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Effects of *Saccharomyces cerevisiae* NK-1 on stool frequency and volume in healthy individuals with infrequent bowel movements: a randomized, placebo, placebo controlled, double-blind study

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ABSTRACT

Background: Constipation and other symptoms of gastrointestinal discomfort, such as abdominal swelling, are common among healthy individuals and have a significant impact on quality of life. Despite the known contribution of gut microbiomes to this pathology, little is known regarding which groups of microorganisms play a key role. Yeasts have been used for fermenting foods since ancient times. *Saccharomyces cerevisiae* is a type of yeast used for industrial and pharmaceutical purposes in the genetic and medical fields because it is

unicellular with a simple biological structure. Yeast also helps improve the intestinal environment. The present study aimed to investigate the effect of foods containing *Saccharomyces cerevisiae* on bowel movement and to validate the safety of its long-term usage. Stool frequency and consistency were also assessed.

Methods: This was a randomized, double-blind, parallel-group study. The test food contained *S. cerevisiae* NK-1 powder (1×10^{10} cells), whereas the placebo did not contain it. The food was made into sticks and provided to healthy individuals with infrequent bowel movements (3–5 movements a week), three times a day for 12 weeks. Then we investigated the changes in stool frequency, volume, and other adverse events.

Results: The number of days with bowel movement significantly increased in the test group compared with the placebo group after 8–12 weeks of consuming the test food ($p < 0.05$). Based on the blood test results, there were no adverse events associated with the consumption of the test food observed.

Conclusions: Consumption of the test food regulated intestinal function by promoting defecation in healthy individuals prone to constipation. Thus, *S. cerevisiae* NK-1 helps facilitate smoother defecation.

Clinical Trial: UMIN #000020476

Keywords: *Saccharomyces cerevisiae* NK-1, bowel movement, stool frequency volume, gastrointestinal discomfort

BACKGROUND

Constipation is a functional bowel disorder usually described as persistent, difficult, infrequent, and/or incomplete defecation associated with three or fewer bowel movements per week [1]. Recently, the efficacy of probiotics and prebiotics in functional constipation was reviewed. The theory that probiotics play key roles in the development of constipation was not validated because the trials were limited, heterogeneous, and poorly designed [2]. Although there has been evidence demonstrating how prebiotic fibers (e.g., psyllium and inulin) positively affect constipation and are accordingly recommended, the quality of evidence is still low [3].

Constipation is usually caused by lack of fiber. Decreased vermiculation of the intestines results in irregular bowel movement. When long periods of constipation persist, the stool loses

its water content because it was retained in the intestines for too long, causing it to harden. Furthermore, chronic retention of stool in the intestines increases the number of putrid bacteria in the intestinal flora, thereby reducing the number of lactobacilli. This phenomenon generates indole, skatole, ammonia, and hydrogen sulfide in the intestines, which results in unpleasant symptoms such as intestinal tissue infection and bloating. Constipation is not only associated with abdominal but also psychological symptoms [4-6]. Abdominal bloating lowers appetite and causes depression. Therefore, regular bowel movements are essential for maintaining a high quality of life. To improve bowel routine, the fiber intake should be increased to elevate the number of lactobacilli or bifidobacteria in the intestinal flora and lower the emission of putrefaction gases. Moreover, increasing fiber intake also improves constipation. However, there have only been a few studies investigating the beneficial effects of fiber intake on bowel movement in humans. Although evidence demonstrates how prebiotic fibers positively affect constipation and are usually recommended, the quality of evidence is still considered low.

Yeasts have been used for fermenting foods, such as bread, sake, and wine, since ancient times. Furthermore, yeast has been used for industrial and pharmaceutical purposes in the genetic and medical fields because it is unicellular with a simple biological structure. *Saccharomyces cerevisiae* is a well-known yeast species. Considering its physiological activity, it is well known for its nutrient tonicity and mineral supplement effects associated with its rich nutrient contents. Moreover, yeast is known to improve bowel movement because it is rich in dietary fiber.

Therefore, we conducted a randomized, double-blind study to assess and compare the effects of a food with *Saccharomyces cerevisiae* NK-1 versus a placebo food.

METHODS

Study design

This was a randomized, placebo controlled, double-blind, parallel-group study. We included 50 individuals and equally divided them into two groups: The *S. cerevisiae* NK-1 group and placebo group. This clinical trial was carried out at Chiyoda Para-Medical Care Clinic. (Tokyo, Japan) The participants were all healthy adults Japanese with infrequent bowel movements (3–5 movements a week) and met the inclusion criteria listed in Table 1. Informed consent was obtained from all the participants in written. The ethics committee of the Japan Conference of Clinical Research reviewed and approved the study prior to its implementation. Furthermore, the study plan was registered under the UMIN Clinical Trials Registry (UMIN #000020476).

Table 1 Inclusion and exclusion criteria of the study

Inclusion criteria
Participants aged 20–64 years
Infrequent bowel movements (3–5 movements a week)
Exclusion criteria
Known allergy or sensitivity to any foods
Participants who use any medecines or supplements
History of severe disease such as intestinal diseases

Randomization

Participants were classified using the stratified block randomization method (stratification factor: number of bowel movements). An individual not involved in the study created a computer program using a random number table to randomly stratify the participants into one of the two groups. Both the participants and investigators were blinded to the group stratifications.

Placebo and test food

S. cerevisiae NK-1 was provided in lyophilized powder. The test food was in the form of a stick containing *S. cerevisiae* NK-1 powder (Nikkenkyo Service Corporation, 1.0×10^{10} cells/stick) and was administered to the participants three times a day. The placebo food did not contain the *S. cerevisiae* NK-1 powder. Both food did not differ in terms of characteristics, including color, smell, and size. The ingredients of the test and placebo food are listed in Table 2.

Table2 Composition of the test (*Saccharomyces cerevisiae* NK-1) and placebo food samples per day*

	Test Foods	Placebo
Saccharomyces cerevisiae NK-1	5.40	-
Lactose	-	5.38
Caramel color	-	0.02
Total	5.40	5.40

*3 sticks/day

Bowel movement

Throughout the study period, participants frequently answered questionnaires investigating fecal characteristics, including the number of bowel movements and volume of stool (number of medium egg-sized stools) per day.

Adverse events

Hematological and blood biochemical tests were conducted before and after 4, 8, and 12 weeks of consuming the food. Participants were also interviewed regarding any adverse events faced during each hospital visit to investigate causal relationships and severity.

Statistical analysis

The Mann–Whitney *U*-test and Wilcoxon signed-rank test were performed to assess the number of days with bowel movement and number of bowel movements. The level of statistical significance was set at 5%. Adverse events were examined using Fisher's exact test. Statistical analyses were conducted at the Kansai University of Welfare Sciences using the SAS software version 9.4 (SAS Inc.)

RESULTS

Analysis set

In total, 50 participants were included (25 per group). Three participants from each group dropped out half-way through the study due to personal reasons. Therefore, the final analysis set for efficacy and safety included only 44 participants. In the test period, Participants did not change water intake and meal amount. The weight of participants did not change. Table 3 presents the profiles of all the included participants.

Table 3 Profile of the participants

	Saccharomyces cerevisiae NK-1-treated gr	Placebo group
Number of participants	22	22
Sex ratio (male-to-female)	7/15	6/16
Age	43.59 ± 8.72	42.36 ± 10.67
Number of days with bowel movement (days/week)	3.29 ± 0.73	3.47 ± 0.41

Bowel movement and stool volume

Stool frequency was calculated daily and tallied weekly. The study results are presented in Table 4 (average calculated every four weeks) and Figure 1 (average calculated every week). After 4, 8, and 12 weeks of consuming the test food ($p < 0.05$), the number of days with bowel movement/week increased significantly in the test group compared to the placebo group. The stool volume significantly increased in the test group compared to the placebo group after 8 and 12 weeks of consuming the test food ($p < 0.05$). Figure 2 shows the increase in stool frequency per day, which significantly increased in the test group compared to the placebo group after 4 and 8 weeks of consuming the test food ($p < 0.05$).

Table 4 Bowel movement and stool volume before and 4, 8, and 12 weeks after consumption

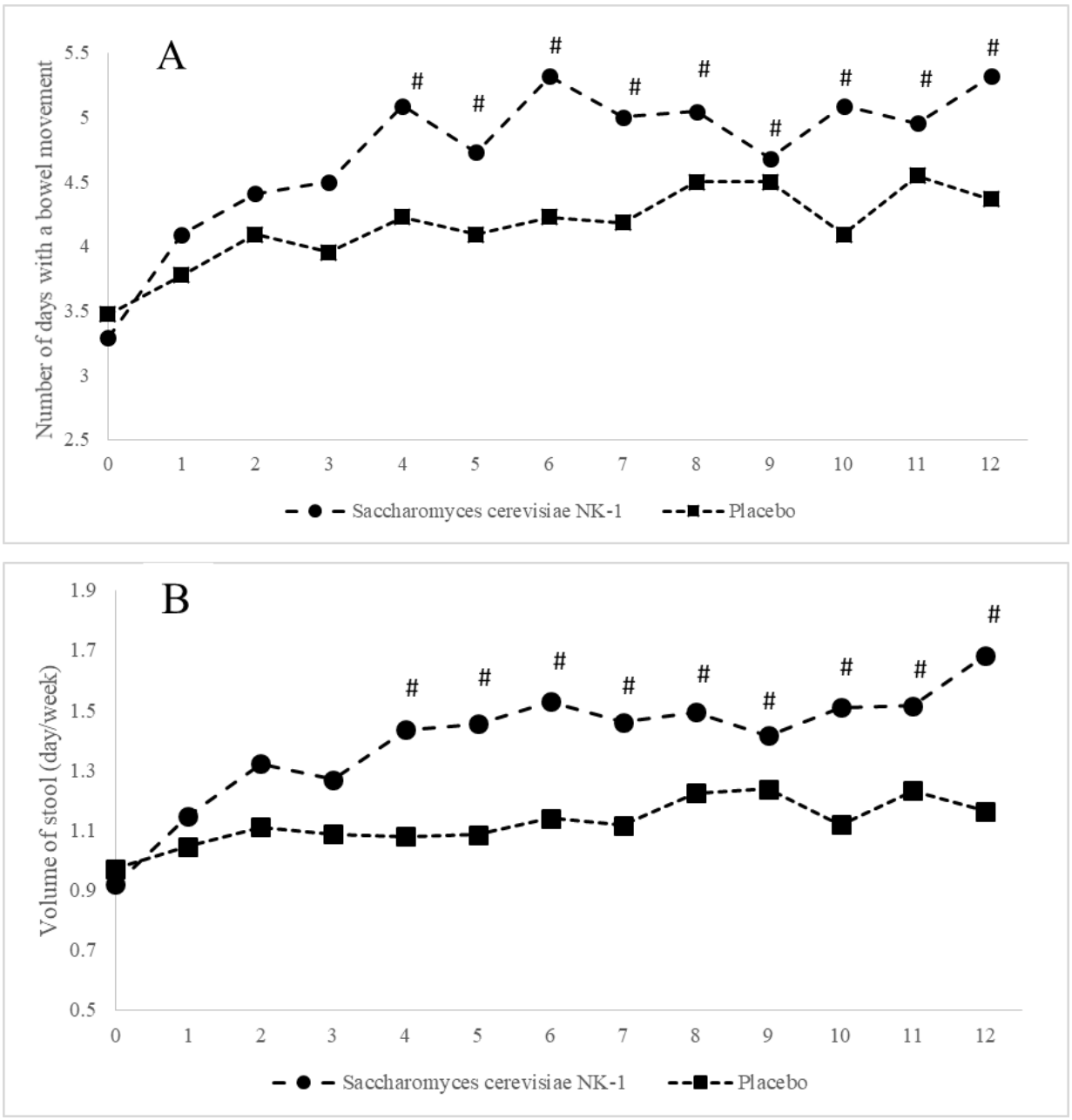
	Group	n	Before	4 weeks	8 weeks	12 weeks
Number of days with a bowel movement (day/week)	*Saccharomyces cerevisiae* NK-1	22	3.29 ± 0.73	4.52 ± 0.84$^{*\#}$	5.02 ± 1.06$^{*\#}$	5.01 ± 0.90$^{*\#}$
	Placebo	22	3.47 ± 0.41	4.01 ± 0.73*	4.25 ± 0.87*	4.38 ± 1.11*
Volume of stool (day/week)	*Saccharomyces cerevisiae* NK-1	22	0.92 ± 0.31	1.29 ± 0.57$^{\$\dagger}$	1.48 ± 0.57$^{\$\dagger}$	1.53 ± 0.55$^{\$\dagger}$
(number of medium egg-sized stools)	Placebo	22	0.97 ± 0.33	1.08 ± 0.52$^{\$}$	1.14 ± 0.52$^{\$}$	1.19 ± 0.53$^{\$}$

*The stool frequency and volume was calculated daily and tallied weekly. This table indicates the average calculated every 4 weeks.

* $p < 0.05$ Wilcoxon signed-rank test vs 0 week, # $p < 0.05$ Mann–Whitney *U*-test vs placebo group

$^{\$}p < 0.05$ paired t-test vs 0 week, †$p < 0.05$ Student's t test vs placebo group

Fig.1 Changes in the number of days with bowel movement (days/week) (A) and stool volume (number of medium egg-sized stools) (days/week) (B)



*The stool frequency and volume was calculated every day and tallied every week. #; significantly increased in the test group compared to the placebo group ($p < 0.05$).

Volume of stool (day/week) was calculated by number of medium egg-sized stools. #; significantly increased in the test group compared to the placebo group ($p < 0.05$).

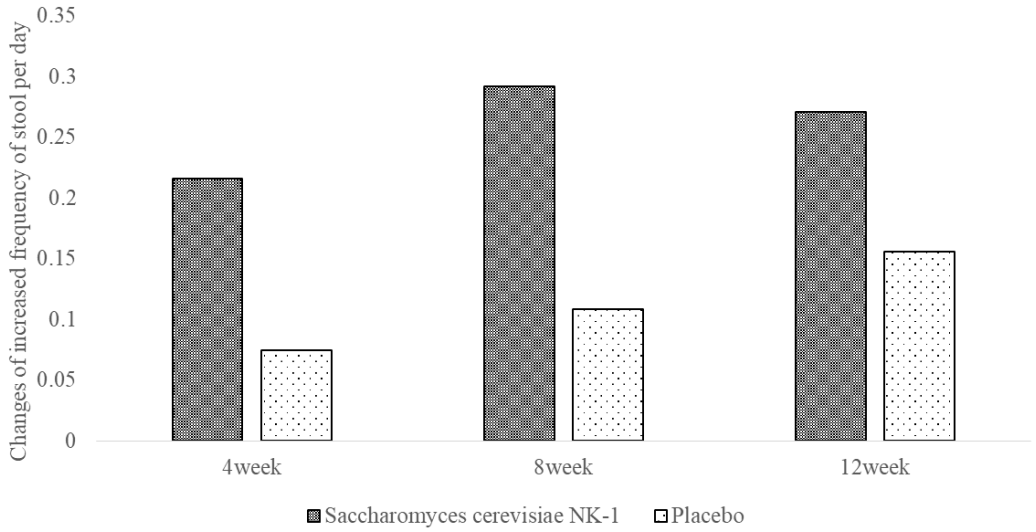


Fig.2 Changes in stool frequency per day,
*significantly increased in the test group compared with the placebo group ($p < 0.05$).

DISCUSSION

The results of the present study indicated that 4, 8, and 12 weeks of consuming the test food resulted in a significantly higher frequency of bowel movement in the test group than in the control group.

Probiotics are living bacteria, viruses, parasites, or yeasts that are beneficial to the consumer. The administration of probiotics is considered promising, safe, and acceptable for treating constipation and irritable bowel syndrome (IBS). Most studies evaluating the effects of probiotics on patients with IBS have been performed using bacterial strains of lactobacilli and/or bifidobacteria [7]. Compared with bacteria, yeasts have numerous benefits, which include antibiotic and phage resistance, higher natural robustness against gastric acid and bile salts, and stronger capacity to regulate innate immune response [8]. However, only two clinical trials to date have assessed the effects of yeast in patients with IBS [9, 10]. No study has yet assessed the effect of yeasts in individuals with constipation.

Yeasts are eukaryotic, unicellular, immotile microorganisms that have cell walls. They have no photosynthetic capacity and derive nutrients via decomposition and absorption of external organic matter. Yeasts are morphologically circular or elliptical in shape with minimal features. Microorganisms of this nature were first identified as yeasts. They multiply by budding or division. Proliferating cells are sometimes incompletely attached to each other and give rise to dendrites. These features indicate that yeasts can easily proliferate in the intestine. Furthermore, because this microorganism promotes the production of good bacteria in the

intestine and is unicellular, it has a dietary fiber-like action which may help improve bowel movement.

CONCLUSION

S. cerevisiae NK-1 powder significantly increases the number of days with bowel movement/week in the test group compared with the placebo group. The results demonstrated how *S. cerevisiae* NK-1 is beneficial due to its regulatory effect on intestinal function.

Abbreviations: UMIN: University hospital Medical Information Network

Competing Interests: The authors declare no conflict of interest.

Authors' Contributions: RT, SI, NK, and MK designed this clinical research. RT, SI, and YE performed this clinical research. RT and SI prepared this manuscript.

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