Prune Juice Containing Sorbitol, Pectin, and Polyphenol Ameliorates Subjective Complaints and Hard Feces While Normalizing Stool in Chronic Constipation: A Randomized Placebo-Controlled Trial

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INTRODUCTION: The aim of this study was to determine the effectiveness of prune juice on chronic constipation.

METHODS: We conducted a double-blind, randomized, placebo-controlled trial in Japanese subjects with chronic constipation.

RESULTS: Prune intake significantly decreased hard and lumpy stools while increasing normal stool and not increasing loose and watery stools. Prune intake also ameliorated subjective complaints of constipation and hard stools, without alteration of flatulence, diarrhea, loose stools, or urgent need for defecation. There were no adverse events or laboratory abnormalities of liver or renal function after prune intake.

DISCUSSION: Prune juice exerted an effective and safe natural food therapy for chronic constipation.

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INTRODUCTION
There are a wide variety of laxatives available for chronic constipation treatment, but they have several problems, including side effects and insufficient efficacy (1,2). Instead of drug treatment, there has been increasing recognition of natural food treatment, which is beneficial in its safety and prevalence (3). Among natural foods, prune potentially exerts an ameliorating effect on constipation (4,5), but little data are available on the effectiveness in chronic constipation subjects or on side effects such as abdominal discomfort or diarrhea symptoms. We aimed to evaluate the effects of prune juice consumption on stool consistency and subjective complaints of constipation symptoms in Japanese subjects with chronic constipation.

METHODS
This study was conducted in accordance with the Declaration of Helsinki with the approval of the institutional review boards of the Miura Clinic (approval number: R2001) and Tokyo Medical University (approval number: T2021-0243). Written informed consent was obtained from all subjects before their enrollment into this study.

This study included subjects aged 20–75 years who presented symptoms of treatment-naive chronic constipation. The criterion for chronic constipation was defined according to Rome IV as fewer than 3 bowel movements per week and/or hard stool defined by the Bristol Stool Form Scale (BSFS) 1 or 2, for the past 3 months, with symptom onset at least 6 months earlier (6). Subjects were randomly assigned to the prune juice group or placebo group and consumed 54 g of each test food in a day for 8 weeks. The placebo is designed to match the flavor, color, and taste of prune juice (see Table 1, Supplementary Digital Content, http://links.lww.com/AJG/C620). Stool consistency by BSFS (7) and subjective complaints by the Gastrointestinal Symptom Rating Scale (GSRS) (8) were assessed for constipation improvement. Stool consistency was recorded at each bowel movement and analyzed as the rate of each score in every week throughout the study period. GSRS was measured at baseline, 4 weeks, and 8 weeks after starting intake. Subjects reported any adverse events (AEs) during the study period. Laboratory parameters were assessed by blood and urine tests at baseline and in the postintake period. The severity of AEs or laboratory abnormalities was evaluated according to the definition by the Common Terminology Criteria for Adverse Events, version 5.0 (9) (ClinicalTrials.gov number, University hospital Medical Information Network Identify Document: 000041384). Detailed methods are provided in Methods (see Supplementary Digital Content, http://links.lww.com/AJG/C621).

RESULTS
A total of 84 subjects were enrolled and included in the intention-to-treat analysis (see Figure 1, Supplementary Digital

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There were no significant differences in baseline characteristics (Table 1) including age, sex, body mass index, dietary habits, BSFS score (Figure 1), and bowel symptoms (Table 2) between the groups. In the prune juice group, the rates of hard and lumpy stools (BSFS 1 or 2) were significantly decreased from baseline and were significantly lower than the placebo group after 3 weeks (Figure 1). The rates of normal stools (BSFS 3 or 4) were significantly increased from baseline and were significantly higher than the placebo group after 3 weeks. The rates of loose and watery stools (BSFS 5, 6, or 7) were not significantly changed during the study period.

Next, we focused on alterations of subjective complaints using GSRS scores after prune juice intake. In the prune juice group, constipation, hard stools, incomplete evacuation, and flatulence scores significantly decreased at week 4 or 8 (Table 2). Prune juice

| Table 1. Baseline characteristics, adverse events, and laboratory abnormalities |
|-----------------|-----------------|-----------------|
|                 | Placebo (n = 42) | Prune juice (n = 41* or 42) | P value |
| Baseline characterisrics |                 |                 |         |
| Age (yr)         | 50.5 ± 10.5      | 50.8 ± 11.1      | 0.904   |
| Sex, female, n (%) | 31 (73.8%)      | 32 (76.2%)      | 0.801   |
| Height (cm)      | 159.5 ± 7.3      | 160.8 ± 8.2      | 0.472   |
| Weight (kg)      | 55.7 ± 8.3       | 55.0 ± 9.3       | 0.540   |
| BMI (kg/m²)      | 21.8 ± 2.5       | 21.2 ± 2.5       | 0.241   |
| Current smoker, n (%) | 3 (7.1%)     | 3 (7.1%)        | 1.000   |
| Alcohol drinker, n (%) | 19 (45.2%) | 15 (35.7%)      | 0.374   |
| Food frequency and rice⁵  | 5.40 ± 0.96     | 5.07 ± 1.24     | 0.245   |
| Food frequency and breads⁵ | 4.14 ± 1.14    | 4.10 ± 1.25     | 0.980   |
| Food frequency and vegetables⁵ | 4.48 ± 1.57  | 3.88 ± 1.76     | 0.105   |
| Food frequency and fruits⁵ | 3.00 ± 1.36    | 2.90 ± 1.25     | 0.904   |
| Food frequency and meats⁵ | 3.95 ± 1.01    | 3.83 ± 1.08     | 0.589   |
| Food frequency, cheese, and yogurt⁵ | 2.90 ± 1.25  | 2.74 ± 1.25     | 0.476   |
| Food frequency and natto⁵ | 1.90 ± 0.93    | 2.29 ± 1.02     | 0.091   |
| Food frequency, soy sauce, and miso⁵ | 3.98 ± 1.33  | 3.95 ± 1.31     | 0.786   |
| Food frequency and pickles⁵  | 1.98 ± 0.84     | 2.38 ± 1.21     | 0.135   |
| Adverse events⁶ |                 |                 |         |
| Nausea, ≥ grade 3 | 0 (0.0%)         | 0 (0.0%)         | —       |
| Headache, ≥ grade 3 | 0 (0.0%)         | 0 (0.0%)         | —       |
| Dizziness, ≥ grade 3 | 0 (0.0%)         | 0 (0.0%)         | —       |
| Laboratory abnormalities⁶ |                 |                 |         |
| Increased AST, ≥ grade 3 | 0 (0.0%)         | 0 (0.0%)         | —       |
| Increased ALT, ≥ grade 3 | 0 (0.0%)         | 0 (0.0%)         | —       |
| Increased ALP, ≥ grade 3 | 0 (0.0%)         | 0 (0.0%)         | —       |
| Increased γ-GTP, ≥ grade 3 | 0 (0.0%)         | 0 (0.0%)         | —       |
| Increased creatinine, ≥ grade 3 | 0 (0.0%) | 0 (0.0%) | —       |
| Proteinuria, ≥ grade 3 | 0 (0.0%)         | 0 (0.0%)         | —       |
| Glucosuria, ≥ grade 3 | 0 (0.0%)         | 0 (0.0%)         | —       |

Data are expressed as n (%) or mean ± SD. The severity of the adverse events or laboratory abnormalities was graded as grade 1 (mild), grade 2 (moderate), grade 3 (severe), or grade 4 (life-threatening consequences) according to the definition by the CTCAE, version 5.0.

ALP, alkaline phosphatase; ALT, alanine aminotransferase; AST, aspartate aminotransferase; BMI, body mass index; CTCAE, Common Terminology Criteria for Adverse Events; γ-GTP, γ-glutamyl transpeptidase.

*One subject withdrew from the postintake laboratory test.

⁵Food frequencies were assessed using a 7-point Likert scale (1, never or rarely; 2, 1 to 3 times/month; 3, 1 to 3 times/week; 4, four to six times/week; 5, once/day; 6, twice/day; and 7, 3 or more times/day) for typical eating patterns in the previous month.

⁶Adverse events were reported at lower grades. The number of cases with mild/moderate symptoms (grade 1/2) is as follows: nausea (1/0, 0/0), headache (2/0, 2/0), and dizziness (1/0, 0/0) for placebo and prune juice groups, respectively.

⁷The number of cases with mild/moderate symptoms (grade 1/2) is as follows: increased AST (1/0, 1/0), increased ALT (4/0, 2/0), increased ALP (1/0, 3/0), increased γ-GTP (1/0, 0/0), increased creatinine (0/0, 2/0), proteinuria (2/0, 0/0), and glucosuria (0/0, 0/0) for placebo and prune juice groups, respectively.

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intake showed significant differences in constipation and hard stools from the placebo group at week 8. Meanwhile, diarrhea, loose stools, and urgent need for defecation scores were not significantly changed from baseline. During the study period, there were no AEs or laboratory abnormalities of liver or renal function based on the Common Terminology Criteria for Adverse Events definition between baseline and postintake period in either group (Table 1).

DISCUSSION
Notably, BSFS 1 (hard stool) rates significantly decreased after 3 weeks, whereas BSFS 4 (normal stool) rates significantly increased after 7 weeks of prune juice intake compared with placebo (Figure 1). Although a previous study has also shown a significant increase in the mean BSFS after prune intake in chronic constipation (4,5), it has not focused on alteration of each BSFS score. Importantly, the persistence of BSFS 4 was reported to be significantly correlated with the quality of life (10). Previous studies focusing on constipation and prune intake have limited evaluation to study periods ≤4 weeks (4,5). Collectively, our study underlies that it is important to improve stool shape in ≥4 weeks, but that quality of life determination should take place after at least 8 weeks.

One issue for prune intake that should be raised is its tendency to cause diarrhea and flatulence (11,12). In our study, frequency of loose and watery stools (BSFS 5, 6, or 7) was not altered by prune juice intake (Figure 1). More importantly, we evaluated subjective complaints using GSRS (Table 2), not assessed in previous studies, and found that prune juice substantially decreased constipation and hard stools without alteration of flatulence, diarrhea, or other bowel discomfort compared with placebo. Furthermore, the safety assessment showed that prune juice intake did not cause AEs or laboratory abnormalities of liver function or renal function (Table 1). These data suggest that prune juice could be used continuously and safely by those with chronic constipation.

The prune juice used in this study contained abundant sorbitol (see Table 1, Supplementary Digital Content, http://links.lww.com/AJG/C620), which has been reported to improve constipation (13). In addition, the prune juice contained dietary fiber, especially pectin, and polyphenols, both of which have been reported to improve constipation (14,15). Accordingly, it was supposed that the observed effects of ameliorating constipation by prune juice were mainly because of the combination of sorbitol, pectin, and polyphenol.

One limitation of our study is that we did not score the emergence of bloating, which was considered a frequent AE of prune juice (5). However, no subjects reported bloating, although subjects were asked about changes in physical condition during the study period.

In conclusion, our study demonstrated that prune juice ameliorates both stool forms and subjective complaints of constipation symptoms, without any abdominal discomfort, in patients with chronic constipation. Our data emphasize the effectiveness of prune juice intake for chronic constipation,
supporting recommendations to select natural food treatment as an alternative or complement to drug use.

**CONFLICTS OF INTEREST**

Guarantor of the article: Hirotaka Yamamoto, PhD. Specific author contributions: T. Koyama and H.Y. designed and planned the study. T. Koyama and N.M. collected the data. K.N. performed statistical analysis. T. Koyama and H.Y. prepared the original draft. N.N. and T. Kawai supported editing of the original draft and critically revised the manuscript. All authors approved the final draft. Financial support: This study was partially funded by MIKI Corporation.

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**Ethics:** This study was conducted in accordance with the Declaration of Helsinki. Human rights of the subjects were well protected, and the study was conducted with the approval of the institutional review boards of the Miura Clinic (approval number: R2001) and Tokyo Medical University (approval number: T2021-0243). Written informed consent was obtained from all subjects before their enrollment into the study.

**Clinical Trial Registration:** This study was registered at ClinicalTrials.gov (https://www.umin.ac.jp/english/, UMIN 00041384).

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**Table 2. Subjective evaluation of gastrointestinal symptom-related QOL by a GSRS questionnaire at baseline and changes from baseline during the intake period (week 4 and 8)**

|                      | Placebo (n = 42) | Prune juice (n = 42) | P value |
|----------------------|-----------------|----------------------|---------|
| Flatulence           |                 |                      |         |
| Baseline             | 2.93 ± 1.11     | 3.02 ± 1.24          | 0.801   |
| Δ4w                  | −0.36 ± 1.21    | −0.48 ± 1.35*        | 0.480   |
| Δ8w                  | −0.38 ± 1.13*   | −0.43 ± 1.36         | 0.982   |
| Constipation         |                 |                      |         |
| Baseline             | 4.50 ± 0.99     | 4.74 ± 1.01          | 0.490   |
| Δ4w                  | −1.24 ± 1.41*   | −1.62 ± 1.36*        | 0.163   |
| Δ8w                  | −1.43 ± 1.56*   | −2.24 ± 1.41*        | 0.024   |
| Diarrhea             |                 |                      |         |
| Baseline             | 1.55 ± 0.80     | 1.57 ± 0.83          | 0.826   |
| Δ4w                  | 0.14 ± 1.20     | 0.07 ± 1.09          | 0.914   |
| Δ8w                  | 0.05 ± 0.94     | −0.05 ± 1.08         | 0.741   |
| Loose stools         |                 |                      |         |
| Baseline             | 1.64 ± 0.91     | 1.48 ± 0.59          | 0.714   |
| Δ4w                  | −0.02 ± 1.00    | 0.21 ± 0.90          | 0.352   |
| Δ8w                  | 0.02 ± 0.87     | 0.26 ± 0.91          | 0.412   |
| Hard stools          |                 |                      |         |
| Baseline             | 4.33 ± 1.37     | 4.81 ± 1.13          | 0.172   |
| Δ4w                  | −1.26 ± 1.58*   | −1.83 ± 1.32*        | 0.082   |
| Δ8w                  | −1.33 ± 1.71*   | −2.31 ± 1.30*        | 0.009   |
| Urgent need for defecation |     |                      |         |
| Baseline             | 2.38 ± 1.13     | 2.33 ± 1.32          | 0.643   |
| Δ4w                  | 0.05 ± 1.38     | −0.10 ± 1.74         | 0.934   |
| Δ8w                  | −0.26 ± 1.15    | −0.21 ± 1.57         | 0.703   |
| Incomplete evacuation |                 |                      |         |
| Baseline             | 4.24 ± 1.49     | 4.36 ± 1.36          | 0.938   |
| Δ4w                  | −1.12 ± 1.70*   | −1.48 ± 1.47*        | 0.219   |
| Δ8w                  | −1.45 ± 1.56*   | −1.81 ± 1.42*        | 0.222   |

Data are expressed as mean ± SD. The P-values with significant difference are described in bold. GSRS, Gastrointestinal Symptoms Rating Scale; QOL, quality of life. *P < 0.05 compared with baseline.