One*. 2015. 10:e0119055. <https://doi.org/10.1371/journal.pone.0119055>
- Justesen JB, Søgaard K, Dalager T, Christensen JR, Sjøgaard G. The effect of intelligent physical exercise training on sickness presenteeism and absenteeism among office workers. *J Occup Environ Med*. 2017. 59:942-948.
- Kessler RC, Barber C, Beck A, Berglund P, Cleary PD, McKenas D, et al. The World Health Organization Health and Work Performance Questionnaire (HPQ). *J Occup Environ Med*. 2003. 45:156-174.
- Komano Y, Shimada K, Naito H, Fukao K, Ishihara Y, Fujii T, et al. Efficacy of heat-killed *Lactococcus lactis* JCM 5805 on immunity and fatigue during consecutive high intensity exercise in male athletes: a randomized, placebo-controlled, double-blinded trial. *J Int Soc Sports Nutr*. 2018. 15:39. <https://doi.org/10.1186/s12970-018-0244-9>
- McNair DM, Lorr M, Droppleman LF. Manual for the profile of mood states. Educational and Industrial Testing Service, San Diego, CA, USA. 1981. p 1-27.
- Michishita R, Jiang Y, Ariyoshi D, Yoshida M, Moriyama H, Obata Y, et al. The introduction of an active rest program by workplace units improved the workplace vigor and presenteeism among workers: a randomized controlled trial. *J Occup Environ Med*. 2017. 59:1140-1147.
- Nagata T, Mori K, Ohtani M, Nagata M, Kajiki S, Fujino Y, et al. Total health-related costs due to absenteeism, presenteeism, and medical and pharmaceutical expenses in Japanese employers. *J Occup Environ Med*. 2018. 60:e273-e280.
- Parsonage M. Policy paper 8: Mental health at work: developing the business case. The Sainsbury Centre for Mental Health, London, UK. 2007. p 1-24.
- Schaufeli WB, Salanova M, González-romá V, Bakker AB. The measurement of engagement and burnout: a two sample confirmatory factor analytic approach. *J Happiness Stud*. 2002. 3: 71-92.
- Shibata T, Kanayama M, Haida M, Fujimoto S, Oroguchi T, Sata K, et al. *Lactococcus lactis* JCM5805 activates anti-viral immunity and reduces symptoms of common cold and influenza in healthy adults in a randomized controlled trial. *J Funct Foods*. 2016. 24:492-500.
- Siegel FP, Kadowaki N, Shodell M, Fitzgerald-Bocarsly PA, Shah K, Ho S, et al. The nature of the principal type 1 interferon-producing cells in human blood. *Science*. 1999. 284:1835-1837.
- Sugimura T, Jounai K, Ohshio K, Tanaka T, Suwa M, Fujiwara D. Immunomodulatory effect of *Lactococcus lactis* JCM5805 on human plasmacytoid dendritic cells. *Clin Immunol*. 2013. 149: 509-518.
- Sugimura T, Takahashi H, Jounai K, Ohshio K, Kanayama M, Tazumi K, et al. Effects of oral intake of plasmacytoid dendritic cells-stimulative lactic acid bacterial strain on pathogenesis of influenza-like illness and immunological response to influenza virus. *Br J Nutr*. 2015. 114:727-733.
- Suzuki H, Tsuji R, Sugamata M, Yamamoto N, Yamamoto N, Kanauchi O. Administration of plasmacytoid dendritic cell-stimulative lactic acid bacteria is effective against dengue virus infection in mice. *Int J Mol Med*. 2019. 43:426-434.