JOURNAL OF MEDICINAL FOOD
J Med Food 29 (1) 2026, 13–21

Published by Mary Ann Liebert, A Part of Sage
DOI: 10.1177/1096620X251384553

The Immune-Boosting Potential of *Lacticaseibacillus paracasei* HY7017 in Adults with Suboptimal Immune Function: A Double-Blind, Randomized, Placebo-Controlled, Clinical Trial

Soomin Jeon,[1,*] Hayera Lee,[1,*] Dong-Ki Hong,[1,*] Soo-Dong Park,[1] Il-Dong Choi,[1] Jae-Jung Shim,[1] Seong-Soo Hong,[2] and Jae-Hwan Lee[1]

[1]*R&BD Center, hy Co., Ltd ., Yongin, Korea.*
[2]*Department of Gastroenterology, Vievis Namuh Hospital, Seoul, Korea.*

ABSTRACT The human immune system is a complex defense mechanism against exogenous pathogens, and optimizing its function is vital for maintaining health. Previous studies have shown that specific probiotics can enhance immune function through mechanisms involving the activation of natural killer (NK) cells and modulation of cytokines such as interferon-γ (IFN-γ) and interleukin-12 (IL-12), which are critical for innate immune responses. In this study, we conducted a clinical trial to investigate the immune effects of *Lacticaseibacillus paracasei* (*Lcb. paracasei*) HY7017. Eighty participants suspected of having reduced immune function were randomized into two groups: the *Lcb. paracasei* HY7017 supplemented group and the control group. Participants in the HY7017 group consumed one capsule daily containing 5.0×10^9 Colony Forming Unit (CFU) of *Lcb. paracasei* HY7017, while the placebo group received identical capsules without live bacteria. After 8 weeks of consumption, NK cell activity was significantly higher in the HY7017 group compared with the control group. In addition, IFN-γ levels were considerably elevated in the HY7017 group at both 4 and 8 weeks, and an increase in IL-12 was observed after 8 weeks. No clinically notable differences in adverse events were observed between the two groups. As NK cells and cytokines are key immunomodulators, the observed increases in these biofactors support the immune-enhancing potential of *Lcb. paracasei* HY7017. These findings support the potential of *Lcb. paracasei* HY7017 as a functional health food ingredient for immune enhancement.

KEYWORDS: • ***immune*** • ***immune-enhancing effect*** • ***Lacticaseibacillus paracasei*** • ***natural killer cell*** • ***probiotics***

INTRODUCTION

The human immune system serves as an intricate defense mechanism that protects the body against exogenous pathogens, and optimizing its function is essential for maintaining health and preventing disease. Innate immunity is a natural defense system present at birth, involving components such as the skin, mucous membranes, and leukocytes, including macrophages and natural killer (NK) cells.[1] It provides an immediate and nonspecific response to external invaders. NK cells are an important component of innate immunity, playing a pivotal role in eliminating virus-infected and tumor cells. They detect abnormalities in cell surface markers, such as reduced MHC class I expression or increased expression of stress-induced ligands, inducing immediate cytotoxic responses. Activated NK cells secrete cytokines such as interferon-γ (IFN-γ) and tumor necrosis factor-α (TNF-α), which activate surrounding immune cells and amplify the immune response.[2] Notably, IFN-γ promotes the activation of macrophages and dendritic cells, contributing to antigen presentation and T cell activation, thereby playing a pivotal role in linking innate and adaptive immune responses. Cytokines mediate signaling between immune cells, regulating the intensity and the nature of immune responses. For example, interleukin (IL)-2 and IL-12 promote NK cell activation and cytotoxicity, while inhibitory cytokines like IL-10 and transforming growth factor-β help maintain immune homeostasis by suppressing excessive immune responses. The balance of this cytokine network is essential for the efficient functioning of the immune system and for understanding the pathogenesis of various diseases, including autoimmune disorders, inflammatory diseases, and cancer. Therefore, the activation of NK cells and the regulation of cytokine-mediated immune responses are emerging as significant targets in the development of immunotherapeutic strategies.

The recent outbreaks of immune-related diseases like COVID-19 have increased interest in supplements that enhance immune function. Research showing the importance

*Joint first authors.

Article received June 24, 2025. Revision accepted September 12, 2025.

Address correspondence to: Jae-Hwan Lee, MS, hy Co., Ltd., Yongin-si, Yongin 17016, Republic of Korea, E-mail: jaehwan@hy.co.kr

of gut microbial balance in immune regulation has further raised expectations for probiotics' immune-boosting effects. Probiotics are beneficial live microorganisms for humans, and previous studies have demonstrated the immune-enhancing effects of various lactic acid bacteria in diverse experimental models. Earlier research has shown that probiotics such as *Lactiplantibacillus plantarum* (*Lpb. plantarum*) and *Lacticaseibacillus rhamnosus* (*Lcb. rhamnosus*) stimulate the production of immune cytokines and activate immune cells such as macrophages and dendritic cells.[3,4] In addition, other studies have demonstrated that *Lpb. plantarum* activates NK cells and macrophages in mouse and cell experiments, thereby increasing immune responses.[5] In human clinical trials, *Lactobacillus helveticus* has been shown to induce dendritic cell activation, whereas *Lpb. plantarum* has been found to suppress pro-inflammatory cytokines and increase anti-inflammatory cytokines, suggesting its potential as an immune-enhancing agent.[6,7] However, many clinical studies have primarily focused on upper respiratory tract infections rather than infectious inflammation. Therefore, to confirm the immunomodulatory efficacy of probiotics in humans, it is necessary to accumulate results from human trials that evaluate overall immune enhancement.

This study was conducted to evaluate the immune-enhancing effects of *Lacticaseibacillus paracasei* (*Lcb. paracasei*) HY7017 in individuals with suspected immune dysfunction due to frequent infections. Participants consumed *Lcb. paracasei* HY7017 daily, and changes in immune function indicators, including NK cell activity and cytokine levels, were measured. Based on these findings, we aimed to highlight the potential of lactic acid bacteria as functional ingredients for supporting immune health and managing overall well-being.

METHODS

Study participants

This study was conducted at the Vievis Namuh Hospital in the Republic of Korea from June 2024 to December 2024. The required sample size was calculated to detect a statistically significant difference in NK cell activity between the experimental and placebo groups using a two-sided superiority test with a significance level of 0.05% and 80% power. The expected mean difference and standard deviation were estimated based on previously published clinical data that assessed changes in NK cell activity.[8] Based on these assumptions, the minimum number of participants required per group was calculated to be 29. To account for a 25% anticipated dropout rate, the final target enrollment was set at 80 participants (40 per group).

The inclusion criteria to identify individuals suspected of having weakened immune function were as follows: participants aged 19–75 years; those with peripheral blood leukocyte counts between 3×10^3 cells/μL and 8×10^3 cells/μL; and individuals who had experienced two or more upper respiratory tract infections within the past year, two or more episodes of stomatitis within the past year, a herpes zoster infection within the past year, or recurrent cystitis three or more times within the past year or twice within the preceding 6 months.

The exclusion criteria were as follows: individuals currently taking medications for underlying diseases; patients with hypertension; patients with diabetes; individuals with thyroid-stimulating hormone levels below 0.1 μIU/mL or above 10 μIU/mL; individuals who received vaccinations within the past 3 months; those who had donated whole blood within the last 2 months or apheresis blood within the last 4 weeks; individuals with aspartate aminotransferase (AST) or alanine aminotransferase (ALT) levels exceeding three times the upper limit of normal; individuals with creatinine levels exceeding 1.5 times the upper limit of normal; individuals who had used corticosteroids, immunosuppressants, proton pump inhibitors, nonsteroidal anti-inflammatory drugs, or antihistamines within the past month; those who had taken health supplements or vitamins within the past 2 weeks; individuals who had continuously consumed antibiotics, stabilizers, probiotics, or prebiotics within the past 2 weeks; and other reasons deemed inappropriate by the investigator.

The research protocol and informed consent form were reviewed and approved by the institution's Independent Review Board (IRB number: VNIRB-202413). The clinical trial was registered with the Clinical Research Information Service (CRIS number: KCT0010828). The clinical trial was conducted by the ethical principles of the Korean Clinical Research Association, the Helsinki Declaration, and the Korean Declaration of Good Clinical Practice. Written informed consent was obtained from all participants prior to their participation in the study.

STUDY DESIGN

This human trial was conducted as a randomized, double-blind, placebo-controlled, parallel study. Participants who signed the consent form underwent demographic surveys, lifestyle assessments, medical history reviews, medication use inquiries, physical examinations, and body measurements. Based on the screening results, eligible individuals were randomly assigned to either the experimental group or the control group. Participants who were deemed eligible based on the inclusion and exclusion criteria were randomly assigned to either the test group or the control group. The investigational products were distributed according to the randomization number, and subjects were instructed to consume the product as directed. To maintain blinding, test products identical in color, shape, and packaging were provided, ensuring that neither the principal investigator nor the participants were aware of group allocation unless unblinding was required due to a serious adverse event. Participants received either *Lcb. paracasei* HY7017 or a placebo for a total of 8 weeks, with a 1:1 randomization ratio between HY7017 intake group (HY7017 group) and placebo group.

Investigational product

The investigational product was a capsule containing 300 mg of *Lcb. paracasei* HY7017 in powder form.

Participants assigned to the experimental group were instructed to take two capsules daily after breakfast, resulting in a daily intake of 600 mg of *Lcb. paracasei* HY7017, which contained 5.0×10^9 CFU. The control group received identically appearing capsules that were visually indistinguishable from the experimental ones. The placebo contained lactose instead of probiotics, while all other excipients and the capsule shell were identical to those of the investigational product. Participants were instructed to take two capsules daily after breakfast. All products were received from hy Co., Ltd.

Primary outcome

NK cells were isolated from peripheral blood mononuclear cells using the density gradient method with centrifugation from EDTA whole blood, followed by sorting with the MojoSort™ NK Cell Isolation Kit (BioLegend, CA, USA). The isolated NK cells, as effector cells, were cultured alongside the target cells, K562, which is a human leukemia cell line, and cytotoxicity was measured using the CytoTox® 96 Nonradioactive Cytotoxicity Assay Kit, with cytotoxicity (%) calculated. The ratio of effector cells to target cells was maintained at 2.5:1, 5:1, and 10:1.

Secondary outcomes

Cytokine levels, including IFN-γ and IL-12, were measured using blood samples. IFN-γ levels in blood serum were determined using the Human IFN-γ Quantikine Kit (R&D Systems, MN, USA) following the manufacturer's instructions. IL-12 levels were measured using the Quantikine™ ELISA Human IL-12 p70 Immunoassay (R&D Systems, MN, USA) with blood samples. White blood cell (WBC) counts were measured from peripheral blood samples collected at visits 1, 3, and 4 using standard hematological analysis methods.

Safety assessment of Lcb. paracasei HY7017

To evaluate the safety of *Lcb. paracasei* HY7017, the study collected information on adverse reactions through indirect questioning of the participants. In addition, adverse reactions were confirmed through spontaneous reporting by the participants, physical examinations, and clinical pathology tests. The clinical assessments included measurements of hemoglobin, red blood cell count, hematocrit, neutrophils, lymphocytes, glucose, ALT, AST, triglycerides, and total cholesterol.

To verify product intake, the remaining capsules returned by participants were assessed to calculate adherence. Adherence was expressed as a percentage, calculated by dividing the number of capsules actually consumed by the number of capsules that should have been taken.

Statistical Analysis

Data obtained from the study participants in this clinical trial were used as follows: Safety analysis was conducted on the safety set, which included all participants who consumed the investigational product at least once after randomization. Efficacy analysis was performed on the per-protocol (PP) set, which included participants who completed the study without any significant protocol violations affecting the results. Statistical analyses were carried out using SAS® (Version 9.4, SAS Institute, Cary, NC, USA). The data collected from this clinical trial were presented as means and standard deviations using appropriate descriptive statistics, and statistical significance was assessed at a two-tailed level of $P < .05$. Within-group differences were analyzed using the paired *t*-test or Wilcoxon signed-rank test based on the normality of the data. Between-group differences were assessed using the independent *t*-test or Mann–Whitney *U* test according to the distribution of the data. In cases where the data exhibited large variance, both the independent *t*-test and ANCOVA were used to account for the potential impact of covariates on the results. For categorical variables, the chi-square test or Fisher's exact test was employed.

RESULTS

Participant recruitment and baseline characteristics

Among the 87 participants who submitted written consent, 80 met the eligibility criteria and were included as study subjects. The participants were randomized and allocated to the experimental and control groups in equal proportions through a double-blind method. The primary analysis population was the PP set, which included 67 participants after excluding one individual for violating inclusion/exclusion criteria, two participants who withdrew consent, four who took prohibited concomitant medications, and six whose adherence was below 80% (Fig. 1).

In this study, the 80 participants included 24 males (10 in the experimental group and 14 in the control group) and 43 females (22 in the experimental group and 21 in the control group) (Table 1). No significant differences were observed between the two groups in baseline characteristics,

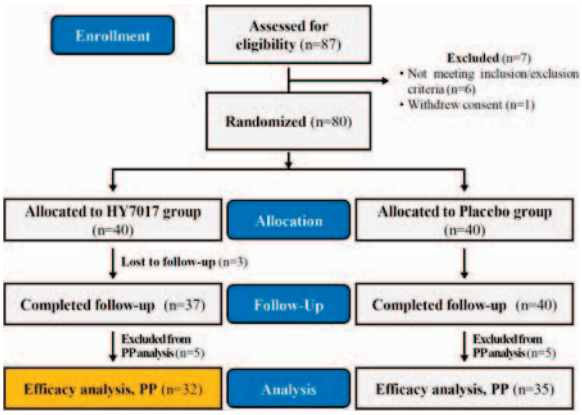

FIG. 1. Flow diagram showing the selection and allocation of participants in the study. The diagram presents the step-by-step selection process of participants in this human clinical trial. Participants who were excluded from the study are listed along with the corresponding reasons and the number of individuals in each category.

Table 1. Demographics and Clinical Characteristics at Baseline

	HY7017 (n = *32*)	*Placebo* (n = *35*)	P *value*[a]
Sex (M/F)	10/22	14/21	.456[c]
Age (years)	34.53 (6.80)	36.37 (10.19)	.840[b]
Height (cm)	166.87 (6.05)	167.65 (9.03)	.856[b]
Weight (kg)	84.88 (15.27)	68.40 (14.11)	.231[b]
BMI (kg/m^2)	23.11 (4.28)	24.14 (3.48)	.154[b]
Systolic Blood Pressure (SBP) (mmHg)	116.16 (11.53)	118.54 (9.07)	.348
DBP (mmHg)	73.22 (10.20)	72.14 (10.27)	.669
Temperature (°C)	36.46 (0.25)	36.42 (10.39)	.431[b]
Alcohol (n, %)	26, 81.25	26, 74.29	.495[c]
Alcohol (units/week)	6.16 (7.20)	4.60 (5.78)	.113[b]
Smoking (n, %)	0, 0.00	3, 8.57	.240[d]
Family (n, %)	2, 6.25	0, 0.00	.224[d]

Values are presented as means (SD).
[a]Analyzed by independent *t*-test between the groups.
[b]Analyzed by Mann–Whitney's *U* test for changed values between the groups.
[c]Analyzed by chi-square test between the groups.
[d]Analyzed by Fisher's exact test between the groups.
BMI, body mass index.

including age, height, weight, blood pressure, pulse, temperature, alcohol consumption, smoking status, or family history of immune-related disorders.

Primary outcome: NK cell activity

To evaluate the effects of HY7017 on immune enhancement, NK cell activity was measured both prior to consumption and after 8 weeks of consumption at E:T (effector-to-target) ratios of 2.5:1, 5:1, and 10:1, both prior to consumption and after 8 weeks of consumption (Fig. 2 and Table 2). Among these, the following results refer specifically to the 10:1 ratio. Before the intervention, NK cell activity was 48.14 ± 1.81% in the experimental group and 52.29 ± 1.77% in the control group, showing no significant difference between the two groups. However, after 8 weeks of consumption, the change in activity was 2.43 ± 1.88% for the experimental group and −3.32 ± 2.12% for the control group, indicating a statistically significant difference between the groups (P = .048). Analysis of Covariance (ANCOVA) results also confirmed these findings, showing a statistically significant difference between the experimental and control groups with a P value of .035. At the other E:T ratios (2.5:1 and 5:1), the experimental group also showed numerically smaller reductions in NK cell activity compared with the control group, but the differences were not statistically significant.

Secondary outcomes: Cytokines and WBC

Along with NK cell activity, two types of cytokines were measured to assess changes in immune function (Fig. 3 and Table 3). Cytokine levels were assessed at three time points: before consumption and 4 and 8 weeks after consumption. At baseline, IFN-γ did not show any differences between the groups. However, at 4 and 8 weeks post-consumption, a significant increase in IFN-γ levels was observed in the experimental group compared with pre-consumption levels (P = .001 and P < .001). Furthermore, when comparing the changes in the experimental group with the control group at both 4 and 8 weeks, a statistically significant difference was observed (P < .0001). ANCOVA results confirmed these findings, with a P value of less than .0001 at 8 weeks.

IL-12 also showed no differences between the groups before consumption. However, after 4 and 8 weeks of consumption, the experimental group exhibited a significant increase compared with baseline (P = .001 and P = .009). Notably, at 8 weeks, the IL-12 level increased by 5.90 ± 2.82 pg/mL in the experimental group, while it decreased by 1.61 ± 1.10 pg/mL in the control group, indicating a statistically significant difference between the two groups (P = .008). ANCOVA also revealed a significant difference with a P value of .007.

WBC counts were measured before consumption and after 8 weeks of consumption (Fig. 4). The pre-consumption WBC count was 5.54 ± 0.16 [× 10^3/μL] in the experimental group

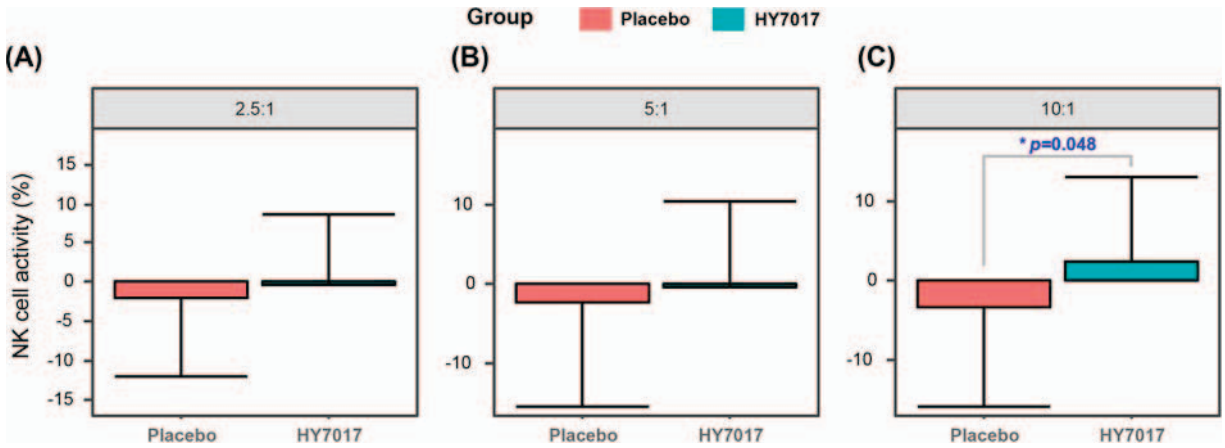

FIG. 2. Effects of HY7017 on NK cell activity. The ratios of NK cells to target cells were as follows: **(A)** 2.5:1, **(B)** 5:1, and **(C)** 10:1. Changes in NK cell activity after 8 weeks are shown as *bar graphs*. Statistically significant P values are indicated in *blue*. NK, natural killer.

Table 2. Changes in NK Cell Activity and Cytokine Levels Following 8 Weeks of HY7017 Supplementation

	HY7017 group (n = *32*)				*Placebo group* (n = *35*)						
	Baseline	*8 weeks*	*Change value*	P *value*	*Baseline*	*8 weeks*	*Change value*	P *value*[a]	P *value*[b]	P *value*[c]
NK cell activity (%)										
2.5:1	18.14 (9.87)	17.75 (7.19)	–0.40 (8.85)	.927[d]	20.10 (7.43)	18.02 (8.68)	–2.08 (9.85)	.221	.379	.421
5:1	33.78 (12.18)	33.37 (11.54)	–0.41 (10.83)	.906[d]	36.79 (11.22)	34.50 (11.63)	–2.29 (13.18)	.312	.534	.497
10:1	48.14 (10.26)	50.58 (10.67)	2.43 (10.62)	.205[a]	52.29 (10.47)	48.97 (12.02)	–3.32 (12.54)	.126	**.048***	**.035***

Values are presented as means (SD).
The bolded data in Table 2 represent statistically significant results.
[a]Analyzed by paired *t*-test between baseline and 8 weeks within each group.
[b]Analyzed by independent t-tests for changed values between the groups.
[c]Analyzed by ANCOVA (adjusted for each at baseline).
[d]Analyzed by Wilcoxon's signed rank test between baseline and 8 weeks within each group.
*$P < .05$, **$P < .01$, ***$P < .001$.
NK, natural killer.

and 5.27 ± 0.17 [× 10^3/μL] in the control group, with no statistically significant difference between the groups. After 8 weeks of consumption, no significant differences in WBC counts were observed between the two groups.

Correlation analysis

In this clinical study, the correlations between NK cell activity, IFN-γ, IL-12, other inflammatory cytokines, and basic anthropometric parameters were analyzed (Fig. 5). The results showed a weak positive correlation between NK cell activity and IFN-γ ($r = 0.297$, $P < .05$), suggesting a relationship between the two variables. In addition, a weak positive correlation was observed between NK cell activity and IL-2 ($r = 0.296$, $P < .05$), indicating that NK cell activation is closely associated with IL-2. On the other hand, a negative correlation was found between IFN-γ and body weight ($r = –0.245$, $P < .05$), with IFN-γ levels tending to decrease as body weight increased.

Safety assessment

Participants' adherence to the investigational product was monitored at each visit by collecting the remaining capsules for verification. This led to the exclusion of 6 individuals from the per-protocol analysis due to adherence rates below 80%. The mean adherence rate was 96.24 ± 0.97% overall, with 94.51 ± 1.33% in the experimental group and 97.82 ± 1.38% in the control group, showing no statistically significant difference between the two groups ($P > .05$).

A total of 13 adverse events were reported during the study period, including mild cases such as low-grade fever, chills, nausea, gastroesophageal reflux, and periungual inflammation. Of these, nine events occurred in the HY7017 group and four in the placebo group. Mild adverse events reported in the test group included gastric erosion ($n = 1$), gastroesophageal reflux ($n = 1$), acute nasopharyngitis ($n = 2$), fever/chills ($n = 1$), hyperthyroidism ($n = 1$), lymphadenitis ($n = 1$), nausea ($n = 1$), and headache ($n = 1$). In the placebo group, periungual inflammation ($n = 1$) and acute nasopharyngitis ($n = 3$) were reported. All adverse events were assessed as unrelated to the consumption of the investigational product and resolved spontaneously without any medical intervention, and no serious adverse events occurred.

DISCUSSION

This clinical trial aimed to evaluate the efficacy and safety of *Lcb. paracasei* HY7017 for enhancing immune

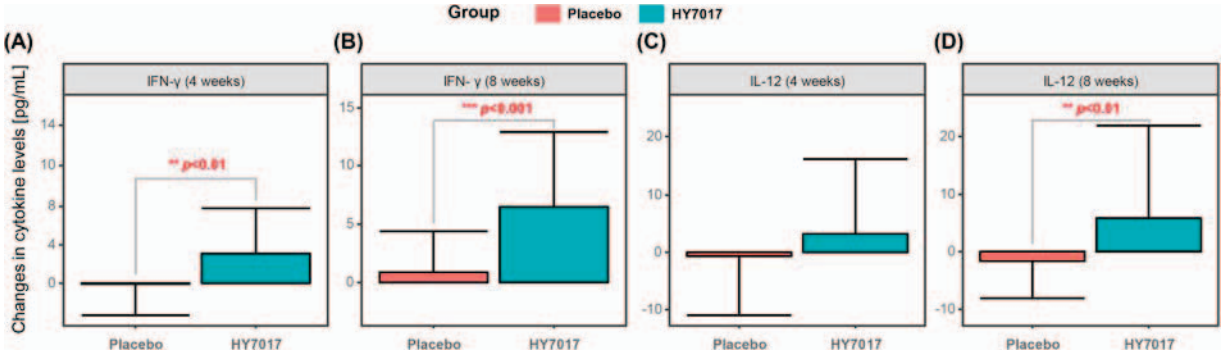

FIG. 3. Changes in cytokine levels according to the week of intake. These graphs show the changes in IFN-γ levels after consumption of *Lcb. paracasei* HY7017 or placebo at **(A)** 4 weeks and **(B)** 8 weeks. The following two graphs show the changes in IL-12 levels at **(C)** 4 weeks and **(D)** 8 weeks. Cytokine changes are presented as *bar graphs*, with statistically significant *P* values indicated on the graphs (**$P < .001$, *$P < .01$). IFN-γ, interferon-γ; IL-12, interleukin-12.

Table 3. Changes in Cytokine Levels of HY7017 Supplementation

	HY7017 group (n = *32*)				*Placebo group* (n = *35*)					
(pg/mL)	*Baseline*	*4 weeks*	*Change value*	P *value*	*Baseline*	*4 weeks*	*Change value*	P *value*	P *value*[a]	P *value*[b]
IFN-γ	15.49 (5.24)	18.59 (6.70)	3.09 (4.69)	.001[c]	17.64 (6.93)	17.57 (6.72)	−0.07 (3.26)	.917[d]	**.005****	—
IL-12	9.21 (10.88)	12.48 (14.43)	3.26 (12.95)	.001[d]	11.67 (10.36)	11.04 (13.19)	−0.63 (10.36)	.341[d]	.190	—
(pg/mL)	*Baseline*	*8 weeks*	*Change value*	P *value*	*Baseline*	*8 weeks*	*Change value*	P *value*		
IFN-γ	15.49 (5.24)	21.99 (7.91)	6.49 (6.38)	<.0001[c]	17.64 (6.93)	18.50 (7.02)	0.86 (3.52)	.157[c]	**<.0001*****	**<.0001*****
IL-12	9.21 (10.88)	15.11 (16.48)	5.90 (15.97)	.009[d]	11.67 (10.36)	10.06 (11.01)	−1.61 (6.49)	.305[d]	**.008****	**.007****

Values are presented as mean (SD).
[a]Analyzed by Mann–Whitney's *U* test for changed values between the groups.
[b]Analyzed by ANCOVA (adjusted for each at baseline).
[c]Analyzed by paired *t*-test between baseline and 4 or 8 weeks within each group.
[d]Analyzed by Wilcoxon's signed rank test between baseline and 4 or 8 weeks within each group.
*$P < .05$, **$P < .01$, ***$P < .001$.
IFN-γ, interferon-γ; IL-12, interleukin-12.

function. The immune-enhancing effects of this strain were demonstrated by significant increases in three immunomodulatory markers—NK cell activity, IL-12, and IFN-γ—after 8 weeks of *Lcb. paracasei* HY7017 consumption, with no clinically significant differences observed in any biomarkers or adverse events. Based on these findings, we propose *Lcb. paracasei* HY7017 as a potential functional health food ingredient for immune enhancement.

Probiotics are generally understood to enhance immune function in the gut through three primary mechanisms: (1) the role of probiotics in the gut, (2) activation of immune cells, and (3) stimulation of pattern recognition receptors (PRRs). First, probiotics produce antimicrobial substances such as bacteriocins and lactic acid, which competitively inhibit pathogenic microorganisms and enhance intestinal barrier function, thereby promoting immune activation.[9,10] Second, probiotics stimulate immune cells upon interaction with the intestinal mucosa.[11,12] This interaction activates macrophages, dendritic cells, and T cells, leading to the secretion of pro-inflammatory cytokines such as IL-12 and TNF-α, which play essential roles in immune modulation. Finally, probiotics stimulate PRRs, which recognize microbial patterns and initiate immune responses.[9,11] By activating these PRRs, probiotics enable the immune system to more effectively recognize and respond to pathogens. During this process, probiotics regulate the balance between Th1/Th2 cell responses and modulate immune-regulatory cytokines, maintaining immune homeostasis.

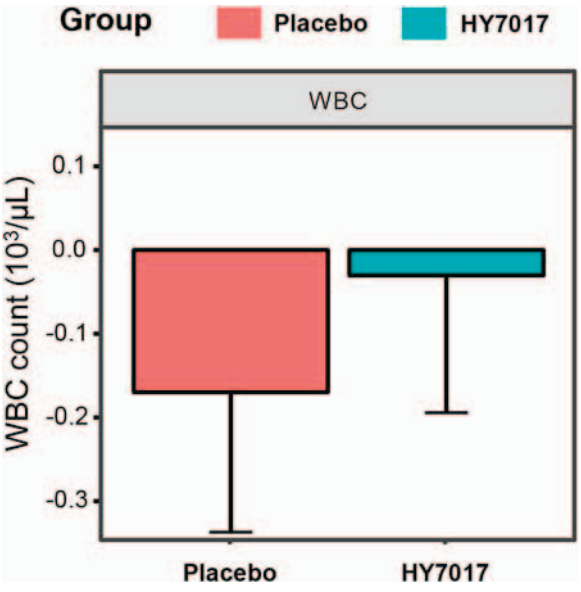

FIG. 4. Comparison of changes in WBC levels after 8 weeks of intake. This graph compares the changes in WBC levels between the placebo and HY7017 groups after 8 weeks of intake. WBC, White blood cell.

Based on these well-established mechanisms of action, we propose that consumption of *Lcb. paracasei* HY7017 likely contributed to immune enhancement through similar pathways. *Lcb. paracasei* is a well-documented probiotic, and numerous studies have reported its ability to reinforce the intestinal barrier and suppress pathogenic microorganisms.[13–15] Furthermore, our findings showing an increase in NK cell activity, IL-12, and IFN-γ confirm that *Lcb. paracasei* HY7017 activated immune cells and influenced cytokine secretion. These immunomodulators are closely interconnected within the innate immune system. IL-12 activates NK cells and induces IFN-γ production and activated NK cells secrete IFN-γ to activate macrophages and amplify the immune response.[16,17] In addition, IFN-γ forms a positive feedback loop that strengthens NK cell activity and promotes IL-12 production, further enhancing the immune response. Through these interactions, NK cells, IL-12, and IFN-γ play key roles in innate immunity, contributing to the initial defense against infections and subsequent induction of adaptive immune responses. The increased levels of these immunomodulators observed following *Lcb. paracasei* HY7017 intake may have been effectively modulated through these interactions. Similar effects have been reported in previous *in vitro* and *in vivo* studies. In cell culture experiments, the HY7017-treated group exhibited significant increases in cytokines (IL-12,

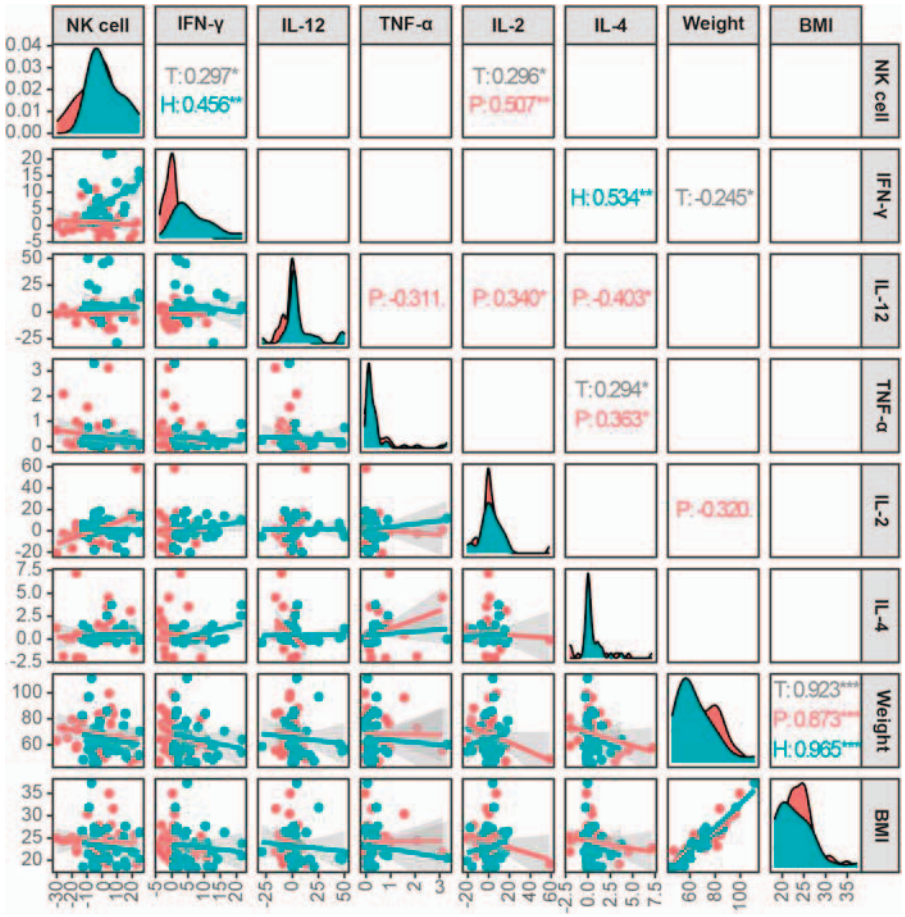

FIG. 5. Correlation between NK cell activity, cytokines, and body weight. Correlation coefficients **(r)** are shown in the upper triangle, and only statistically significant correlations are displayed. T indicates the total group, P the placebo group (*pink*), and H the HY7017 group (*blue*). Significance levels are denoted as follows: ***$P < .001$; **$P < .01$; *$P < .05$; $P < .1$. "NK cell" indicates NK cell activity, and "BMI" represents body mass index.

IFN-γ, TNF-α, IL-6, IL-10), nitric oxide (NO), inducible nitric oxide synthase (iNOS), cyclooxygenase-2, and NK cell activity, suggesting its effectiveness in immune enhancement.[18] In animal studies, significant increases in cytokines such as IL-12 and IFN-γ, splenocyte proliferation, WBC count, and NK cell activity were also observed. The immune-related effects previously observed in cell lines and animal models were consistently reproduced in this human intervention study. These results suggest that *Lcb. paracasei* HY7017 modulates early-stage innate immune responses through the coordinated action of NK cells, IL-12, and IFN-γ, thereby enhancing host immunity.

While clinical evidence is still limited, several studies—including both preclinical experiments and clinical trials—have investigated the immune-enhancing effects of various *Lcb. paracasei* strains. One study confirmed the induction of IL-10 production and the inhibition of IL-1β production in mouse and human immune cells treated with *Lcb. paracasei* KW3110.[19] A study by Paturi et al. demonstrated that *Lcb. paracasei* LAFTI L26 increased IL-10 and IFN-γ in mice.[20] In a clinical study using an influenza vaccination model, *Lcb. paracasei* ssp. *paracasei* significantly enhanced vaccine-specific IgG, IgG1, and IgG3 levels in plasma and increased secretory IgA in saliva, indicating improved systemic and mucosal immune responses in healthy adults.[21] These results suggest that *Lcb. paracasei* regulates immunity through various pathways and that the detailed mechanisms of action may differ by strain.

In addition, a correlation analysis was performed between NK cell activity, cytokine levels, and various physical parameters; however, no significant findings with strong positive correlations or statistically significant *P* values were observed. While it is generally recognized that body weight and BMI are associated with immune function, only body weight showed a weak negative correlation with IFN-γ.[22,23] Although body weight and BMI are generally associated with immune function, no consistent correlations were observed in this study, possibly due to other unmeasured factors influencing immune responses.

Despite the promising results, this study has some limitations that should be acknowledged. First, while previous *in vitro* and animal studies, along with the present clinical trial, suggest that HY7017 enhances NK cell activity and modulates IFN-γ expression, the specific bioactive

components responsible for these effects remain unclear. Further studies are needed to identify which constituents—such as cell wall components, exosomes, or metabolites—are involved in mediating these immune responses. Second, although HY7017 is a probiotic, we did not analyze changes in the gut microbiota composition. Investigating shifts in microbial communities could provide deeper insight into the mechanism of action and host–microbe interactions. Future studies addressing these points will be essential to better understand the full immunological impact of HY7017.

In conclusion, *Lcb. paracasei* HY7017 consumption significantly enhanced immune function by increasing NK cell activity and levels of IFN-γ and IL-12. These results suggest that *Lcb. paracasei* HY7017 is an effective probiotic for modulating and enhancing the immune system. It is anticipated that the results of this study may contribute to the development of immune-supportive functional foods using *Lcb. paracasei* HY7017 and the establishment of prevention and treatment strategies for infectious diseases.

AUTHORS' CONTRIBUTIONS

J.S. and H.D.K. wrote the article. L.H and H.D.K. conceptualized and conducted the clinical trial. P.S.D. and C.I.D. reviewed and edited the article. P.S.D. designed the study, and S.J.J. and L.J.H. supervised the project.

AUTHOR DISCLOSURE STATEMENT

No competing financial interests exist.

FUNDING INFORMATION

No funding was received for this article.

REFERENCES

1. Levy O. Innate immunity of the newborn: Basic mechanisms and clinical correlates. Nat Rev Immunol 2007;7(5):379–390; doi: 10.1038/nri2075
2. Benveniste EN, Benos DJ. TNF-α-and IFN-γ-mediated signal transduction pathways: Effects on glial cell gene expression and function. Faseb J 1995;9(15):1577–1584; doi: 10.1096/fasebj.9.15.8529837
3. Yang SJ, Lee JE, Lim SM, et al. Antioxidant and immune-enhancing effects of probiotic Lactobacillus plantarum 200655 isolated from kimchi. Food Sci Biotechnol 2019;28(2):491–499; doi: 10.1007/s10068-018-0473-3
4. Braat H, van den Brande J, van Tol E, et al. Lactobacillus rhamnosus induces peripheral hyporesponsiveness in stimulated CD4+ T cells via modulation of dendritic cell function. Am J Clin Nutr 2004;80(6):1618–1625; doi: 10.1093/ajcn/80.6.1618
5. Moon PD, Lee JS, Kim HY, et al. Heat-treated Lactobacillus plantarum increases the immune responses through activation of natural killer cells and macrophages on *in vivo* and *in vitro* models. J Med Microbiol 2019;68(3):467–474; doi: 10.1099/jmm.0.000938
6. Wada H, Mawatari T, Saito Y, et al. Lactobacillus helveticus induces two types of dendritic cell activation and effectively suppresses onset of the common cold: A randomized, double-blind, placebo-controlled trial. Nutrients 2024;17(1):101; doi: 10.3390/nu17010101
7. Chong HX, Yusoff NAA, Hor YY, et al. Lactobacillus plantarum DR7 improved upper respiratory tract infections via enhancing immune and inflammatory parameters: A randomized, double-blind, placebo-controlled study. J Dairy Sci 2019;102(6):4783–4797; doi: 10.3168/jds.2018-16103
8. Cho JM, Yoo D, Lee JY, et al. Supplementation with a natural source of amino acids, Sil-Q1 (silk peptide), enhances natural killer cell activity: A redesigned clinical trial with a reduced supplementation dose and minimized seasonal effects in a larger population. Nutrients 2021;13(9):2930; doi: 10.3390/nu13092930
9. Liu Y, Wang J, Wu C. Modulation of gut microbiota and immune system by probiotics, pre-biotics, and post-biotics. Front Nutr 2021;8:634897; doi: 10.3389/fnut.2021.634897
10. Hernández González JC, Martínez Tapia A, Lazcano Hernández G, et al. Bacteriocins from lactic acid bacteria. A powerful alternative as antimicrobials, probiotics, and immunomodulators in veterinary medicine. Animals 2021;11(4):979; doi: 10.3390/ani11040979
11. Mazziotta C, Tognon M, Martini F, et al. Probiotics mechanism of action on immune cells and beneficial effects on human health. Cells 2023;12(1):184; doi: 10.3390/cells12010184
12. Zhang C, Wang H, Chen T. Interactions between intestinal microflora/probiotics and the immune system. Biomed Res Int 2019;2019(1):6764919; doi: 10.1155/2019/6764919
13. Hill D, Sugrue I, Tobin C, et al. The Lactobacillus casei group: History and health related applications. Front Microbiol 2018;9:2107; doi: 10.3389/fmicb.2018.02107
14. Eutamene H, Lamine F, Chabo C, et al. Synergy between Lactobacillus paracasei and its bacterial products to counteract stress-induced gut permeability and sensitivity increase in rats. J Nutr 2007;137(8):1901–1907; doi: 10.1093/jn/137.8.1901
15. Coman M, Verdenelli MC, Cecchini C, et al. In vitro evaluation of antimicrobial activity of Lactobacillus rhamnosus IMC 501®, Lactobacillus paracasei IMC 502® and SYNBIO® against pathogens. J Appl Microbiol 2014;117(2):518–527; doi: 10.1111/jam.12544
16. de Groen RA, Boltjes A, Hou J, et al. IFN-λ-mediated IL-12 production in macrophages induces IFN-γ production in human NK cells. Eur J Immunol 2015;45(1):250–259; doi: 10.1002/eji.201444903
17. Zwirner NW, Ziblat A. Regulation of NK cell activation and effector functions by the IL-12 family of cytokines: The case of IL-27. Front Immunol 2017;8:25; doi: fimmu.2017.00025
18. Mo S-J, Nam B, Bae C-H, et al. Characterization of novel Lactobacillus paracasei HY7017 capable of improving physiological properties and immune enhancing effects using red ginseng extract. Fermentation 2021;7(4):238; doi: 10.3390/fermentation7040238
19. Yamazaki T, Ohshio K, Sugamata M, et al. Lactic acid bacterium, Lactobacillus paracasei KW3110, suppresses inflammatory stress-induced caspase-1 activation by promoting interleukin-10 production in mouse and human immune cells. PLoS One 2020;15(8):e0237754; doi: 10.1371/journal.pone.0237754
20. Paturi G, Phillips M, Jones M, et al. Immune enhancing effects of Lactobacillus acidophilus LAFTI L10 and Lactobacillus paracasei LAFTI L26 in mice. Int J Food Microbiol 2007;115(1):115–118; doi: 10.1016/j.ijfoodmicro.2006.10.007

21. Rizzardini G, Eskesen D, Calder PC, et al. Evaluation of the immune benefits of two probiotic strains Bifidobacterium animalis ssp. lactis, BB-12® and Lactobacillus paracasei ssp. paracasei, L. casei 431® in an influenza vaccination model: A randomised, double-blind, placebo-controlled study. Br J Nutr 2012;107(6):876–884; doi: 10.1017/S000711451100420X
22. Phillips CL, Grayson BE. The immune remodel: Weight loss-mediated inflammatory changes to obesity. Exp Biol Med (Maywood) 2020;245(2):109–121; doi: 10.1177/1535370219900185
23. Ilavská S, Horváthová M, Szabová M, et al. Association between the human immune response and body mass index. Hum Immunol 2012;73(5):480–485; doi: 10.1016/j.humimm.2012.02.023