Safety Evaluation and Plasma Carotenoid Accumulation in Healthy Adult Subjects after 12 Weeks of Paprika Oleoresin Supplementation

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Abstract: Paprika oleoresin is obtained by solvent extraction from Capsicum annuum L. fruits and contains multiple carotenoids, such as capsanthin, β-carotene, zeaxanthin, and β-cryptoxanthin, which are considered protective against various diseases. Herein, we investigated the effect of paprika oleoresin supplementation on plasma carotenoid accumulation and evaluated the safety of the oleoresin. We used a double-blinded, placebo-controlled comparative clinical study design and tested the effects of varying doses in healthy adult subjects. In total, 33 subjects were randomly divided into three groups to take capsules containing 0, 20, or 100 mg of paprika oleoresin daily for 12 consecutive weeks. Plasma carotenoid concentrations were measured at 0, 4, 8, and 12 weeks, and the safety of paprika oleoresin capsules was investigated using analyses of blood biochemistry, hematology, and urine contents. In these experiments, β-cryptoxanthin and zeaxanthin dose-dependently accumulated in plasma within the dose range of the study over 12 consecutive weeks of paprika oleoresin supplementation. Moreover, β-cryptoxanthin accumulated to higher levels than the other paprika oleoresin carotenoids. In contrast, capsanthin was not detected in plasma before or during the 12-week treatment period. Finally, no adverse events were associated with intake of paprika oleoresin (20 and 100 mg/day) in safety evaluations. Paprika oleoresin is a suitable source of carotenoids, especially β-cryptoxanthin.

Key words: safety evaluation, plasma carotenoid accumulation, β-cryptoxanthin, capsanthin, paprika oleoresin

1 INTRODUCTION

Paprika oleoresin is a solvent extract from the fruits of Capsicum annuum L. and is commonly used as a natural colorant in several food products. The major coloring compound capsanthin is a carotenoid that is exclusively synthesized in capsicum species. Various other carotenoids are also present, including β-carotene, zeaxanthin, and β-cryptoxanthin1. Although β-carotene and zeaxanthin are present at high concentrations in green and yellow vegetables, β-cryptoxanthin is only present at high concentrations in some foods, including capsicum species and citrus fruits. According to the Standard Tables of Food Composition in Japan2, β-cryptoxanthin contents are highest in dried capsicum. Paprika oleoresin may represent a suitable source of β-cryptoxanthin and capsanthin for human consumption.

Higher dietary intake and plasma concentrations of β-cryptoxanthin have been increasingly correlated with lower risks of human disease. In particular, epidemiological studies show inverse associations of serum β-cryptoxanthin concentrations with risks of atherosclerosis3, type 2 diabetes4, liver dysfunction5, 6, and osteoporosis7 in Japanese populations. Other epidemiological studies revealed inverse correlations between rheumatoid arthritis morbidity and daily intake of β-cryptoxanthin8, 9. Therefore, maintenance of high plasma β-cryptoxanthin concentrations may
prevent the development of these diseases.

The bioavailability of \( \beta \)-cryptoxanthin and other carotenoids has been investigated in several studies. Although \( \beta \)-cryptoxanthin intake is lower than that of zeaxanthin, greater absorption of \( \beta \)-cryptoxanthin is observed after a single oral administration of paprika oleoresin\(^{10} \). Similarly, \( \beta \)-cryptoxanthin had 2.9 and 2.3 times higher bioavailability than \( \beta \)-carotene and lycopene, respectively\(^{11} \). Hence, repeated intake of paprika oleoresin may provide higher plasma accumulation of \( \beta \)-cryptoxanthin than other carotenoids. In this study, we investigated changes in plasma carotenoid concentrations following daily intake of paprika oleoresin for 12 consecutive weeks and performed safety evaluations to inform future clinical trials.

2 MATERIALS AND METHODS

2.1 Materials

Paprika oleoresin with standardized \( \beta \)-cryptoxanthin contents (>1.5%) was purchased from Riken Vitamin Co., Ltd. (Tokyo, Japan). This paprika oleoresin preparation contains 3.5% capsanthin, 2.9% \( \beta \)-carotene, and 1.6% zeaxanthin, and the \( \beta \)-cryptoxanthin content (1.7%) is higher than that in most other commercial products. Test supplements were formulated as soft capsules filled with edible oil and paprika oleoresin at 20 or 100 mg per capsule. Placebo capsules were filled with edible oil only. Test and placebo capsules had indistinguishable appearance, flavor, and packaging.

2.2 Subjects

Subjects were healthy adult males and females of 40–60 years of age and with body mass indexes (BMI) of 18.5–25.0. Subjects who frequently ate \( \beta \)-cryptoxanthin-rich foods, such as satsuma mandarin oranges (\textit{Citrus unshiu} Marc.) or related processed foods, were excluded from the study along with subjects taking medicines, herbal medicines, or dietary supplements and subjects with excessive intake of alcohol, smoking habits, and possible allergies or history of hypersensitivity to the test materials of this study. Patients with serious liver, renal, heart, lung, cardiovascular, respiratory, endocrine, or metabolic disorders requiring treatment were deemed unsuitable by the physician in charge and were excluded from the study. A total of 33 subjects met the inclusion criteria and were randomly assigned to one of the three dose groups based on data from screening tests. Study groups did not differ in age or sex.

The present study was approved by the medical corporation Bokushinkai CLINTEXE Clinic Ethics Committee (approval No. 2013-0802) and was conducted in accordance with the Declaration of Helsinki. Subjects were fully informed of the contents of the capsules and the study methods prior to providing written informed consent. This study was conducted from July 2013 to December 2013.

2.3 Study design

We used a double-blinded, placebo-controlled, comparative, clinical study design, and subjects received placebo capsules (placebo group) or test capsules containing 20 mg (low-dose group) or 100 mg (high-dose group) of paprika oleoresin. Subjects were instructed to take one capsule each day for 12 consecutive weeks. Subjects visited the clinic (medical corporation Ouryokukai Youku Sakura Dori Clinic) before intake (0 week) and at 4, 8, and 12 weeks after the start of the study. The subjects were instructed to fast for 10 h before blood sampling visits, and plasma carotenoid concentrations were subsequently determined. Heparin sodium was used as the anticoagulant, and plasma was then separated by centrifugation. Plasma samples were stored at \(-20^\circ\text{C}\) until analysis.

Safety evaluations comprised physical examinations of body weights, BMI, systolic pressure, diastolic pressure, and pulse rates; measurements of the blood biochemical parameters such as total protein, albumin (ALB), blood urea nitrogen (BUN), creatinine (CRE), uric acid (UA), aspartate aminotransferase (AST), alanine aminotransferase (ALT), \( \gamma \)-glutamyl transpeptidase (\( \gamma \)-GTP), alkaline phosphatase (ALP), lactate dehydrogenase (LDH), total-cholesterol, LDL-cholesterol, HDL-cholesterol, triglyceride (TG), total-bilirubin (t-BIL). Na, K, Glucose, and Hemoglobin (HbAlc); hematological analyses of white blood cell counts (WBC), red blood cell counts (RBC), hematoglobin (Hgb), hematocrit (Hct), mean corpuscular volumes (MCV), mean corpuscular hemoglobin (MCH), mean corpuscular hemoglobin concentrations (MCHC), platelet counts (PLT), prothrombin times (PT), and PT-international normalized ratios (INR); and urinalysis tests of specific gravity and pH.

2.4 Measurements of plasma carotenoid concentrations

Concentrations of the major paprika oleoresin carotenoids \( \beta \)-cryptoxanthin, zeaxanthin, \( \beta \)-carotene, and capsanthin were determined in 0.2-mL plasma samples. Plasma was mixed with 5 mL of hexane, 1 mL of distilled water, and 1 mL of ethanol solution containing \( \beta \)-apo-8′-carotenal (0.2 \( \mu \)g/mL) as an internal standard. Mixtures were vortexed for 20 s and were then centrifuged at 3000 rpm for 5 min. Supernatants were then evaporated to dryness under a nitrogen gas stream, and residues were dissolved in 0.3 mL of acetone:ethanol (1:1, v/v) and were finally sonicated for 1 min. Sample solutions were then filtered through 0.2-\( \mu \)m Millipore filters and were then fractionated using ultra-high-performance liquid chromatography.

Carotenoids in fractions were quantified using reversed-phase analyses with a Waters ACQUITY H Class LC system (Waters, Milford, MA, USA) and ACQUITY UPLC HSS T3
columns (2.1 mm i.d. × 150 mm) at 45°C. The injection volume was 2 μL, and the mobile phase comprised solvent A (0.1% formic acid in water), solvent B (methanol), and solvent C (acetone) at a flow rate of 0.4 mL/min. Gradient elution was performed as follows: 0.0 min (A:B:C = 17:33:50), 5.3 min (9:33:58), 7 min (0:0:100), 9 min (0:0:100), and 13 min (17:33:50). Eluted analytes were monitored at 480 nm for capsanthin and at 450 nm for the other carotenoids.

Carotenoid peaks were identified according to retention times using authentic capsanthin, β-carotene, β-cryptoxanthin, and zeaxanthin (Extrasynthese, Genay, France) standards. For quantification, the internal standard method was performed using β- apo-8'-carotenal (Sigma-Aldrich, St. Louis, MO, USA). Calibration curves were constructed by plotting peak area ratios (carotenoids/internal standard) against weight ratios (carotenoids/internal standard). Regression equations and correlation coefficients ($r^2$) were as follows: $y = 0.8178x + 0.0021$ ($r^2 = 1.000$) for capsanthin, $y = 0.8514x - 0.0195$ ($r^2 = 0.9998$) for β-carotene, $y = 0.8828x - 0.0161$ ($r^2 = 0.9998$) for β-cryptoxanthin, and $y = 0.8573x - 0.0007$ ($r^2 = 1.0000$) for zeaxanthin.

### 2.5 Statistical analyses

Data were presented as means ± standard deviations (SD). Group differences in plasma carotenoid concentrations at baseline (0 week) were identified using Tukey’s test. Changes in plasma carotenoid concentrations from baseline were identified using two-factor repeated measures analysis of variance (ANOVA) and were compared between low-dose, high-dose, and placebo groups at 4, 8, and 12 weeks after the start of the treatment period. Post-hoc analyses of group differences were performed using Tukey’s test. Safety data, including those from physical examinations, blood biochemistry, hematology, and urinalysis tests, were analyzed using Dunnett’s multiple comparison test. Statistical analyses were performed using SPSS Ver. 22.0 (IBM SPSS Statistics, IBM Corporation, Armonk, NY, USA), and differences were considered significant when $p < 0.05$.

### 3 RESULTS

#### 3.1 Subject characteristics

All 33 subjects completed the study, and their demographic characteristics are presented in Table 1. Plasma β-cryptoxanthin, zeaxanthin, and β-carotene concentrations did not differ significantly between the three groups before intake of paprika oleoresin, and no capsanthin was detected in plasma.

#### 3.2 Plasma carotenoid accumulation

Figure 1 shows changes in plasma β-cryptoxanthin concentrations from baseline. Two-factor repeated measures ANOVA revealed significant differences among dosage groups ($p < 0.001$) and significant time × group interactions ($p < 0.001$). Plasma β-cryptoxanthin concentrations in low- and high-dose groups were increased by 2.9- and 6.0-fold from 124.2 ± 39.6 to 365.4 ± 158.4 ng/mL and from 135.8 ± 51.6 to 808.2 ± 256.3 ng/mL, respectively, after 12 weeks of paprika oleoresin intake. These changes in plasma zeaxanthin concentrations from baseline differed between groups ($p < 0.001$), but no time × group interactions ($p = 0.55$) were identified (Fig. 2). Plasma zeaxanthin concentrations were increased by 1.8- and 2.5-fold from 39.2 ± 9.9 to 72.2 ± 24.5 ng/mL and from 39.1 ± 25.5 to 99.5 ± 25.7 ng/mL, respectively, after 12 weeks of paprika oleoresin intake. Plasma β-cryptoxanthin and zeaxanthin accumulation was dose dependent, and although xanthophylls in paprika oleoresin were mainly present as mono- or di-esters of

| Table 1 Demographic characteristics of study subjects before intake of paprika oleoresin. |
|---------------------------------|-----------------|-----------------|-----------------|
|                                | Low-dose (n = 11) | High-dose (n = 11) | Placebo (n = 11) |
| Female (n)                     | 6               | 6               | 6               |
| Age (years)                    | 48.3 ± 6.4      | 48.3 ± 5.2      | 48.4 ± 5.2      |
| Body weight (kg)               | 57.6 ± 4.7      | 57.6 ± 7.9      | 57.5 ± 6.6      |
| Body height (cm)               | 163.7 ± 3.9     | 163.2 ± 8.8     | 165.6 ± 7.1     |
| Body mass index (kg/m²)        | 21.5 ± 1.1      | 21.5 ± 1.3      | 21.0 ± 2.1      |
| Plasma carotenoid concentration (ng/mL) |                |                 |                 |
| β-cryptoxanthin                | 124.2 ± 39.6    | 135.8 ± 51.6    | 166.4 ± 58.5    |
| Zeaxanthin                     | 39.2 ± 9.9      | 39.1 ± 25.5     | 49.5 ± 20.6     |
| β-carotene                     | 504.5 ± 547.8   | 728.5 ± 719.1   | 591.6 ± 226.4   |
| Capsanthin                     | n.d.            | n.d.            | n.d.            |

Values are presented as means ± standard deviations (SD); n.d., not detected.
fatty acids, only free β-cryptoxanthin and zeaxanthin were detected in plasma.

Changes in plasma β-carotene concentrations (Fig. 3) differed significantly between treatment groups \((p < 0.05)\), whereas no time x group interactions were identified \((p = 0.36)\). In contrast to β-cryptoxanthin and zeaxanthin, changes in plasma β-carotene concentrations did not differ significantly between groups after 12 weeks of paprika oleoresin intake. Moreover, capsanthin was not detected in any plasma samples before or after 12 weeks of paprika oleoresin intake.

3.3 Physical examinations

No significant differences in body weight, BMI, or systolic or diastolic blood pressure were identified during the study (Table 2). Although pulse rates increased significantly at the 8-week time point in the low-dose group, these did not differ from those in the placebo group.

3.4 Blood biochemistry tests

Significant changes in UA, AST, and TG levels were sporadically observed, whereas no changes in the other biochemical parameters were recorded (Table 3).

3.5 Hematological tests

Hematological tests revealed significant increases in MCHC at 8 weeks and significant decreases in PLT at 4 weeks in the high-dose group compared with the placebo group (Table 4). No other hematological parameters were affected significantly during the study.

3.6 Urinalysis

Urinalyses (Table 5) showed no significant differences in any parameter.
Safety and Carotenoid Accumulation Following Intake of Paprika Oleoresin

Table 2  Effects of paprika oleoresin supplementation on physical parameters in healthy adult subjects.

| Items                | Group | 0 week     | 4 week     | 8 week     | 12 week     |
|----------------------|-------|------------|------------|------------|-------------|
| Body weight (kg)     | L     | 57.6 ± 4.7 | 58.4 ± 5.5 | 58.8 ± 5.7 | 59.0 ± 6.2  |
|                      | H     | 57.6 ± 7.9 | 58.0 ± 8.0 | 57.8 ± 8.3 | 57.9 ± 8.1  |
|                      | P     | 57.5 ± 6.6 | 57.7 ± 7.2 | 58.0 ± 7.1 | 58.4 ± 7.9  |
| Body mass index (kg/m²) | L     | 22.9 ± 6.6 | 23.6 ± 5.5 | 23.5 ± 5.6 | 24.0 ± 5.5  |
|                      | H     | 22.0 ± 5.1 | 22.9 ± 5.1 | 22.5 ± 5.3 | 22.6 ± 5.1  |
|                      | P     | 21.0 ± 8.6 | 21.0 ± 8.3 | 21.3 ± 8.5 | 21.9 ± 7.9  |
| Systolic pressure (mmHg) | L     | 109.3 ± 11.3 | 108.9 ± 12.0 | 110.5 ± 16.1 | 108.9 ± 13.4 |
|                      | H     | 108.7 ± 10.4 | 107.8 ± 12.4 | 105.3 ± 10.9 | 106.7 ± 15.4 |
|                      | P     | 108.0 ± 12.1 | 104.7 ± 12.2 | 107.1 ± 11.5 | 108.4 ± 16.9 |
| Diastolic pressure (mmHg) | L     | 66.7 ± 9.1 | 69.6 ± 9.0 | 68.9 ± 12.2 | 64.2 ± 12.0 |
|                      | H     | 65.8 ± 6.2 | 68.7 ± 8.8 | 65.8 ± 6.5 | 65.6 ± 6.4  |
|                      | P     | 69.3 ± 9.3 | 68.2 ± 9.1 | 65.5 ± 9.4 | 66.4 ± 11.2 |
| Pulse rate (beats/min) | L     | 63.0 ± 7.9 | 69.5 ± 6.0 | 70.7 ± 7.6* | 67.8 ± 5.7  |
|                      | H     | 64.7 ± 6.4 | 67.8 ± 7.7 | 72.2 ± 7.8 | 68.2 ± 8.8  |
|                      | P     | 63.3 ± 6.3 | 69.5 ± 7.8 | 67.8 ± 6.5 | 68.5 ± 8.0  |

Values are presented as means ± SD; L, low-dose group; H, high-dose group; P, placebo group.

* Significantly different from baseline (0 weeks), p < 0.05.

3.7 Adverse events

Adverse events that were observed during the intake period included eight cases of cold-like symptoms (two in the placebo, one in the low-dose, and five in the high-dose groups), two cases of joint pain (one in the low-dose group and one in the high-dose group), two cases of stomachache (one in the placebo group and one in the high-dose group), one case each of headache, viral enteritis, and labial herpes in the high-dose group, one case each of dizziness and menstrual pain in the low-dose group, and one case each of gum inflammation in the placebo group. Daily diary entries and clinical interviews indicated that none of these adverse events were related to paprika oleoresin intake.

4 DISCUSSION

In this study, we investigated the effects of paprika oleoresin supplementation (20 and 100 mg/day) on plasma carotenoid accumulation and evaluated safety profiles in healthy adult subjects. We observed dose dependent accumulation of β-cryptoxanthin and zeaxanthin in plasma over 12 consecutive weeks of paprika oleoresin supplementation. Plasma β-cryptoxanthin accumulation was greater than that of zeaxanthin, despite similar doses. In a previous epidemiological study, Sugiura et al. showed that the estimated dietary intake of β-cryptoxanthin in Japan is lower than that of lutein and zeaxanthin. However, in agreement with our study, serum concentrations of β-cryptoxanthin were higher than those of these carotenoids. Several studies suggest that β-cryptoxanthin is better absorbed from foods and is more bioavailable than other common carotenoids. Moreover, clearance of β-cryptoxanthin from plasma is similar or faster than that of other carotenoids, such as β-carotene, lutein, and zeaxanthin. Therefore, observations of high plasma β-cryptoxanthin accumulation likely reflect greater absorption rather than clearance compared with other carotenoids.

Although changes in plasma β-carotene concentrations in the high-dose group were significantly higher than those in low-dose and placebo groups after 4 weeks, no significant differences were observed at the 12-week time point. In this study, subjects were instructed to avoid β-cryptoxanthin-rich foods, whereas β-carotene-rich foods were not restricted, and subjects likely consumed β-carotene from green and yellow vegetables. Consequently, plasma
Table 3  Effects of paprika oleoresin supplementation on blood biochemistry parameters in healthy adult subjects.

| Items           | Standard value | Group | 0 week    | 4 week    | 8 week    | 12 week   |
|-----------------|----------------|-------|-----------|-----------|-----------|-----------|
| Total protein   | 6.7–8.3        | L     | 6.9 ± 0.3 | 6.8 ± 0.2 | 6.7 ± 0.2 | 6.8 ± 0.2 |
|                 |                | H     | 7.1 ± 0.3 | 7.0 ± 0.3 | 7.0 ± 0.3 | 7.0 ± 0.3 |
|                 |                | P     | 7.0 ± 0.3 | 6.9 ± 0.3 | 6.8 ± 0.2 | 6.9 ± 0.2 |
| ALB             | 3.8–5.3        | L     | 4.3 ± 0.2 | 4.3 ± 0.1 | 4.2 ± 0.1 | 4.3 ± 0.1 |
|                 |                | H     | 4.4 ± 0.2 | 4.4 ± 0.2 | 4.4 ± 0.2 | 4.4 ± 0.2 |
|                 |                | P     | 4.4 ± 0.2 | 4.4 ± 0.2 | 4.3 ± 0.2 | 4.4 ± 0.2 |
| BUN             | 8–22           | L     | 11.7 ± 3.3| 11.5 ± 2.2| 12.0 ± 2.6| 12.5 ± 3.3|
|                 |                | H     | 12.6 ± 2.6| 12.9 ± 2.6| 13.1 ± 3.1| 14.5 ± 2.5|
|                 |                | P     | 12.4 ± 3.8| 12.6 ± 3.4| 12.6 ± 3.0| 11.8 ± 2.5|
| CRE             | M: 0.61–1.04   | L     | 0.76 ± 0.17| 0.73 ± 0.15| 0.70 ± 0.15| 0.74 ± 0.16|
|                 | F: 0.47–0.79   | H     | 0.78 ± 0.06| 0.74 ± 0.06| 0.73 ± 0.07| 0.74 ± 0.07|
|                 |                | P     | 0.76 ± 0.15| 0.75 ± 0.13| 0.72 ± 0.15| 0.73 ± 0.12|
| UA              | M: 3.7–7.0     | L     | 4.9 ± 1.3 | 5.1 ± 1.0 | 4.8 ± 1.2 | 4.7 ± 1.2 |
|                 | F: 2.5–7.0     | H     | 5.4 ± 1.1  | 5.3 ± 1.0 | 5.3 ± 1.0 | 5.3 ± 1.0 |
|                 |                | P     | 4.3 ± 0.9 | 4.6 ± 1.0 | 4.4 ± 1.0 | 4.2 ± 1.0 |
| AST             | 10–40          | L     | 16.2 ± 3.0| 16.5 ± 2.8| 18.1 ± 4.1| 17.7 ± 3.6|
|                 |                | H     | 19.4 ± 3.1| 19.6 ± 2.9| 21.1 ± 4.0| 20.4 ± 3.9|
|                 |                | P     | 19.1 ± 4.7| 18.0 ± 4.1| 17.1 ± 3.0| 20.3 ± 8.0|
| ALT             | 5–45           | L     | 14.6 ± 4.7| 13.9 ± 2.5| 17.5 ± 4.6| 15.7 ± 4.1|
|                 |                | H     | 15.8 ± 4.0| 16.4 ± 4.6| 17.0 ± 5.3| 16.9 ± 4.9|
|                 |                | P     | 19.0 ± 9.7| 14.8 ± 4.0| 14.0 ± 4.4| 18.3 ± 8.6|
| γ-GTP           | M: ≤ 75        | L     | 22.2 ± 18.0| 21.2 ± 16.9| 23.9 ± 21.1| 22.5 ± 19.2|
|                 | F: ≤ 45        | H     | 27.5 ± 21.5| 26.0 ± 18.7| 30.5 ± 24.9| 28.3 ± 23.3|
|                 |                | P     | 23.3 ± 19.8| 19.0 ± 13.1| 18.7 ± 10.5| 19.7 ± 14.0|
| ALP             | 110–360        | L     | 184.5 ± 54.4| 190.4 ± 59.5| 187.5 ± 60.0| 193.5 ± 59.5|
|                 |                | H     | 173.3 ± 49.4| 168.2 ± 47.0| 179.2 ± 52.0| 181.5 ± 53.7|
|                 |                | P     | 202.7 ± 72.5| 201.9 ± 70.3| 194.7 ± 70.0| 199.0 ± 65.4|
| LDH             | 115–245        | L     | 155.9 ± 11.7| 168.9 ± 19.0| 165.1 ± 15.3| 166.9 ± 13.0|
|                 |                | H     | 174.3 ± 33.1| 165.5 ± 33.5| 175.1 ± 39.8| 176.2 ± 33.7|
|                 |                | P     | 157.5 ± 19.3| 158.4 ± 20.1| 154.2 ± 23.4| 166.2 ± 23.5|
| Total-cholesterol| 130–219       | L     | 200.0 ± 20.9| 202.5 ± 17.2| 201.8 ± 16.7| 203.9 ± 22.9|
|                 |                | H     | 205.5 ± 21.1| 203.6 ± 27.0| 210.1 ± 16.8| 199.8 ± 21.8|
|                 |                | P     | 188.7 ± 27.3| 189.5 ± 31.0| 191.7 ± 24.7| 186.6 ± 23.1|
β-carotene concentrations were influenced by regular diet and may not have been affected by the present intervention.

Although capsanthin doses were equivalent to 3.5 mg in the high-dose and 0.7 mg in the low-dose groups and were higher than those of the other carotenoids, no capsanthin was detected in human plasma after 12 weeks. In contrast, Nishino et al.\textsuperscript{16} reported increases in plasma capsanthin concentrations to approximately 40 ng/mL after 4 weeks of paprika juice consumption (equivalent to a daily intake of 6.5 mg capsanthin), although capsanthin was not detected in plasma before intake. Oshima et al.\textsuperscript{17} also reported increased capsanthin concentrations in human plasma after a single administration of paprika juice (equivalent to 20 mg capsanthin). However, capsanthin was previously not detected in human chylomicrons after single oral treatments with paprika oleoresin (equivalent to 35.0 mg capsanthin)\textsuperscript{10}. Although these inconsistencies are poorly un-

### Table 3  Continued.

| Items            | Standard value | Group | 0 week | 4 week | 8 week | 12 week |
|------------------|----------------|-------|--------|--------|--------|---------|
| LDL-cholesterol  |                | L     | 111.4 ± 19.9 | 113.0 ± 16.6 | 114.6 ± 20.9 | 118.1 ± 19.5 |
| (mg/dL)          |                | H     | 118.1 ± 25.1 | 118.5 ± 19.9 | 122.7 ± 24.1 | 117.5 ± 23.5 |
|                  |                | P     | 104.7 ± 10.7 | 105.5 ± 27.1 | 105.1 ± 21.7 | 104.1 ± 22.3 |
| HDL-cholesterol  | M: 40–86       | L     | 70.9 ± 27.1 | 72.6 ± 28.4 | 70.1 ± 23.5 | 73.5 ± 27.8 |
| (mg/dL)          | F: 40–96       | H     | 70.2 ± 16.0 | 70.1 ± 13.5 | 72.5 ± 15.2 | 70.5 ± 16.4 |
|                  |                | P     | 70.4 ± 14.9 | 72.0 ± 12.5 | 72.5 ± 9.0  | 73.1 ± 12.9 |
| TG               | 35–149         | L     | 94.1 ± 31.2 | 96.0 ± 49.1 \textsuperscript{*} | 84.5 ± 37.3 | 75.0 ± 38.9 |
| (mg/dL)          |                | H     | 82.5 ± 35.7 | 84.3 ± 38.0 | 79.5 ± 38.0 | 70.3 ± 29.4 |
|                  |                | P     | 67.7 ± 23.1 | 51.4 ± 16.8 | 55.2 ± 20.8 | 61.2 ± 27.9 |
| T-BIL            | 0.2–1.1        | L     | 0.78 ± 0.50 | 0.73 ± 0.43 | 0.71 ± 0.51 | 0.64 ± 0.27 |
| (mg/dL)          |                | H     | 1.00 ± 0.61 | 0.85 ± 0.51 | 0.78 ± 0.48 | 0.75 ± 0.23 |
|                  |                | P     | 0.81 ± 0.32 | 0.70 ± 0.39 | 0.71 ± 0.28 | 0.67 ± 0.30 |
| Na               | 135–147        | L     | 141.0 ± 1.5 | 140.7 ± 0.8 | 140.5 ± 1.6 | 141.0 ± 1.3 |
| (mEq/L)          |                | H     | 140.8 ± 1.7 | 141.0 ± 1.5 | 139.5 ± 1.8 | 140.5 ± 2.0 |
|                  |                | P     | 141.0 ± 1.2 | 140.3 ± 1.5 | 139.9 ± 1.1 | 141.0 ± 1.4 |
| K                | 3.6–5.0        | L     | 4.3 ± 0.3   | 4.2 ± 0.3   | 4.1 ± 0.2   | 4.2 ± 0.2   |
| (mEq/L)          |                | H     | 4.3 ± 0.3   | 4.4 ± 0.2   | 4.4 ± 0.2   | 4.4 ± 0.3   |
|                  |                | P     | 4.4 ± 0.3   | 4.3 ± 0.4   | 4.3 ± 0.2   | 4.3 ± 0.4   |
| Cl               | 98–108         | L     | 106.1 ± 2.1 | 106.3 ± 2.1 | 105.2 ± 2.4 | 105.5 ± 2.0 |
| (mEq/L)          |                | H     | 105.6 ± 1.9 | 106.0 ± 1.7 | 106.7 ± 1.6 | 104.8 ± 2.0 |
|                  |                | P     | 105.5 ± 1.6 | 106.2 ± 1.5 | 106.4 ± 2.5 | 105.3 ± 2.1 |
| Glucose          | 70–109         | L     | 85.6 ± 5.4  | 90.4 ± 6.1  | 90.3 ± 6.7  | 87.5 ± 4.5  |
| (mg/dL)          |                | H     | 88.4 ± 7.7  | 92.3 ± 5.8  | 91.5 ± 8.1  | 88.8 ± 6.5  |
|                  |                | P     | 87.5 ± 3.6  | 88.2 ± 4.6  | 89.3 ± 3.5  | 85.1 ± 4.5  |
| HbA1c            | 4.6–6.2        | L     | 5.16 ± 0.22 | 5.31 ± 0.20 | 5.24 ± 0.22 | 5.34 ± 0.15 |
| (%)              |                | H     | 5.30 ± 0.22 | 5.36 ± 0.26 | 5.35 ± 0.23 | 5.44 ± 0.21 |
|                  |                | P     | 5.21 ± 0.21 | 5.32 ± 0.23 | 5.32 ± 0.22 | 5.36 ± 0.22 |

Values are presented as means ± SD; L, low-dose group; H, high-dose group; P, placebo group.

\textsuperscript{*}Significantly different from the placebo group, \( p < 0.05 \).
Table 4  Effects of paprika oleoresin supplementation on hematological parameters in healthy adult subjects.

| Items     | Standard value | Group  | 0 week            | 4 week            | 8 week            | 12 week           |
|-----------|----------------|--------|-------------------|-------------------|-------------------|-------------------|
| WBC       | M: 3900–9800   | L      | 4955 ± 1074       | 4418 ± 920        | 4400 ± 931        | 4764 ± 1332       |
|           | F: 3500–9100   | H      | 4855 ± 1488       | 4727 ± 991        | 5473 ± 2186       | 4673 ± 1260        |
|           | P              | P      | 4464 ± 814        | 5000 ± 1055       | 4773 ± 882        | 4900 ± 1145        |
| RBC       | M: 427–570     | L      | 438.8 ± 42.1      | 445.5 ± 42.6      | 438.5 ± 51.9      | 448.8 ± 46.8       |
|           | F: 376–500     | H      | 454.8 ± 42.6      | 454.5 ± 48.9      | 457.3 ± 46.6      | 452.7 ± 43.2       |
|           | P              | P      | 443.1 ± 38.4      | 451.8 ± 36.1      | 443.7 ± 36.4      | 446.0 ± 40.4       |
| Hgb       | M: 13.5–17.6   | L      | 13.5 ± 1.6        | 13.6 ± 1.5        | 13.4 ± 1.9        | 13.8 ± 1.8         |
|           | F: 11.3–15.2   | H      | 13.9 ± 1.2        | 13.9 ± 1.3        | 14.1 ± 1.4        | 13.9 ± 1.2         |
|           | P              | P      | 13.1 ± 1.8        | 13.3 ± 1.8        | 13.1 ± 1.7        | 13.2 ± 2.1         |
| Hct       | M: 39.8–51.8   | L      | 40.6 ± 4.5        | 39.9 ± 4.1        | 39.7 ± 4.7        | 40.8 ± 4.5         |
|           | F: 33.4–44.9   | H      | 42.1 ± 3.6        | 41.4 ± 4.0        | 41.5 ± 3.3        | 41.3 ± 3.6         |
|           | P              | P      | 40.5 ± 4.1        | 40.0 ± 4.3        | 39.3 ± 3.8        | 40.0 ± 5.0         |
| MCV       | M: 83–102      | L      | 92.7 ± 4.6        | 89.6 ± 4.1        | 90.5 ± 4.4        | 91.1 ± 5.0         |
|           | F: 79–100      | H      | 92.7 ± 4.1        | 91.3 ± 4.8        | 91.0 ± 4.2        | 91.5 ± 3.8         |
|           | P              | P      | 91.7 ± 8.3        | 88.8 ± 8.2        | 88.6 ± 7.8        | 89.8 ± 8.5         |
| MCH       | M: 28.0–34.6   | L      | 30.7 ± 1.9        | 30.5 ± 1.8        | 30.6 ± 1.9        | 30.7 ± 2.0         |
|           | F: 26.3–34.4   | H      | 30.5 ± 1.4        | 30.6 ± 1.5        | 30.9 ± 1.6        | 30.7 ± 1.3         |
|           | P              | P      | 29.6 ± 3.5        | 29.5 ± 3.6        | 29.6 ± 3.6        | 29.6 ± 3.7         |
| MCHC      | M: 31.6–36.6   | L      | 33.2 ± 0.8        | 34.0 ± 1.0        | 33.8 ± 1.1        | 33.7 ± 1.1         |
|           | F: 30.7–36.6   | H      | 32.9 ± 0.7        | 33.5 ± 1.0        | 34.0 ± 1.1*       | 33.6 ± 0.7         |
|           | P              | P      | 32.2 ± 1.3        | 33.1 ± 1.7        | 33.2 ± 1.6        | 32.8 ± 1.4         |
| PLT       | 13.0–36.9      | L      | 25.1 ± 4.1        | 25.0 ± 4.2        | 25.3 ± 4.2        | 26.0 ± 4.5         |
|           | F: 26.3–34.4   | H      | 19.7 ± 3.7        | 18.9 ± 2.9*       | 19.9 ± 3.9        | 20.7 ± 3.6         |
|           | P              | P      | 24.2 ± 7.1        | 23.9 ± 5.7        | 23.9 ± 6.5        | 24.8 ± 7.0         |
| PT        | 9.4–12.2       | L      | 11.1 ± 0.3        | 11.2 ± 0.4        | 11.0 ± 0.5        | 10.9 ± 0.5         |
|           | H              | H      | 11.1 ± 0.4        | 11.1 ± 0.4        | 10.9 ± 0.4        | 10.9 ± 0.3         |
|           | P              | P      | 11.2 ± 0.4        | 11.3 ± 0.4        | 11.1 ± 0.5        | 11.1 ± 0.4         |
| PT-INR    | 0.88–1.17      | L      | 0.98 ± 0.03       | 0.99 ± 0.03       | 1.02 ± 0.04       | 1.01 ± 0.04        |
|           | H              | H      | 0.98 ± 0.03       | 0.99 ± 0.03       | 1.01 ± 0.04       | 1.01 ± 0.03        |
|           | P              | P      | 0.99 ± 0.04       | 1.01 ± 0.04       | 1.03 ± 0.04       | 1.03 ± 0.04        |

Values are presented as means ± SD; L, low-dose group; H, high-dose group; P, placebo group.

* Significantly different from baseline, \( p < 0.05 \).

# Significantly different from the placebo group, \( p < 0.05 \).
derstood, Pérez-Gálvez et al. speculated that food matrix effects are causative of differences in carotenoid absorption. Moreover, capsanthin is absorbed more slowly than other carotenoids. Thus, the present doses of capsanthin may have been insufficient to increase plasma concentrations, warranting further studies of capsanthin absorption and plasma accumulation.

Safety evaluations of paprika oleoresin supplementation over 12 consecutive weeks revealed several significant but sporadic changes. However, physical examinations, blood biochemistry analyses, and hematological tests showed small changes that were within the normal range, and only UA was significantly higher in the high-dose paprika oleoresin group compared with the placebo group after 12 weeks. Moreover, because these differences were present before paprika oleoresin intake, they were considered clinically insignificant and unrelated to treatments. Hence, no adverse changes were related to paprika oleoresin intake in any of the study subjects.

**5 CONCLUSION**

In conclusion, the present study demonstrates that plasma β-cryptoxanthin accumulation is greater than that of other carotenoids, including zeaxanthin, following paprika oleoresin supplementation. No adverse effects were associated with intake of paprika oleoresin (20 and 100 mg/day) in safety evaluations. Taken together, these results suggest that paprika oleoresin is a suitable dietary source of β-cryptoxanthin.

**Conflict of Interest**

This study was funded and supported by Riken Vitamin Co., Ltd. NU and KM are employees of Riken Vitamin Co., Ltd.

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