Effect of phytic acid on postprandial serum uric acid level in healthy volunteers: a randomized, double-blind, crossover study

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ABSTRACT
Phytic acid, a constituent of various plants, has been related to health benefits. Phytic acid has been shown to inhibit purine nucleotide metabolism in vitro and suppress elevation of plasma uric acid levels after purine administration in animal models. This study investigated the effect of phytic acid on postprandial serum uric acid (SUA) in humans. This randomized, double-blind, crossover design study included 48 healthy subjects with normal fasting SUA. Subjects consumed a control drink and a phytic acid drink with purine-rich food, and serum and urine uric acid levels were measured for 360 min after purine loading. Phytic acid lowered the incremental area under the curve (0–360 min) and incremental maximum concentration of SUA after purine loading (p < 0.05); tended to lower cumulative urinary uric acid excretion (0–360 min) after purine loading (p < 0.10); and suppressed postprandial SUA in this clinical study. Altogether, our findings suggest that phytic acid may play a beneficial role in controlling postprandial SUA.

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1. Introduction
Purines are constituents of nucleic acids and are essential for life. Purines are contained in animal and plant cells, and are found in high concentration in red meat, liver, fish, and seafood, and are common in human diets. Purines ingested in meals are metabolized to uric acid in the liver and other organs. Uric acid serves as an antioxidant and helps to prevent damage caused by reactive oxygen species. However, chronically elevated levels of serum uric acid (SUA) are commonly associated with increased risk for some diseases. An SUA level that exceeds the normal upper limit
of 7.0 mg/dL increases the risk of gouty arthritis, renal dysfunction, and metabolic syndrome. Therefore, it is necessary to maintain normal SUA levels. Dietary purine restriction may lower elevated SUA levels. However, many foods such as sardines that are commonly considered “good for health” contain purines; therefore, strict dietary restriction may be difficult to achieve. Dietary nucleic acids are converted into nucleotides in the intestinal tract. The purine nucleotides are then hydrolyzed to highly absorbable purine nucleosides and purine bases. Once absorbed, most purine nucleosides and purine bases are degraded to uric acid. Therefore, we hypothesized that inhibition of metabolism of purine nucleotides to purine nucleosides and purine bases may suppress absorption of dietary purines. Soy milk fermented with lactic acid bacteria was a candidate food for suppression of dietary purine absorption, as a negative association between frequency of soy milk intake and prevalence of hyperuricemia has been reported. We observed an inhibitory effect on purine nucleotide metabolism with ingestion of fermented soy milk and confirmed suppression of elevated SUA levels after purine loading in healthy adults. Furthermore, we identified phytic acid as the main active component in fermented soy milk.

Phytic acid is found in substantial amounts in whole grains, cereals, legumes, nuts, and seeds, and is the primary energy source for germinating plants. For decades, phytic acid has been regarded as an anti-nutrient that may inhibit the absorption of some essential trace elements and minerals from the intestine. Conversely, some reports have described the important health-related beneficial properties of phytic acid including antioxidant and anticancer effects, and renal stone prevention. Although we confirmed that phytic acid suppresses elevation of plasma uric acid levels after purine administration in animal models, its effectiveness has not yet been examined clinically.

Therefore, the aim of the present study was to investigate the effects of phytic acid on postprandial SUA after a purine loading meal in healthy subjects, based on its inhibitory action on purine nucleotide metabolism.

2. Materials and methods

2.1. Subjects

Forty-eight healthy Japanese adults (24 men and 24 women) were recruited for this study. Eligibility was determined using the following inclusion criteria: 1) age 20–64 y; 2) fasting SUA level <7.0 mg/dL; and 3) for women, postmenopausal status (absence of a period for at least 1 y). The exclusion criteria were: 1) gout; 2) serum creatinine level ≥1.3 mg/dL in men and ≥1.0 mg/dL in women; 3) body mass index (BMI) ≥30 kg/m²; 4) food
allergies; 5) alcohol abuse; 6) smoking >20 cigarettes per day; 7) taking any prescribed medications or dietary supplements likely to interfere with study endpoints; and 8) determination by a physician that the results of blood tests and urinalysis would affect the primary endpoints. Subjects were randomly allocated to group A or group B (1:1 ratio) after stratification by sex, age, height, weight, BMI, SUA incremental area under the curve (iAUC, 0–360 min), SUA incremental maximum concentration (iCmax), SUA Cmax, time to maximum SUA level (Tmax), cumulative urinary uric acid excretion (0–360 min), fasting SUA levels, fasting plasma glucose levels, and fasting triglyceride levels at screening. Randomization was performed by entering the described variables of a subject into SAS software, version 9.3 (SAS Institute, Cary, NC, USA), to automatically allocate and generate a unique ID code. This study was conducted according to the guidelines laid down in the Declaration of Helsinki and the Ethical Principles for Medical Research Involving Human Subjects (Ministry of Education, Culture, Sports, Science and Technology and Ministry of Health, Labor and Welfare, Japan). All procedures involving human subjects were approved by the Hakata Clinic Institutional Review Board. Written informed consent was obtained from all subjects.

2.2. Test drink

Subjects ingested 50 mL of a phytic acid drink containing 600 mg of rice-derived phytic acid and 50 mL of mineral water as a control drink corresponding to placebo. The dose of phytic acid was calculated using the results of a previous clinical study,[13] in which an amount equivalent to that in 300 mL of fermented soy milk lowered the SUA iAUC (0–360 min). The inhibitory action of fermented soy milk on purine nucleotide metabolism was examined and the amount of phytic acid corresponding to this activity level was calculated.

2.3. Study design

This was a randomized, double-blind, crossover design study with 2 different drink types. The investigators and subjects remained blinded throughout the study procedure and statistical analysis. An independent assistant who was not related to the study held the blinding codes. The 2 test drinks were the same in appearance and smell, but were different in taste. Subjects were not informed about taste and could not distinguish which test drink was effective. We treated this as a double-blind study with no blinding problem as it met the criteria of the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human
Use (ICH). A total of 6 visits were required: 3 screening visits (visit 1, visit 2, and visit 3), 2 crossover visits (visit 4 and visit 5), and a follow-up visit (visit 6), with a washout period of 1 week. The purine loading tests were performed at 2 screening visits (visit 2 and visit 3) and 2 crossover visits (visit 4 and visit 5). All visits took place at Fukuoka Mirai Hospital Clinical Research Center, Souseikai Medical Corporation. Subjects were instructed to maintain a normal lifestyle and to abstain from eating purine-rich food and drinking alcohol during the 3 days prior to the purine loading test day. Before the test day, subjects visited the hospital in the morning and were instructed to consume standardized meals in the morning, afternoon, and evening before 2100 h. They were not allowed to consume foods other than the standardized meals. They were then required to fast until the next morning, but were allowed to drink the same amount of water as much as possible during each crossover period. Smokers were asked to abstain from smoking on the test day and the day before.

At 0900 h on each purine loading test day, subjects consumed a purine loading meal (white rice 200 g, tuna 200 g (purine nucleotide 800 mg), soy sauce 5 g) and a purine drink (consisting of a commercial seasoning containing sodium 5’-sodium inosinate 0.25 g and sodium 5’-guanylate 0.25 g dissolved in 150 mL of mineral water) with 50 mL of test drink for breakfast within a 20 min period. Subjects were not allowed to consume foods other than the purine loading meal, but were allowed to drink 100 mL of water at 60, 120, and 240 min after the purine loading test. Blood samples were collected from the brachial vein just before (0 min) and at 30, 60, 120, 240, and 360 min after the purine loading test. Urine samples were collected at 0–30, 30–60, 60–120, 120–240, and 240–360 min. Serum and urine uric acid levels (mg/dL) were measured at a clinical laboratory (SRL Inc., Tokyo, Japan) using the Uricase-POD method.

2.4. Statistical analyses

Statistical analyses were performed using SAS software, version 9.3 (SAS Institute, Cary, NC, USA). The primary outcome variable was SUA iAUC (0–360 min). The iAUC was calculated by using the trapezoidal rule. The secondary outcome variables were SUA iCmax, SUA level, and cumulative urinary uric acid excretion (0–360 min). SUA iAUC (0–360 min) and SUA iCmax were determined using an analysis of covariance (ANCOVA) model suited to a 2-period, 2-treatment, and 2-sequence crossover design, with fasting SUA level at pretreatment baseline as a covariate. Cumulative urinary uric acid excretion (0–360 min) was evaluated using an analysis of variance (ANOVA) model suited to a 2-period, 2-treatment, and 2-sequence crossover design. SUA level was evaluated using a general linear
mixed model. Statistical significance was defined as $p < 0.05$. All data are presented as means ± standard error. The full analysis set (FAS) consisted of enrolled subjects who received the test drink at least once. The primary per protocol set (PPS) was used for efficacy analysis and consisted of subjects in the FAS, except for several ineligible individuals according to the protocol. The calculated sample size was based on our previous pilot study (unpublished data), and required a total of 48 subjects, assuming 15% dropout, to obtain 90% statistical power, correlation coefficient of 0.5, and a significance level of 0.05, using a 2-sided paired $t$-test to detect a proper sample size from a difference of 35.4, with an estimated standard deviation of 65.1 between groups for determination of SUA iAUC.

3. Results

3.1. Subjects

Subject flow is summarized in Figure 1. There were 3 screening test sessions in this study. We assessed subjects for eligibility at the first screening (visit 1), and excluded subjects with large fluctuations in fasting SUA levels, SUA iAUC, and/or SUA iCmax at the second screening (visit 2) and third

Figure 1. Flow diagram of enrollment, random assignment, withdrawals, and follow-up of study subjects.
screening (visit 3). A total of 188 subjects were screened at visit 1 and 65 were excluded (9 subjects did not meet inclusion criteria, 18 met exclusion criteria, 22 declined to participate, and 16 had other abnormal blood results). A total of 123 subjects were screened at visit 2 and 23 were excluded (4 met exclusion criteria, 15 declined to participate, 2 had other abnormal blood results, 1 had large variation in an SUA-related index, and 1 could not continue). A total of 100 subjects were screened at visit 3 and 52 were excluded (4 met exclusion criteria, 3 declined to participate, 14 had other abnormal blood results, 13 had large variation in an SUA-related index, 6 could not continue, and 12 had other reasons. A total of 48 subjects were randomly assigned to group A and group B, and these completed the control drink phase. One subject dropped out before ingesting phytic acid because of discomfort. The FAS included 48 subjects. During the control drink period, one subject was lost due to failure to participate. Fourteen subjects were protocol noncompliant. One subject declined to participate and 13 had blood tests and urinalysis results that affected the primary endpoint (7 subjects had large variation in fasting SUA levels, 3 had large variation in fasting plasma glucose levels, and 3 had an abnormal estimated glomerular filtration rate < 60 ml/min/1.73 m²). Ultimately, the PPS included 34 subjects. Characteristics of the PPS are shown in Table 1.

### Table 1. Background characteristics of subjects eGFR, estimated glomerular filtration rate.

| Number | Male (n = 16) | Female (n = 18) | All (n = 34) |
|--------|---------------|-----------------|-------------|
| Age (years) | 38.3 ± 13.4 | 57.1 ± 4.9 | 48.3 ± 13.6 |
| Height (cm) | 171.1 ± 8.5 | 154.9 ± 4.0 | 162.5 ± 10.5 |
| Weight (kg) | 63.0 ± 6.5 | 52.1 ± 6.7 | 57.3 ± 8.6 |
| BMI (kg/m²) | 21.6 ± 2.5 | 21.6 ± 2.1 | 21.6 ± 2.2 |
| Serum uric acid (mg/dL) | 5.5 ± 0.6 | 4.5 ± 1.0 | 5.0 ± 1.0 |
| eGFR (ml/min/1.73 m²) | 92.9 ± 13.4 | 80.6 ± 11.0 | 86.4 ± 13.5 |

Values are mean ± SD.

### 3.2. SUA iAUC (0–360 min), SUA icmax, SUA levels, and cumulative urinary uric acid excretion (0–360 min)

As SUA iAUC (0–360 min) and SUA icmax were related to fasting SUA levels before ingestion of a purine loading meal, ANCOVA was performed using fasting SUA levels as a covariate. SUA levels, SUA iAUC (0–360 min), and SUA icmax are shown in Figures 2, 3, and 4. SUA levels were significantly lower after phytic acid drink ingestion compared with levels after control drink ingestion in the PPS ($p < 0.05$). SUA iAUC values were significantly lower after phytic acid drink ingestion ($522 ± 15$ mg-min-dL$^{-1}$ for the PPS; $509 ± 98$ mg-min-dL$^{-1}$ for the FAS) than after control drink ingestion ($536 ± 15$ mg-min-dL$^{-1}$ for the PPS; $518 ± 112$ mg-min-dL$^{-1}$ for the FAS) in both the PPS and FAS ($p < 0.05$). SUA icmax values were significantly lower after phytic acid drink ingestion...
(1.78 ± 0.04 mg/dL for the PPS; 1.75 ± 0.02 mg/dL for the FAS) compared with values after control drink ingestion (1.85 ± 0.05 mg/dL for the PPS; 1.79 ± 0.02 mg/dL for the FAS) in both the PPS and FAS ($p < 0.05$).

Cumulative urinary uric acid excretion (0–360 min) is shown in Figure 5. A trend ($p < 0.10$) was observed in the PPS, with a significant difference in the FAS ($p < 0.05$), between phytic acid drink (313 ± 67 mg for the PPS; 305 ± 78 mg for the FAS) and control drink groups (327 ± 70 mg for the PPS; 325 ± 63 mg for the FAS).

Figure 2. Mean ± SE incremental serum uric acid levels from baseline following consumption of control drink and phytic acid drink over a period of 360 min. (a) Full analysis set. (b) Per protocol set.

Figure 3. Mean ± SE of the postprandial incremental area under the serum uric acid response curve (iAUC) following consumption of control drink and phytic acid drink over a period of 360 min. (a) Full analysis set. (b) Per protocol set.

*Significant difference was observed between control drink and phytic acid drink, $p < 0.05$. 
4. Adverse events

No adverse events related to the consumption of phytic acid drink and control drink were observed throughout the study according to monitoring during the purine loading test, daily records, and interviews with doctors.
5. Discussion

Hyperuricemia, hyperglycemia, and hyperlipidemia are health risks closely related to dietary habits. SUA levels should be maintained at < 7.0 mg/dL throughout life. However, the general public has insufficient knowledge about hyperuricemia, and only a few reports have discussed food ingredients useful for its prevention. It has been reported that a single dose of chrysanthemum flower oil can inhibit uric acid synthesis and has a uricosuric effect, and tended to suppress diet-induced SUA elevation in a stratified analysis of subjects with baseline SUA \( \geq 7.1 \text{ mg/dL} \) \((p < 0.10)\).\(^{[19]}\) However, its effect has not yet been confirmed clinically in healthy subjects. Therefore, we focused on the suppression of purine nucleoside and base absorption by inhibiting purine nucleotide metabolism rather than uric acid synthesis and uricosuric activity in healthy subjects. The aim of this study was to examine the inhibitory effect of phytic acid on purine nucleotide metabolism in healthy subjects by investigating postprandial SUA responses after a purine loading meal. We demonstrated a significant reduction in postprandial SUA response after ingestion of a phytic acid drink, compared with that after ingestion of a control drink in subjects with baseline SUA < 7.0 mg/dL (Figure 3). To the best of our knowledge, this is the first study to show suppression of postprandial SUA response with a single intake of food ingredients in healthy subjects and to confirm the effect on SUA levels through inhibition of purine nucleotide metabolism.

Three possible mechanisms may explain the suppressive effect of phytic acid on the postprandial SUA response: 1) promotion of urinary uric acid excretion, 2) suppression of uric acid synthesis, 3) inhibition of purine absorption. A less likely mechanism is promotion of urinary uric acid excretion. Cumulative urinary uric acid excretion (0–360 min) was not higher after phytic acid drink ingestion than after control drink ingestion in the present study. This result indicates that the efficacy of phytic acid is not due to promotion of urinary uric acid excretion. Another less likely mechanism is suppression of uric acid synthesis. It has been reported that phytic acid inhibits the activity of xanthine oxidase (XO),\(^{[20]}\) but the inhibition of XO by phytic acid (at half maximal inhibitory concentration (IC50) = 30 mM) is much lower than that with allopurinol (IC50 = 5.9 \( \mu \text{M} \)), a therapeutic drug for gout.\(^{[21]}\) In addition, it has been reported that there is little increase in plasma phytic acid levels after ingestion of a single dose of 1,400 mg of sodium phytate (equivalent to about 1,000 mg of phytic acid).\(^{[22]}\) These results suggest that the efficacy of phytic acid is not due to suppression of uric acid synthesis. The most likely mechanism is inhibition of purine absorption by inhibition of purine nucleotide metabolism. The nucleoproteins in foods are converted to nucleic acids in the intestinal tract.
by proteases. The nucleic acids are degraded by pancreatic nucleases to free nucleotides.[23] The free nucleotides are then hydrolyzed to nucleosides by alkaline phosphatase and nucleotidases, and may be further broken down by nucleosidases to produce purine and pyrimidine bases.[23] Investigations in animals suggest that purine nucleosides are the primary form absorbed,[10,24] and that over 90% of purine nucleosides and bases are absorbed into the enterocyte.[25,26] Once absorbed, most of the purine nucleosides and bases are rapidly degraded into uric acid.[25,26] Thus, we hypothesized that inhibition of purine nucleoside and base absorption in the intestine would suppress the postprandial SUA response. Concentrative nucleoside transporter 2 (CNT2) is expressed in the apical membrane of the enterocyte and is the main transporter that contributes to absorption of purine nucleosides.[27,28] It has been reported that CNT2 inhibitors almost completely inhibited dietary RNA-induced hyperuricemia and the increase in urinary excretion of uric acid in Cebus monkeys.[29] This result supports the hypothesis that inhibition of purine nucleoside and base absorption would suppress the postprandial SUA response. On the other hand, we have confirmed that phytic acid inhibits metabolism of purine nucleotides to purine nucleosides in vitro.[13] This result suggests that phytic acid decreases the amount of purine nucleosides and bases in the intestinal tract and suppresses absorption. Therefore, we speculate that the efficacy of phytic acid in this study is due to the suppression of purine nucleoside and base absorption by inhibiting purine nucleotide metabolism. In addition, cumulative urinary uric acid excretion (0–360 min) was significantly lower after phytic acid drink ingestion compared with that after control drink ingestion in the FAS analysis (p < 0.05). This result also supports our hypothesis.

Phytic acid is considered an anti-nutrient because of its ability to chelate minerals such as zinc, iron, calcium, and magnesium, reducing their bioavailability.[14] Indeed, it has been shown that under non-balanced dietary conditions, phytic acid may affect the bioavailability and status of iron, zinc, and calcium.[30–32] Our previous study confirmed the efficacy and safety of phytic acid in subjects with mild hyperuricemia who ingested a phytic acid drink containing 600 mg of phytic acid twice a day for 2 weeks. No abnormal change in serum calcium or iron concentration was observed after the treatment. [33] Phytic acid has been authorized as a food additive in dietary supplements in the United States, and the estimated user intake is 610 mg/day at the 90th percentile of phytic acid intake, and no problems have been reported so far.[34] This information suggests that the daily intake of phytic acid may not adversely affect the mineral status under normal balanced diet conditions. However, the data are still limited, and thus, future studies on long-term or excessive intake with larger numbers of subjects are needed.
This study has several limitations. First, we used mineral water as a control drink in this study, as phytic acid has a peculiar taste and it was difficult to prepare placebo drinks. However, this study maintained blinding using ICH criteria. As the main endpoint of this study was objective evaluation of SUA levels, water intake, food intake, and exercise were strictly controlled to prevent an effect on SUA levels and to ensure the same conditions from the day before the purine loading test until ingestion of the control and phytic acid drinks. Therefore, we could conclude that the difference in taste between a phytic acid drink and a control drink did not affect the results of the present study and that phytic acid was responsible for the effect on postprandial SUA responses. The PPS was used to exclude subjects who might affect the study results. However, both the PPS and FAS analysis showed significant differences in the primary endpoint, with no confounding of the results. These findings indicate that phytic acid had an effect on the SUA level. Second, the effect of the phytic acid drink in this study was significant but rather modest. The purpose of this study was to clarify the effect of phytic acid on SUA level and the appropriate single dose. Our previous study with the same single dose for 2 weeks in subjects with mild hyperuricemia showed a significant and clinically meaningful effect on fasting SUA level.\textsuperscript{33} The size of the impact on the SUA level may differ depending on the subject’s condition. For example, the results may be different in subjects who are prone to accumulate uric acid because of renal insufficiency. Further studies on various subject conditions are required to confirm the effect of phytic acid on postprandial SUA responses.

In conclusion, this study showed that a phytic acid drink suppressed the postprandial SUA responses after a purine loading meal, without any adverse event. A phytic acid drink could help to maintain and improve health by controlling postprandial SUA responses.

7. Disclosure statement

H. Tsukikawa, K. Matsuguma and T. Yamamoto declare no competing interests. T. Ikenaga, H. Noguchi, K. Kakumoto and N. Kohda are employees of Otsuka Pharmaceutical Co., Ltd.

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