Effect of paprika xanthophyll supplementation on oxygen uptake in athletes: a randomized, double-blind, placebo-controlled study

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Abstract Xanthophylls have been attracting attention as phytochemicals with antioxidant activity and various beneficial effects demonstrated by randomized clinical trials. Ripe red paprika has high xanthophyll content and is a valuable source of dietary xanthophylls. Our previous study revealed that paprika xanthophylls were detected in the plasma of healthy volunteers after oral administration and preferentially accumulated in erythrocytes, suggesting a potential beneficial effect on erythrocytes. The present study was performed to investigate the effect of paprika xanthophyll supplementation on respiratory parameters in athletes performing treadmill exercise. In a randomized, double-blind, placebo-controlled, parallel group study, 14 athletes were assigned to daily intake of a drink containing 9.0 mg of paprika xanthophylls or a placebo drink. Before and after the 4-week intervention period, blood samples were collected to measure plasma carotenoid levels. The athletes also performed treadmill exercise (12 km/hr for 20 min) before and after the 4-week intervention period, and respiratory parameters were analyzed. After 4 weeks, the paprika xanthophyll group had significantly higher levels of total plasma xanthophylls and total plasma carotenoids (p = 0.014 and 0.043, respectively) than the placebo group. \( V_{\text{O}} \), \( V_{\text{CO}} \), and \( V_{\text{E}} \) were significantly lower in the paprika xanthophyll group than the placebo group. These results suggest that paprika xanthophyll supplementation allowed athletes to perform exercise at a set intensity with lower oxygen uptake. Subjective fatigue after exercise was also significantly less severe in the paprika xanthophyll group.

Keywords : paprika xanthophyll, respiration, oxygen uptake, fatigue, randomized controlled study

Introduction

The brain and the muscles are two major organs which have a high requirement for oxygen. Insufficient oxygen supply to the muscles affects the performance and endurance of athletes. Erythrocytes in the blood are responsible for distributing oxygen to the cells in peripheral tissues and organs. Because of carrying oxygen, erythrocytes are at risk of damage by reactive oxygen species (ROS) and have systems to protect cellular components from oxidative stress (OS). OS occurs when the level of ROS production exceeds the anti-oxidant capacity of a cell or tissue. Carotenoids and polyphenols are two major phytochemicals with antioxidant activity, and their beneficial effects on health have been receiving attention.

Carotenoids are natural pigments found in green-yellow vegetables that have strong antioxidant activity, and they are recognized as a principal component of dietary antioxidants. There are over 750 known carotenoids and these compounds can be divided into two classes, which are carotenes (pure hydrocarbons) and xanthophylls (hydrocarbons containing oxygen)\(^1\). Carotenoids cannot be synthesized by humans, so dietary intake is the only source of these beneficial compounds. There have been several reports that dietary carotenoids can be detected in plasma and in erythrocytes\(^2\). Recent studies have clearly suggested that xanthophylls, rather than carotenes, are preferentially localized in erythrocytes\(^3\). In human volunteers, oral supplementation with xanthophylls was reported to increase the xanthophyll levels in erythrocytes and decrease phospholipid peroxides (PLOOH)\(^4,5\). The phospholipid composition influences elasticity of the erythrocyte.

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membrane, cellular functions, and oxygen supply to the peripheral tissue and organs.

Ripe red paprika is a valuable source of xanthophylls, since it contains two ubiquitous xanthophylls (β-cryptoxanthin and zeaxanthin) together with five rare xanthophylls (capsanthin, cucurbitaxanthin A, cryptocapsin, capsanthin 3,6 epoxide, and capsorubin)\(^6\). Among these rare xanthophylls, capsorubin, capsanthin, and cucurbitaxanthin A are of particular interest, since they have much higher singlet oxygen-scavenging capacity than astaxanthin, a xanthophyll well known for its strong antioxidant activity\(^6\).

In our previous human study, we demonstrated that all of these paprika xanthophylls were found in plasma and preferentially in erythrocytes after oral supplementation. Oral intake of paprika carotenoids (15 mg of total carotenoids per day for 4 weeks) resulted in a 2.2-fold increase of xanthophylls in erythrocytes and xanthophylls accounted for more than 80% of erythrocyte carotenoids\(^6\). Taking the results of this supplementation study together with the reported importance of xanthophylls for erythrocytes, it seems that paprika xanthophyll supplementation is potentially beneficial for protecting erythrocytes from OS and for improving oxygen distribution to the peripheral tissues including brain and muscles. Therefore, the present randomized clinical trial was performed in athletes to investigate the effect of paprika xanthophyll supplementation on plasma carotenoid levels, and oxygen uptake during exercise. The subjective level of fatigue after exercise was also assessed by using a visual analog scale (VAS).

Materials and Methods

**Study design.** The present study was conducted according to the guidelines in the Declaration of Helsinki, and all procedures involving human subjects were approved by the ethics committees of Fukushima University (approval number: 26-06). Fourteen healthy female students belonging to the track and field club of Fukushima University were enrolled in this 4-week randomized, double-blind, placebo-controlled intervention study. Prior to enrollment, written consent was obtained from each subject. The subjects included sprinters, middle-distance runners, long jumpers, pole vaulters and walkers.

Subjects were randomized to one of two groups. The paprika group (n = 7, aged 20 ± 0 years, weight: 51.3 ± 6.6 kg) ingested 100 ml of a drink containing 4.5 mg of paprika xanthophylls twice a day (morning and evening) for 4 weeks. The placebo group (n = 7, aged 20 ± 1 year, weight: 54.2 ± 4.7 kg) ingested 100 ml of a drink not containing paprika xanthophylls twice a day (morning and evening) for 4 weeks. Subjects trained 5 days per week for 3 hours a day in weeks 1, 3, and 4, while they performed light exercise for about 1 hour daily in week 2 because of the winter break.

The paprika xanthophylls used in this study were obtained as a commercial paprika xanthophyll preparation (“PapriX-nano”, Glico Nutrition Co., Ltd., Osaka, Japan). The test drink for the paprika group was prepared as follows: 0.5 g of PapriX-nano was mixed with 3 g of highly branched cyclic dextrin (“CCD”, Glico Nutrition Co., Ltd., Osaka, Japan), 7 g of sucrose, 0.18 g of anhydrous citric acid, 0.12 g of sodium citrate, 0.005 g of sodium chloride, 0.008 g of potassium chloride, and 100 ml of water. Then the pH was adjusted to 3.5 with 10% torosodium citrate solution. This test drink for the paprika group had a total xanthophyll content of 4.5 mg, including 2.5 mg of capsanthin and 0.25 mg of β-cryptoxanthin. The test drink for the placebo group was made in the same way, except that PapriX-nano was omitted and artificial coloring was added. The test drinks for both groups were indistinguishable with respect to appearance and taste.

**Blood sampling and analysis of plasma carotenoids.** Before and after the 4-week intervention period, a blood sample was collected from each volunteer to measure plasma carotenoid levels. The blood sample (10 ml) was collected into a heparinized vacuum tube and let stand for 30 min at room temperature, followed by centrifugation (1,000 g) for 10 min at room temperature. Then aliquots (1 ml) of the plasma thus separated were stored at -80ºC. For analysis of carotenoids, 2 ml of ethanol was added to each aliquot (1 ml) of plasma and stirred with a vortex mixer, after which carotenoids were extracted with 5 ml of ether: hexane (2:8) solution. After being let stand for 10 min, the upper layer was filtered through a Millipore membrane filter (Millipore Corporation, Massachusetts, USA) and then evaporated to dryness. The residue was dissolved in acetone: hexane (2:8) and HPLC was employed for measurement of carotenoid as described by our previous report\(^6\). Subjects did not ingest the test drink or any food within 12 h (hours) before blood sampling.

**Treadmill exercise and respiratory analysis.** For this study, the athletes performed exercise for 20 min on a motor-driven treadmill set at 12 km/h. During treadmill exercise, respiratory data were collected using a breath-by-breath gas analysis system (Aero Monitor AE300S, Minato Medical Science, Osaka, Japan) that displayed the minute oxygen uptake (\(\text{VO}_2\)), minute carbon dioxide production (\(\text{VCO}_2\)), and minute ventilation (\(\text{VE}\)). The gas analysis system was calibrated before each test by using two precision gas mixtures. The respiratory quotient (RQ) was calculated as \(\text{VCO}_2/\text{VO}_2\). Subjects did not ingest the test drink or any food within 12 h before exercise. The treadmill speed was set to allow steady submaximal exercise for each subject, since this exercise intensity is near to that causing accumulation of blood lactate and was routinely performed by the athletes during warm-up. A steady level of absolute exercise was used because this study aimed to investigate the effect of paprika xanthophyll supplementation on running performance, especially in terms of running economy.
**Subjective assessment of fatigue.** The subjective level of fatigue after treadmill exercise was assessed by using a VAS, which is recommended in the guidelines of the Japanese Society of Fatigue Science. The participants were asked to rate their fatigue from 0 to 100 on a 100-mm line, with 0 meaning no fatigue at all and 100 meaning the most severe fatigue. The change in the fatigue score was calculated (fatigue score after 4 weeks of intervention - fatigue score before intervention).

**Statistical analysis.** Results are shown as the mean ± standard deviation (SD). Welch’s t-test was used for between-group comparisons (placebo group vs. paprika group), while within-group comparisons were performed with the paired t-test. When employing the t-test, “not detected” was calculated as 0. A p value < 0.05 was considered to indicate statistical significance.

**Results**

**Effect of paprika xanthophyll supplementation on body weight.** There was no significant difference of mean body weight between before and after intervention in the paprika group (before: 51.3 ± 6.6 kg, after 4 weeks: 51.7 ± 7.4 kg). Similarly, there was no significant change of weight in the placebo group (before: 54.2 ± 5.0 kg, after 4 weeks: 53.4 ± 4.7 kg). In addition, there were no significant differences of weight between the paprika group and the placebo group.

**Effect of paprika xanthophyll supplementation on plasma carotenoid levels.** The major xanthophylls in the paprika xanthophyll preparation used for this study were capsanthin, β-cryptoxanthin, zeaxanthin, cryptocapsin, and cucurbitaxanthin A. As shown in Table 1, plasma levels of these five xanthophylls were all significantly higher after 4 weeks in the paprika group than before the study intervention (capsanthin: p = 0.001, β-cryptoxanthin: p = 0.015, zeaxanthin: p = 0.061, cryptocapsin: p < 0.001, cucurbitaxanthin A: p = 0.042). On the other hand, these plasma xanthophylls were not increased in the placebo group. After 4 weeks, the plasma concentrations of capsanthin, β-cryptoxanthin, zeaxanthin, and cryptocapsin were significantly higher in the paprika group than in the placebo group (capsanthin: p < 0.001, β-cryptoxanthin: p = 0.011, zeaxanthin: p = 0.050, cryptocapsin: p < 0.001). In the paprika group, total plasma xanthophylls and total plasma carotenoids were also significantly higher after 4 weeks than before intervention (p = 0.012 and 0.007, respectively), while no significant changes were observed in the placebo group. Furthermore, total plasma xanthophylls and total plasma carotenoids were significantly higher in the paprika group than in the placebo group after 4 weeks (p = 0.01 and 0.043, respectively). These results clearly indicate that oral paprika xanthophyll supplementation increases plasma xanthophyll levels.

**Respiratory analysis during treadmill exercise.** The volunteer athletes performed treadmill exercise (12 km/h for 20 min) before and after the 4-week intervention, and respiratory parameters were analyzed throughout the 20-min exercise period. VO₂, VO₂CO₂, VE, and RQ were calculated for a 2-min rest period before exercise and for each 5 min of exercise (0-5 min, 6-10 min, 11-15 min, and 16-20 min), and the mean values are displayed in Fig. 1. When treadmill exercise was performed before inter-

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**Table 1.** Plasma carotenoid levels before and after the 4-week intervention.

| Carotenoids (pmol/ml) | Placebo group | Paprika group | Between-group |
|-----------------------|--------------|---------------|---------------|
|                       | Before        | 4 weeks       | p value       | Before        | 4 weeks       | p value       | p value (Before) | p value (4 weeks) |
| Total carotenes       | 1758.3 ± 429.3 | 1696.7 ± 341.3 | 0.557         | 1526.1 ± 445.6 | 2014.0 ± 533.4 | 0.014         | 0.169           | 0.470            |
| β-cryptoxanthin       | 797.3 ± 168.0  | 877.4 ± 177.7  | 0.424         | 877.8 ± 290.6  | 1376.7 ± 372.6 | 0.015         | 0.169           | 0.470            |
| 3-OH-b,e-Caro-3’-one  | 29.6 ± 9.1     | 33.1 ± 9.0     | 0.613         | 35.6 ± 6.0     | 29.9 ± 7.1     | 0.037         | 0.169           | 0.470            |
| Cryptocapsin          | Not detected   | Not detected   | -             | Not detected   | 2.8 ± 0.8      | <0.001        | -               | <0.001           |
| Cucurbitaxanthin A    | 18.0 ± 5.2     | 19.4 ± 6.4     | 0.442         | 19.0 ± 2.9     | 25.8 ± 6.9     | 0.042         | 0.646           | 0.099            |
| Capsanthone           | Not detected   | Not detected   | -             | Not detected   | 24.6 ± 12.5    | 0.002         | -               | <0.001           |
| Lutein                | 298.6 ± 57.5   | 301.2 ± 65.5   | 0.939         | 373.5 ± 116.6  | 348.3 ± 137.9  | 0.689         | 0.162           | 0.436            |
| Zeaxanthin            | 12.4 ± 3.8     | 15.1 ± 6.2     | 0.226         | 16.1 ± 3.7     | 43.5 ± 30.7    | 0.061         | 0.089           | 0.050            |
| Capsanthin            | Not detected   | Not detected   | -             | Not detected   | 41.8 ± 14.8    | <0.001        | -               | <0.001           |
| Total xanthophylls    | 2914.0 ± 595.5 | 2942.9 ± 494.1 | 0.871         | 2848.2 ± 645.4 | 3908.2 ± 964.0 | 0.007         | 0.846           | 0.043            |
| Total carotenoids     | 1155.7 ± 205.9 | 1246.2 ± 201.8 | 0.418         | 1322.1 ± 281.6 | 1894.2 ± 506.6 | 0.012         | 0.233           | 0.014            |

Total carotenes is the sum of α-carotene, β-carotene, and lycopene.
Total carotenoids is the sum of total carotenes, β-cryptoxanthin, 3-OH-b,e-caro-3’-one, cryptocapsin, cucurbitaxanthin A, capsanthone, lutein, zeaxanthin, and capsanthin.
Total xanthophylls is the sum of β-cryptoxanthin, 3-OH-b, e-caro-3’-one, cryptocapsin, cucurbitaxanthin A, capsanthone, lutein, zeaxanthin, and capsanthin.
Values are expressed as the mean ± SD. For the t-test, “not detected” was calculated as 0.
vention, \( \dot{V}O_2 \), \( \dot{V}CO_2 \), \( V_E \), and RQ were not significantly different between the paprika group and the placebo group (Fig. 1, panels A, B, C, and D). However, when treadmill exercise was performed after the 4-week intervention period, \( \dot{V}O_2 \) and \( \dot{V}CO_2 \) were significantly lower in the paprika group than the placebo group at 5-10 min, 10-15 min, and 15-20 min (Fig. 1, panels E and F). \( V_E \) and RQ were also significantly lower in the paprika group than the placebo group at 10-15 min and 15-20 min (Fig. 1, panels G and H).

After treadmill exercise, the blood lactate concentration was 3.7 ± 1.7 mg/ml in the paprika group and 4.6 ± 1.2 mg/ml in the placebo group, showing slight elevation compared to before exercise (3.2 ± 1.7 mg/ml and 3.4 ± 1.0 mg/ml, respectively), but there was no significant difference between the two groups.

**Subjective fatigue after treadmill exercise.** Subjective fatigue was assessed just after treadmill exercise. VAS scores before and after intervention, as well as the changes in each group, are displayed in Table 2. The VAS score for fatigue showed a significant decrease in the paprika group (\( p < 0.01 \)), but not in the placebo group. In addition, the decrease of the VAS score for fatigue after 4 weeks was significantly larger in the paprika group than in the placebo group (\( p < 0.05 \)). These results clearly indicated that subjective fatigue was reduced by oral paprika xanthophyll supplementation.

**Discussion**

In the present study, oral supplementation with paprika xanthophylls (9 mg of total xanthophylls daily for 4

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**Table 2.** VAS evaluation of subjective fatigue before and after intervention.

| Group          | Treatment period | Change from before |
|----------------|------------------|--------------------|
|                | before  | 4 weeks          |                    |
| Placebo group  | 51.9 ± 12.4 | 53.9 ± 9.5  | 2.0 ± 14.9          |
| Paprika group  | 59.1 ± 13.1 | 43.9 ± 16.2 * | -15.3 ± 7.7 #       |

Data are expressed as the mean ± SD (mm). Differences between the paprika and placebo groups were investigated with Welch’s t-test. Comparisons between before treatment and after 4 weeks of treatment were performed by the paired t-test. #: \( p < 0.05 \) vs. placebo group; *: \( p < 0.01 \) vs. before.
weeks) had significant effects on the respiratory parameters of athletes performing exercise. VO₂, VCO₂, and VE were all significantly lower in the paprika xanthophyll group than in the placebo group (Fig. 1). These results suggest that paprika xanthophyll supplementation allowed athletes to perform exercise at a set intensity with lower oxygen uptake. In other words, paprika xanthophyll supplementation significantly improved running economy (the O₂ cost of running at a certain speed or a certain distance). It has recently been reported that running economy is an important factor with respect to inter-individual differences of running performance⁶⁻⁸, and it is considered to be a key to continued improvement of long distance performance⁹. Running economy shows considerable inter-individual variability¹⁰, but the reasons are not understood and might include genetics, training levels, or biomechanical factors¹¹⁻¹². The effect of paprika xanthophylls on running economy revealed in the present study is potentially beneficial for improvement of endurance or performance by a wide range of athletes, and further investigation is warranted.

The mechanism underlying this beneficial effect of paprika xanthophylls for athletes is not known, but the preferential localization of xanthophylls in erythrocyte membranes may be involved. Our previous human study using the same paprika xanthophyll preparation (12 mg of total xanthophylls daily for 4 weeks) revealed that plasma and erythrocyte total carotenoid levels were increased to 117% and 200% of baseline, respectively, with xanthophylls being preferentially localized in the erythrocyte fraction while carotenones were preferentially localized to the plasma⁶. Although we did not measure erythrocyte carotenoid levels in the present study, it is likely that the significant increase of total plasma xanthophylls (Table 1) was associated with increased uptake by erythrocytes as observed in our previous study. It is generally known that membrane flexibility is important for allowing erythrocytes to pass through narrow capillaries and deliver oxygen to the tissues and organs. To achieve sufficient flexibility, the erythrocyte membrane is composed of phospholipids rich in poly-unsaturated fatty acids¹³⁻¹⁴. Since poly-unsaturated fatty acids are easily damaged by ROS, accumulation of xanthophylls in erythrocytes may contribute to maintenance of membrane flexibility by preventing the oxidation of membrane phospholipids through strong anti-oxidant activity. It has already been reported that astaxanthin or lutein supplementation in healthy subjects not only increased erythrocyte levels of these xanthophylls, but also decreased erythrocyte levels of oxidized phospholipids⁵⁻⁶. It has also been reported that intake of eicosapentaenoic acid (EPA)-rich fish oil by healthy subjects reduces blood viscosity¹⁵⁻¹⁶. This reduction of blood viscosity is reported to improve aerobic performance by increasing oxygen supply to muscles¹⁷. Paprika xanthophyll supplementation probably contributes to more effective oxygen delivery to the muscles by protecting erythrocytes from oxidative stress through strong anti-oxidant activity against singlet oxygen¹⁸ and hydroxyl radicals¹⁸.

Effective delivery of oxygen to the muscles is very important for the performance of athletes. High-altitude training has been recognized as an effective method of enhancing performance¹⁹⁻²⁰, since such training may improve the delivery of oxygen by increasing the number of circulating erythrocytes²⁰⁻²¹. Paprika xanthophyll supplementation is potentially a good alternative to high-altitude training for improving oxygen delivery and athletic performance, but this subject requires further investigation.

Conflict of Interests

The authors have read the journal’s policy and have the following conflicts: T. Ichihara, A. Nishino, T. Takaha and T. Kuriki are employees of Ezaki Glico Co., Ltd. K. Kawamoto received research grants from Ezaki Glico Co., Ltd. This does not alter the authors’ adherence to all the JPFSM policies on sharing data and materials.

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