Effect of Passion Fruit Seed Extract Rich in Piceatannol on the Skin of Women: A Randomized, Placebo-Controlled, Double-Blind Trial

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Summary Piceatannol has been reported to have a wide variety of effects on the skin, including promoting collagen production, inhibiting melanin synthesis, inducing the antioxidant glutathione, and eliminating reactive oxygen species. In this study, a randomized, placebo-controlled, double-blind trial was conducted to clinically evaluate the effects of piceatannol-rich passion fruit seed extract on the skin of healthy Japanese women (age, 35–54 y). Thirty-two women with dry skin received either passion fruit seed extract (5 mg piceatannol) or a placebo (dextrin) for 8 wk. Skin hydration and other parameters on the face were assessed at 0, 4, and 8 wk by using specialized equipment. Furthermore, questionnaire interviews were conducted regarding the physical condition of subjects at 0, 4, and 8 wk. The results showed that consumption of passion fruit seed extract led to significant increases in the moisture content of human skin after 4 and 8 wk compared with that before the trial. The amount of transepidermal water loss decreased over time, although the differences were not significant. Moreover, a stratified analysis of subjects with moisture values of ≥200 μS revealed increased moisture content in the passion fruit seed extract group as compared with the placebo group. Furthermore, the results of questionnaires showed significant reductions in “perspiration” and “fatigue” in the passion fruit seed extract group as compared with the placebo group. These results indicate that oral intake of passion fruit seed extract that is rich in piceatannol could improve the moisture of dry skin and reduce fatigue.

Key Words passion fruit seed, piceatannol, resveratrol, skin moisture, fatigue

Piceatannol (Fig. 1) is a polyphenol with a similar structure (apart from having an extra hydroxyl group) to resveratrol, which has been reported to activate the longevity gene SIRT1. Whereas resveratrol can be found in many edible plants and plant products such as red wine and is an active topic of research, piceatannol is found in low amounts in plants and has not been studied yet. We discovered that passion fruit seeds are rich in piceatannol, which has shown effects such as antioxidant action (2), endothelial nitric oxide synthase induction (3), SIRT1 induction (4), and improvement of metabolic disorders (5–7). As for the skin, effects of piceatannol, including inhibition of melanin synthesis (8, 9), promotion of collagen production (9), and MMP-1 suppression by eliminating active oxygen (10), have been demonstrated.

Dry skin is a common problem that is associated with skin roughness, itchiness, and wrinkling. Signs of dry skin depend on age, state of health, and the environment. In particular, ultraviolet (UV) damage is known to disrupt the barrier function of the skin, thus inducing dryness (11). Antioxidants such as polyphenols are effective in preventing UV damage, and application of antioxidant substances has been reported to protect against dryness and structural damage of the skin. Moreover, regular intake of polyphenols has gained considerable attention, as these compounds are considered protective agents against the adverse effects of UV radiation (12). However, studies on the effect on the skin of ingestion of these agents are scarce.

In the present study, we investigated the effects on human skin of consumption of passion fruit seed extract (PFSE) containing 5 mg piceatannol, in a placebo-controlled double-blind trial. In addition, changes in physical condition during consumption of PFSE were evaluated using the 36-Item Short-Form Health Survey (SF-36v2) and a visual analogue scale (VAS) questionnaire, and through analysis of the intestinal flora.

MATERIALS AND METHODS

Study design and subjects. This study was a randomized, placebo-controlled, double-blind trial in healthy Japanese women aged at least 35 and <55 y. The study was approved by the ethics committee of the Society for Glycative Stress Research and conducted in accordance with the Declaration of Helsinki. Informed consent was obtained in writing from the subjects before starting the study. This study was registered in the University Hospital Medical Information Network Clinical Trial Registry (Japan, registration no. UMIN000025920) in 2017.

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Details are available at https://upload.umin.ac.jp/cgi-open-bin/ctr/ctr_view.cgi?recptno=R000029781&language=E. The following subjects were excluded:
1) Subjects who took medicine for chronic diseases.
2) Subjects with atopic dermatitis or chronic dermatitis.
3) Subjects with tendencies for excessive sunburn.
4) Subjects with severe allergy to foods and medicine.
5) Subjects who were pregnant or lactating, or planning to become pregnant in the near future.
6) Subjects with a history of serious disorders.
7) Subjects who were receiving treatment from a physician.
8) Subjects with severe anemia.
9) Subjects with possibilities for lifestyle change during the study.
10) Subjects with allergy to cosmetics and other ingredients.
11) Subjects who were participating in other clinical studies.
12) Subjects who were judged by the investigator as unsuitable for the study.

Thirty-four women who complained of dry skin were recruited to participate, and two women were excluded because of failure to meet the criteria (one subject with an adverse event in the control group, and another subject with a low ingestion rate in the PFSE group).

**Test substance.** PFSE containing 5 mg piceatannol (Morinaga & Co., Ltd., Japan) was used as the test substance, whereas dextrin was used as the placebo control. The study subjects, divided into the PFSE group and the placebo group, took two capsules containing their assigned treatment once daily for 8 wk. The recommendation was to take the capsules before going to bed. The compositions of the two capsule types are shown in Table 1.

**Questionnaires.** At weeks 0, 4, and 8, the subjects answered the SF-36v2 and VAS questionnaires. A Japanese version of the self-administered SF-36v2 was provided under license by iHOPE International Corporation (Kyoto, Japan), the Japanese agent for QualityMetric.

Analysis of the SF-36v2 was performed according to the questionnaire instructions, and norm-based scores were calculated based on the national standard values (13). For the VAS questionnaire, each condition was rated on a single-item 100 mm VAS anchored at each end by the descriptions “very attractive” (0 mm) and “very unattractive” (100 mm). The distance of the point from the left-hand side (0 mm) was measured, and the change in the distance before and after treatment was analyzed. The subjects rated 20 questionnaire items: Lines on the skin, Skin fitness, Dry skin, Oily skin, Skin roughness, Makeup, Porous skin, Stretching after cleansing, Acne, Mottling and wrinkles, Dullness, Face color, Dark circles under the eyes, Glossy hair, Glossy nail, Constipation, Perspiration, Waking up rested, Sleeping well, and Fatigue.

**Analysis of intestinal flora.** All subjects provided fecal samples during the week before the start of treatment (week 0) and on week 4 of treatment, which were tested by using a feces sampling kit (TechnoSuruga Laboratory Co., Ltd., Shizuoka, Japan). The samples were analyzed with terminal restriction fragment polymorphism, performed by TechnoSuruga Laboratory Co., Ltd. (Shizuoka, Japan).

**Skin measurements.** The skin of the subjects was evaluated at weeks 0, 4, and 8. The sites of measurements were the cheeks. After washing and rinsing the face, the subjects were acclimatized for 15 min in a temperature- and humidity-controlled room (temperature 20 ± 2°C, humidity 50 ± 10%) before starting the measurements. Moisture content was evaluated by using a skin conductance measurement device (SKICON-200EX; Yayoi Co., Ltd., Himeji, Japan). Measurement was conducted five to seven times, and the mean of three stable measurements was taken to be the moisture content of the stratum corneum at the site. Transepidermal water loss was measured by using an AS-CT1 cyclone moisture transpiration monitor (Asahibiomed Co., Ltd., Yokohama, Japan). Measurement was carried out at least three times, and the mean of three stable measurements was taken to be the moisture content of the stratum corneum at the site. Transepidermal water loss was measured by using an AS-CT1 cyclone moisture transpiration monitor (Asahibiomed Co., Ltd., Yokohama, Japan). Measurement was carried out at least three times, and the mean of three stable measurements was taken to be the moisture content of the stratum corneum at the site. Transepidermal water loss was measured by using an AS-CT1 cyclone moisture transpiration monitor (Asahibiomed Co., Ltd., Yokohama, Japan). Measurement was carried out at least three times, and the mean of three stable measurements was taken to be the moisture content of the stratum corneum at the site. Transepidermal water loss was measured by using an AS-CT1 cyclone moisture transpiration monitor (Asahibiomed Co., Ltd., Yokohama, Japan). Measurement was carried out at least three times, and the mean of three stable measurements was taken to be the moisture content of the stratum corneum at the site. Transepidermal water loss was measured by using an AS-CT1 cyclone moisture transpiration monitor (Asahibiomed Co., Ltd., Yokohama, Japan). Measurement was carried out at least three times, and the mean of three stable measurements was taken to be the moisture content of the stratum corneum at the site. Transepidermal water loss was measured by using an AS-CT1 cyclone moisture transpiration monitor (Asahibiomed Co., Ltd., Yokohama, Japan). Measurement was carried out at least three times, and the mean of three stable measurements was taken to be the moisture content of the stratum corneum at the site. Transepidermal water loss was measured by using an AS-CT1 cyclone moisture transpiration monitor (Asahibiomed Co., Ltd., Yokohama, Japan). Measurement was carried out at least three times, and the mean of three stable measurements was taken to be the moisture content of the stratum corneum at the site. Transepidermal water loss was measured by using an AS-CT1 cyclone moisture transpiration monitor (Asahibiomed Co., Ltd., Yokohama, Japan). Measurement was carried out at least three times, and the mean of three stable measurements was taken to be the moisture content of the stratum corneum at the site.
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Table 2. Difference of visual analogue scale indices for conditions.

|                      | Placebo n=16 | Passion fruit seed extract n=16 | p-value |
|----------------------|--------------|-------------------------------|---------|
|                      | 4 wk | 8 wk | 4 wk | 8 wk | 4 wk | 8 wk |
| Lines on the skin   | 0.15±0.30 0.56±0.41 | 0.62±0.32 0.53±0.39 | 0.295 0.960 |
| Skin fitness        | 0.95±0.41 1.12±0.50 | 0.59±0.56 0.75±0.55 | 0.606 0.624 |
| Dry skin            | 1.28±0.36 1.59±0.43 | 0.66±0.34 1.00±0.52 | 0.216 0.383 |
| Oily skin           | 0.09±0.46 -0.48±0.52 | 0.85±0.36 0.39±0.42 | 0.200 0.204 |
| Skin roughness      | 0.55±0.57 0.49±0.57 | 0.68±0.65 1.59±0.63 | 0.880 0.205 |
| Makeup              | 1.04±0.27 1.15±0.35 | 0.59±0.51 1.10±0.38 | 0.445 0.933 |
| Porous skin         | 0.92±0.33 0.79±0.32 | 0.45±0.44 0.86±0.35 | 0.398 0.876 |
| Stretching after cleansing | 0.95±0.41 1.20±0.40 | 0.66±0.41 1.20±0.51 | 0.623 0.996 |
| Acne                | 0.54±0.41 0.14±0.63 | 0.61±0.78 0.65±0.61 | 0.941 0.563 |
| Mottling and wrinkles | 0.81±0.24 1.14±0.39 | 0.15±0.34 0.64±0.49 | 0.122 0.427 |
| Dullness            | 0.83±0.31 0.33±0.28 | 0.20±0.30 0.7±0.55 | 0.157 0.545 |
| Face color          | 0.56±0.27 0.85±0.41 | 1.13±0.63 1.23±0.43 | 0.409 0.520 |
| Dark circles under the eyes | 0.42±0.38 0.37±0.48 | 0.79±0.49 1.13±0.52 | 0.554 0.294 |
| Glossy hair         | -0.12±0.41 -0.32±0.43 | 0.64±0.47 0.75±0.45 | 0.235 0.094 |
| Glossy nail         | -0.33±0.37 -0.16±0.56 | 0.55±0.62 1.00±0.75 | 0.230 0.226 |
| Constipation        | 0.38±0.38 0.11±0.54 | 0.39±0.23 0.74±0.65 | 0.989 0.463 |
| Perspiration        | 0.96±0.44 0.61±0.61 | -1.56±0.72 -2.13±0.77 | 0.005 0.009 |
| Waking up rested    | -0.59±0.48 0.28±0.23 | -0.45±0.38 0.22±0.28 | 0.820 0.863 |
| Sleeping well       | 0.13±0.26 0.33±0.53 | 0.84±0.55 0.52±0.48 | 0.251 0.795 |
| Fatigue             | -0.45±0.51 -0.54±0.39 | 0.82±0.34 0.69±0.31 | 0.046 0.018 |

n=number of subjects. Data are shown as mean±standard error of the mean. p<0.05, significant difference between the placebo group and the passion fruit seed extract group.

as it rises linearly when negative pressure is applied. Uv (delayed distension) is the nonlinear increase in skin height observed following Ue. Ue mainly reflects skin elasticity; Uv mainly reflects skin viscosity; and Uv/Ue represents the degree to which viscosity contributes to skin changes. Skin color was measured by using a CM-2600d spectrophotometer (color meter; Konica Minolta Inc., Tokyo, Japan). The skin color parameters were L*, a*, and b*. Measurement was carried out at least three times, and the mean of three stable measurements was used. To assess skin quality, images were taken with VISIA Evolution (Canfield Imaging Systems, Fairfield, NJ). Scores for skin pores, mottling, wrinkles, roughness, and redness were measured by using the internal software of the device.

Statistical analysis. The results were expressed as mean±standard error of the mean for each group. Changes in parameters compared with week 0 were calculated, except for the analysis of intestinal flora. Statistical analysis was carried out by using the software IBM SPSS Statistics 19 (SPSS IBM Japan Inc., Tokyo, Japan). Comparison of differences from the baseline values (week 0) in the placebo group and the PFSE group were tested by using Student’s unpaired two-tailed t-test. Changes from the baseline for each group were tested by using Student’s paired two-tailed t-test for the two time points in intestinal flora analysis, and those at the three time points for the other measurements were tested by using Dunnett’s test. p<0.05 was considered to indicate a statistically significant change.

RESULTS

Questionnaires
No significant difference was seen in the placebo group or the PFSE group concerning SF-36v2 (data not shown). The results from the VAS questionnaire are summarized in Table 2. There was no significant difference between the placebo group and the PFSE group before the study. Improvements in skin-related conditions were seen in the PFSE group; however, the placebo group also showed improvements, and no significant difference was seen between groups. Significant improvements in conditions such as “perspiration” and “fatigue” were seen in the PFSE group as compared with the control group.

Fecal analysis
No significant difference was seen in the placebo group or the PFSE group in terms of the intestinal flora. In the placebo group, a significant increase was seen in potentially harmful bacteria from Clostridium subcluster XIVa after treatment (data not shown).

Skin measurements
The skin measurement data at week 0 are summarized in Table 3. There was no statistical difference between the placebo and PFSE groups. The changes...
in moisture content and water loss are summarized in Fig. 2. Increases in moisture content were seen in both the placebo and PFSE groups; however, a significant improvement from before treatment was seen only in the PFSE group ($p<0.05$). A stratified analysis using subjects with moisture values of $\geq 200$ µS revealed increased moisture content in the PFSE group as compared with the placebo group ($p<0.05$). The amount of transepidermal water loss decreased over time only in the PFSE group, although the difference was not statistically significant.

The results for the indices of elasticity (R2 and R6) and the skin color indices ($L^*$, $a^*$, and $b^*$) are summarized in Table 4. No significant changes were seen in elasticity. Concerning the skin color indices, a significant decrease compared with week 0 was seen only in $L^*$ in both the placebo group and the PFSE group at week 4.

The results of the evaluation of skin quality with

|                         | Placebo $n=16$ | Passion fruit seed extract $n=16$ | $p$-value |
|-------------------------|----------------|----------------------------------|-----------|
| Moisture content (µS)   | 153.6±20.9     | 117.9±12.7                       | 0.15      |
| Transepidermal water loss (g/m²/h) | 13.4±1.3     | 15.0±1.9                         | 0.48      |
| R2                      | 0.71±0.01      | 0.73±0.01                        | 0.30      |
| R6                      | 0.42±0.01      | 0.42±0.02                        | 0.97      |
| $L^*$                   | 64.49±0.62     | 63.6±0.77                        | 0.38      |
| $a^*$                   | 7.14±0.52      | 7.86±0.51                        | 0.33      |
| $b^*$                   | 16.34±0.59     | 16.17±0.46                       | 0.82      |
| Pore score              | 682.6±115.6    | 644.4±82.1                       | 0.79      |
| Mottling score          | 78.4±9.0       | 82.0±5.6                         | 0.74      |
| Wrinkle score           | 5.1±1.6        | 3.8±0.8                          | 0.46      |
| Roughness score         | 645.1±127.2    | 556.7±54.1                       | 0.53      |
| Redness score           | 47.9±6.0       | 53.4±4.0                         | 0.44      |

$p$=number of subjects. Data are shown as mean±standard error of the mean.

$p<0.05$, significant difference between the placebo group and the passion fruit seed extract group.
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Table 4. Elasticity and lightness of skin.

|               | Placebo | Passion fruit seed extract | p-value |
|---------------|---------|---------------------------|---------|
|               | n=16    | n=16                      |         |
|               | 4 wk    | 8 wk                      | 4 wk    | 8 wk |
| R2            | 0.03±0.01 | 0.03±0.02           | -0.01±0.01 | -0.01±0.02 | 0.08 | 0.12 |
| R6            | -0.02±0.02 | -0.04±0.01       | -0.01±0.02 | -0.02±0.01 | 0.62 | 0.35 |
| L*            | -1.41±0.42 | -0.46±0.49         | -1.40±0.52 | -0.59±0.38 | 0.99 | 0.83 |
| a*            | 0.67±0.34 | -0.22±0.32          | 0.33±0.45 | -0.29±0.33 | 0.55 | 0.87 |
| b*            | -0.10±0.33 | 0.39±0.33        | -0.62±0.28 | -0.05±0.29 | 0.24 | 0.34 |

n=number of subjects. Data are shown as mean±standard error of the mean. p<0.05, significant difference between the placebo group and the passion fruit seed extract group.

Table 5. Evaluation of skin using VISIA.

|               | Placebo | Passion fruit seed extract | p-value |
|---------------|---------|---------------------------|---------|
|               | n=16    | n=16                      |         |
|               | 4 wk    | 8 wk                      | 4 wk    | 8 wk |
| Pore score    | 23.9±47.3 | -28.0±44.9                | -0.7±46.0 | -29.2±43.6 | 0.71 | 0.98 |
| Mottling score| 1.6±2.5 | 2.1±2.1                   | -1.1±1.9 | -0.8±2.4 | 0.39 | 0.39 |
| Wrinkle score | -0.2±0.7 | -0.1±0.7                  | 0.4±0.6 | 0.3±0.7 | 0.54 | 0.75 |
| Roughness score| 11.0±43.5 | -12.8±41.9                | 1.8±39.0 | -27.4±26.3 | 0.88 | 0.77 |
| Redness score | 2.8±2.6 | 1.1±3.1                   | 2.5±1.6 | 2.2±2.4 | 0.92 | 0.78 |

n=number of subjects. Data are shown as mean±standard error of the mean. p<0.05, significant difference between the placebo group and the passion fruit seed extract group.

VISIA are summarized in Table 5. Although no significant changes were seen in skin quality, decreases in the mean values for mottling and roughness were seen in the PFSE group; however, no decrease was seen in the placebo group.

DISCUSSION

We conducted the first randomized, placebo-controlled, double-blind study on PFSE containing 5 mg piceatannol, which has been reported to have a variety of effects on the skin. Our results showed that consumption of PFSE containing 5 mg piceatannol for 4 or 8 wk significantly increased the moisture content of human skin compared with before the study. In addition, a stratified analysis using subjects with low moisture values revealed increased moisture content in the PFSE group as compared with the placebo group. Although the differences were not significant, it was evident that the transdermal water loss in the PFSE group also decreased over time. On the other hand, no significant changes were seen in elasticity or skin color. The composition of PFSE is 11.3% moisture, 10.7% protein, 0.3% lipid, 6.3% ash, and 73% polyphenols (conversion into epicatechin). Piceatannol, a major polyphenol of passion fruit seed (9), makes up approximately 20% of the polyphenols, and we think piceatannol is an active ingredient of PFSE.

Skin moisture is affected by external environmental factors such as UV radiation and by internal factors such as hormones (14). The antioxidant activity and collagen production enhancement effect of piceatannol may improve skin barrier properties, thereby improving skin moisture content. However, the dose and consumption regimen may need to be investigated to explain the lack of significant changes observed in skin elasticity or color in this study. The metabolism of piceatannol has only been reported in animals, and it is known to be rapidly absorbed and to rapidly disappear from the blood (15). Greater efficacy can probably be expected with more frequent doses, such as twice daily. In addition, in the case of resveratrol, which has an analogous structure, an improvement in the index of elasticity R7 was reported with consumption of lingonberry (Vaccinium vitis-idaea) extract containing resveratrol for 12 wk (unpublished data). Therefore, greater efficacy might be expected by increasing the period of consumption and/or the dose of PFSE.

There have been reports on changes in the intestinal environment induced by piceatannol in animals (16, 17). Hijona et al. reported that piceatannol slightly changed several Lactobacillus, Clostridium, and Bacteroides species in the gut microbiota of obese rats. Tung et al. reported that piceatannol increased Firmicutes and Lactobacillus, and decreased Bacteroidetes in the gut microbiota of mice given a high-fat diet. Bacteria from Clostridium subcluster XIVa was increased in the placebo group, although there was no statistical difference between groups. PFSE treatment might suppress harm-
ful bacteria: such as Clostridium. Clostridium subcluster XI a has been reported to be related to immunity and inflammation (18). Piceatannol is widely known for its anti-inflammatory effect (19). Therefore, this anti-inflammatory effect might influence Clostridium species. It would be interesting to examine the intestinal environment in a further study.

From the results of the questionnaires, it was evident that consumption of piceatannol decreased fatigue and the tendency to perspire. Piceatannol is a polyphenol with high antioxidant activity, and lychee polyphenol (oligonol) has been reported as a similar substance. In the case of lychee polyphenol, decreases in the percentage and volume of perspiration in humans have been reported as objective indices (20). In addition, alleviation of fatigue from daily life and exercise has been reported (21, 22). PFSE containing piceatannol can also be expected to be studied in these fields in the future.

In addition, no particularly problematic adverse events were observed in this study after 8 wk of treatment with PFSE containing piceatannol. These findings suggest that PFSE could be a safe skin-improving supplement.

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