

# Ameliorating Effects of Delphinol<sup>®</sup>, Anthocyanin Standardized Maqui Berry Extract, on Skin Brightness and Redness in Japanese Females: A Randomized Double-Blind Placebo-Controlled Pilot Study

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## Abstract

Maqui berries are widely grown or cultivated in the Patagonian region in Chile. The berries contain large amounts of anthocyanins, especially delphinidin glycosides, which are strong anti-oxidants. We previously reported that standardized maqui berry extract, which contained lots of anthocyanins, has ameliorative effects against dry eyes and visible light-induced photoreceptor cell damage. However, the influence of maqui berry extract on the human skin has not been evaluated even though many skin troubles are related to active oxygen species. Therefore, we conducted a randomized double-blind placebo-controlled pilot study with Delphinol<sup>®</sup>, a maqui berry extract standardized for anthocyanins, especially delphinidins and cyanidins, in healthy Japanese female subjects. Capsules containing Delphinol<sup>®</sup> (60 mg) or placebo were orally administered to subjects aged 27 to 57 years old for eight weeks. Skin conditions [pigmentation, redness, skin tone, wrinkles, texture, oil content, water content, trans epidermal water loss (TEWL), collagen score, dermal thickness, and elasticity] were measured before and after intervention. In the Delphinol<sup>®</sup> group, the saturation significantly increased after eight weeks and reddish spots significantly decreased after four weeks of intake. The collagen score, which decreases with age, slightly increased with age by Delphinol<sup>®</sup> ingestion for eight weeks. Thus, the anthocyanin-standardized maqui berry extract Delphinol<sup>®</sup> increased skin brightness and collagen content, and improved facial skin redness. This study suggests that the daily oral intake of maqui berry extract can help maintain a healthy facial condition.

## Keywords

Maqui Berry, Delphinidin Glucoside, Anthocyanins, Skin, Brightness, Saturation, Redness, Collagen Score

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## 1. Introduction

Maqui berry (*Aristotelia chilensis*) is a shrub distributed in Southern Chile, especially in the Patagonia region. The dark purple fruit is high in anthocyanins [1], including delphinidin glycosides and cyanidin glycosides [2], and exhibits excellent anti-oxidant activity [3], which can protect food from oxidation [4]. It is not only consumed as fresh fruit, but also as processed foods including liquors [5], beverages [6], and functional foods [7]. Recently, the amount of exported maqui berry products has increased. In order to prolong the shelf life of anthocyanins in processed foods, trials selecting suitable binders that can stabilize maqui berry juice or extract in powder form [8], and conditioning to increase anthocyanin stability in liquid form [9] have been performed.

Regarding the beneficial health effects of maqui berry, anti-inflammatory [10] [11] [12] [13], anti-diabetic [14], antidepressant [15], anti-obese [16], and memory improving [17] effects have been reported. Moreover, we previously confirmed that maqui berry extract (MBE) possesses excellent ameliorating effects against dry eyes in animal models [18] and clinical trials [19] [20] with Japanese subjects. Moreover, we found that the extract has photoprotective activity in photoreceptor cells in mouse eyes [21]. On the other hand, we developed a MBE named Delphinol®, which has a standardized anthocyanin content including delphinidin glycosides. Delphinol® exhibits potent anti-oxidant [22], hypoglycemic [23] [24], and anti-bone loss [25] activities. However, the effects of MBE on the skin condition have not been examined except for its skin photoprotective activity in model cells [26]. Therefore, we conducted a clinical trial of MBE ingestion regarding facial skin parameters in Japanese female subjects.

## 2. Materials and Methods

### 2.1. Participants

Female employees aged 27 to 57 years were recruited by Oryza Oil & Fat Chemical Co., Ltd. Their work categories are office workers and researchers. They have an employment relationship with Oryza Oil & Fat Chemical Co., Ltd. Exclusion criteria were as follows:

- 1) Current use of medications for treatment of chronic diseases.
- 2) Allergy to the test product.
- 3) Having atopic dermatitis.
- 4) Use of oral or topical medications.

Then, 16 subjects were randomly allocated to each of two groups by a third member who was not involved in the study. The average age was  $37.3 \pm 8.9$  years

old in the Delphinol® group and  $38.5 \pm 10.5$  years old in the placebo group. Informed consent was received from all subjects prior to the study. After a full explanation of the study, including the purpose, methods, and test product, in addition to the voluntary nature of participation and no disadvantages from refusing to participate, written consent was received from all participants. The subjects were asked to maintain a regular lifestyle during the study period.

## 2.2. Preparation of the Test Products

The test products (indistinguishable brown capsules containing MBE or placebo) were prepared by Oryza Oil & Fat Chemical Co., Ltd. MBE capsules (active) contained 60 mg of Delphinol® (standardized MBE, Oryza Oil & Fat Chemical Co., Ltd.), composed of  $\geq 35\%$  anthocyanin glycosides,  $\geq 25\%$  delphinidin glycosides, and 120 mg of maltodextrin. The placebo capsules contained 180 mg of maltodextrin only.

## 2.3. Study Protocol

The study design was a placebo-controlled double-blind comparison of two groups treated concurrently and was carried out at Oryza Oil & Fat Chemical Co., Ltd. Subjects in the placebo and Delphinol® groups took one capsule daily (placebo or Delphinol®, respectively) with water after breakfast for eight weeks. Each participant was examined at the Oryza Oil & Fat Chemical Co., Ltd. (Aichi, Japan). The temporal scope of the study comprised duration from October 17, to December 12, 2019. Subjects were examined for skin conditions before the start of treatment, and after four and eight weeks of intervention. The outcomes were pigmentation, redness, skin tone, wrinkles, texture, oil content, water content, trans epidermal water loss (TEWL), collagen score, dermal thickness, and elasticity.

## 2.4. Evaluation of Skin Parameters

All skin parameters were measured in an air-conditioned room at  $25^{\circ}\text{C} \pm 1^{\circ}\text{C}$  and  $50\% \pm 5\%$  RH. Prior to the study, the subject washed her face. After wiping, the subject was acclimated for 15 min. First, an image of the left side of the face was captured by a ROBO SKIN ANALYZER CS50 (Inforward, Inc., Tokyo). The evaluated items were pigmentation, redness, skin tone, wrinkles, texture, oil content, and water content. Redness was expressed as number of spots and the area. Redness is defined as two groups in the three-dimensional space of a color image (RGB): a group of flesh-colored areas including reddish color, and a group of natural skin areas not including reddishness and pigmentation. Redness is measured based on the density of the one-dimensional (monochrome) image color information, which is the vector connecting the groups. The redness evaluated by the ROBO SKIN ANALYZER can be detected in Lv. 1  $\rightarrow$  Lv. 2  $\rightarrow$  Lv. 3 as the degree of redness increases. As redness Lv. 1 is the maximum detection sensitivity, Lv. 2 is approximately 38% and Lv. 3 is approximately 23% the detection sensitivity conversion of Lv. 1.

Skin elasticity was measured at the mid-point of a line between the right eye and right ear by a Triplesense (MORITEX Co., Saitama, Japan). Evaluation of TEWL was performed using a VapoMeter (Delfin Technologies Ltd., Kuopio, Finland). Lastly, the collagen score and dermal thickness were analyzed via DermaLab (Cortex Technology, Hadsund, Denmark).

### **2.5. Ethics, Adherence, and Compliance**

This study was performed according to the Declaration of Helsinki (2013 revision, Fortaleza, Brazil) and was carried out in conformity with ethical considerations. The ethics committee of Oryza Oil & Fat Chemical Co., Ltd. was convened to assess the ethicality and appropriateness of the study protocol. The study was implemented according to the protocol approved by the ethics committee, and any substantial protocol deviations required authorization by the committee. All subjects received a full explanation about the purpose and procedures of the study before consenting to participation.

### **2.6. Statistical Analysis**

The results are reported as the mean and standard deviation (SD). A two-tailed paired *t*-test was used for comparisons between before and after the ingestion of capsules. The unpaired *t*-test was used to compare the placebo group with the Delphinol® group. A probability of less than 5% was considered significant.

## **3. Results**

### **3.1. Study Performance**

None of the subjects took less than 90% of the specified capsules during the study period. Accordingly, data on all subjects were included in the analysis.

### **3.2. Skin Tone (Hue, Saturation, and Brightness)**

The skin tone (hue, saturation, and brightness) scores before and after ingestion, and the degree of change after ingestion are shown in **Table 1**. Eight weeks after ingestion, there was significant improvement between the placebo group and the Delphinol® group in saturation. The saturation is represented as a value from 0 to 100 evaluated by the ROBO SKIN ANALYZER, and reflects blood circulation and dullness. A low value ( $\leq 20$ ) reflects a thick stratum corneum and detection of dermal blood circulation is thus impeded. Higher values ( $\geq 75$ ) indicate clear skin without dullness.

### **3.3. Skin Redness**

The number (Lv. 1, 2, 3) and area (Lv. 1, 2, 3) of redness before and after ingestion, and the degree of change after ingestion are shown in **Table 2**. There was a significant reduction in the change in red area and number (Lv.2) after ingestion for four weeks between the placebo group and Delphinol® group. The analyzed images of two representative subjects in each group are shown in **Figure 1**.

**Table 1.** Changes in skin tone parameters.

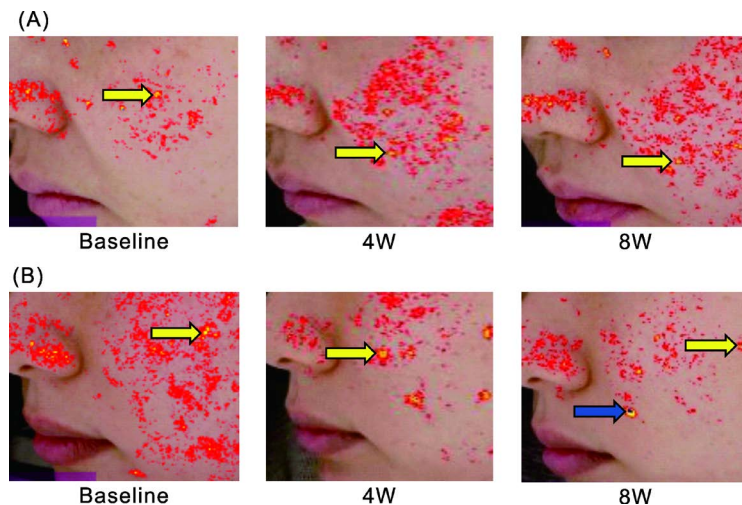
		Baseline	4 weeks	8 weeks
Hue	Placebo	52.7 ± 5.2	53.7 ± 6.9 (1.0 ± 4.5)	53.5 ± 7.8 (0.8 ± 7.2)
	Delphinol®	54.9 ± 7.9	55.7 ± 7.2 (0.8 ± 2.2)	56.1 ± 6.2 (1.1 ± 4.2)
Saturation	Placebo	35.4 ± 1.7	35.3 ± 2.1 (-0.1 ± 1.0)	34.7 ± 1.5 (-0.7 ± 1.1)
	Delphinol®	32.7 ± 2.8	33.3 ± 3.0 (0.6 ± 1.2)	33.0 ± 2.7 (0.3 ± 0.6)*
Brightness	Placebo	63.7 ± 1.6	64.1 ± 2.1 (0.4 ± 2.3)	64.1 ± 3.0 (0.4 ± 3.5)
	Delphinol®	64.5 ± 4.5	65.2 ± 3.2 (0.6 ± 1.6)	65.7 ± 3.2 (1.2 ± 2.0)

Actual scores (upper lines) and changes in the scores (lower lines) are represented as the mean ± SD (n = 8 in both groups). An asterisk indicates a significant difference vs. placebo at \*: p < 0.05.

**Table 2.** Changes in redness degree and area.

		Baseline	4 weeks	8 weeks
Number of redness Lv. 1	Placebo	337.6 ± 448.8	391.4 ± 401.6 (53.8 ± 240.8)	445.3 ± 390.9 (107.6 ± 332.7)
	Delphinol®	596.9 ± 609.3	480.9 ± 623.0 (-116.0 ± 413.8)	548.8 ± 690.5 (-48.1 ± 441.2)
Area of redness Lv. 1	Placebo	223.5 ± 424.5	315.4 ± 513.8 (91.9 ± 177.2)	277.6 ± 363.2 (54.1 ± 192.3)
	Delphinol®	393.5 ± 393.6	289.9 ± 274.6 (-103.6 ± 274.9)	336.6 ± 346.8 (-59.9 ± 315.9)
Number of redness Lv. 2	Placebo	36.5 ± 84.4	65.4 ± 115.4 (28.9 ± 46.5)	52.4 ± 73.1 (15.9 ± 51.8)
	Delphinol®	64.1 ± 58.9	35.8 ± 30.0 (-28.4 ± 34.9)*	53.9 ± 70.1 (-10.3 ± 43.6)
Area of redness Lv.2	Placebo	11.1 ± 23.6	21.0 ± 39.5 (9.9 ± 17.4)	20.0 ± 36.1 (8.9 ± 16.4)
	Delphinol®	20.6 ± 22.2	11.4 ± 11.7 (-9.3 ± 13.3)*	21.4 ± 23.8 (0.8 ± 16.5)
Number of redness Lv. 3	Placebo	0.9 ± 2.1	2.0 ± 3.4 (1.1 ± 1.7)	4.1 ± 7.1 (3.3 ± 5.4)
	Delphinol®	2.4 ± 4.2	1.6 ± 2.6 (-0.8 ± 1.8)	4.5 ± 7.3 (2.1 ± 3.8)
Area of redness Lv. 3	Placebo	0.1 ± 0.4	0.4 ± 1.1 (0.3 ± 1.2)	0.6 ± 1.1 (0.5 ± 1.2)
	Delphinol®	1.6 ± 3.1	0.9 ± 2.1 (-0.8 ± 1.5)	1.8 ± 3.8 (0.1 ± 1.6)

Actual scores (upper lines) and changes in the scores (lower lines) are represented as the mean ± SD (n = 8 in both groups). Asterisks indicate significant differences vs. placebo at \*: p < 0.05.



**Figure 1.** Redness measurement image: redness detection part of placebo group (A) and Delphinol® group (B). The red spots are redness level 1, the yellow spots (indicated by the yellow arrow) are redness level 2 and the blue spots (indicated by the blue arrow) are redness level 3.

### 3.4. Collagen Score

The collagen scores before and after ingestion, and the degree of change after ingestion are summarized in **Table 3**. There was no significant difference between the placebo group and the Delphinol® group during all periods.

On the other hand, as shown in **Figure 2**, the collagen score slightly decreased with age (as at baseline). However, after taking Delphinol® for eight weeks, the correlation between age and collagen score slightly increased.

### 3.5. Other Skin Parameters

Comparison of values before and after intervention and between placebo and the Delphinol® groups revealed no significant difference in the items, including pigmentation, number and length of wrinkles, texture, oil content, water content, TEWL, thickness of dermis, and elasticity (**Table 4**).

## 4. Discussion

In the present study, ingestion of Delphinol® for eight weeks improved the skin tone saturation compared with the placebo group. The saturation is presented as a value ranging from 0 to 100, and a higher value means improvement of the skin color tone, termed shining skin tone. Therefore, Delphinol® can improve the saturation, suggesting color tone-up effects. In the three-dimensional space of chromatic colors (hue, saturation, and brightness), a higher skin saturation value is related to higher emotion and attractiveness [27]. Moreover, color saturation is an important optical parameter of skin that determines the visual age of skin in addition to lightness and local light-diffusing ability [28]. Thus, the upregulating effects of Delphinol® on saturation may reflect a positive influence on the facial skin condition.

**Table 3.** Changes in the collagen score.

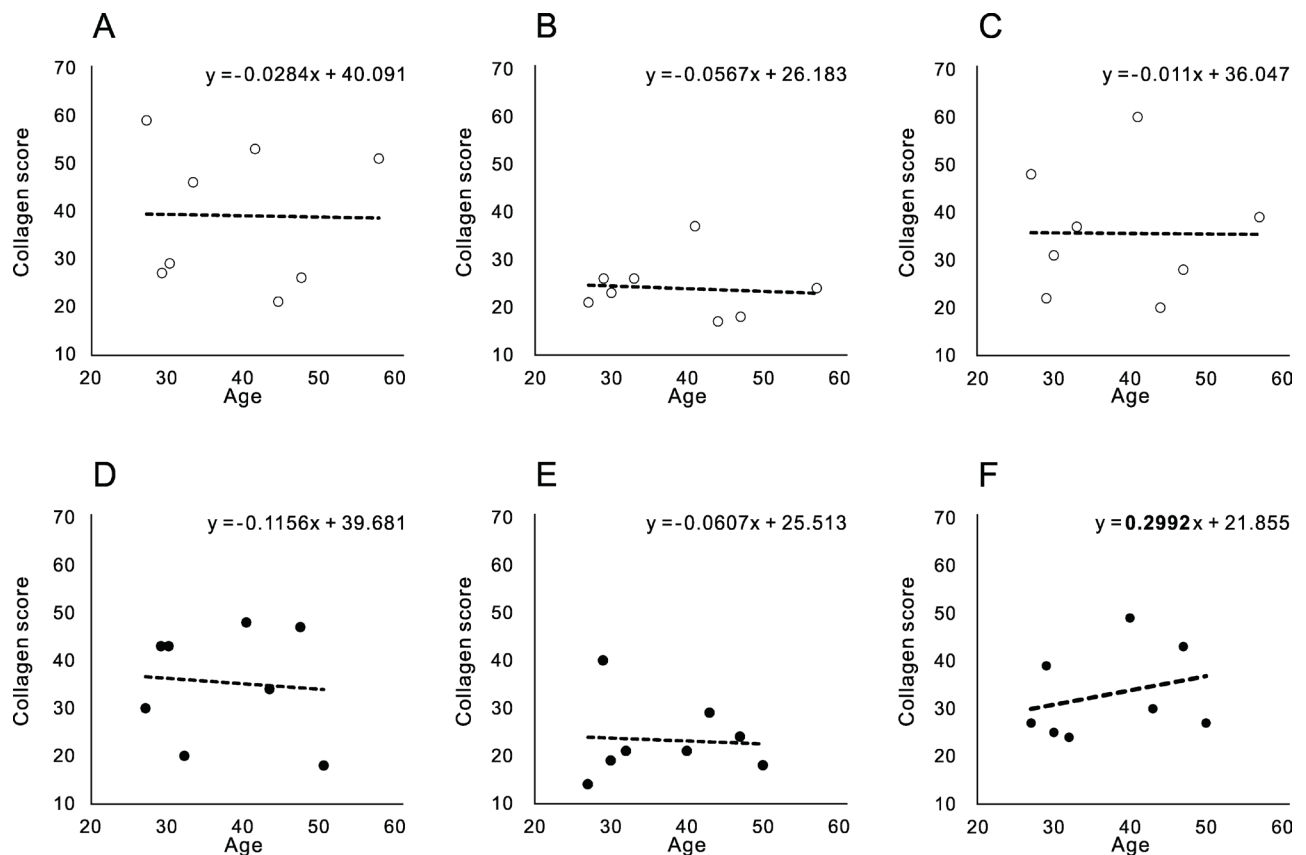
		Baseline	4 weeks	8 weeks
Collagen score	Placebo	39.0 ± 14.8	24.0 ± 6.2 (-15.0 ± 12.8)	35.6 ± 13.5 (-3.4 ± 6.9)
	Delphinol®	35.4 ± 11.8	23.3 ± 8.1 (-12.1 ± 11.6)	33.0 ± 9.4 (-2.4 ± 7.9)

Actual scores (upper lines) and changes in the scores (lower lines) are represented as the mean ± SD (n = 8 in both groups).

**Table 4.** Changes in skin parameters.

		Baseline	4 weeks	8 weeks
Pigmentation	Placebo	9.5 ± 2.9	14.0 ± 4.0 (1.0 ± 5.0)	11.8 ± 4.7 (-1.3 ± 3.5)
	Delphinol®	11.0 ± 5.9	15.5 ± 6.0 (-0.3 ± 5.3)	14.5 ± 9.8 (-1.3 ± 4.6)
Wrinkle number	Placebo	1.1 ± 0.8	1.1 ± 0.8 (0.0 ± 1.4)	1.6 ± 1.2 (0.5 ± 1.1)
	Delphinol®	1.1 ± 0.8	1.0 ± 0.5 (-0.1 ± 0.6)	1.3 ± 0.9 (0.1 ± 0.6)
Wrinkle length	Placebo	36.3 ± 17.8	32.5 ± 26.8 (-3.8 ± 19.0)	23.5 ± 20.8 (-12.8 ± 12.3)
	Delphinol®	27.6 ± 18.1	39.4 ± 31.1 (11.8 ± 21.1)	41.5 ± 23.5 (13.9 ± 24.5)
Texture	Placebo	45.8 ± 13.3	51.6 ± 12.6 (5.9 ± 9.9)	58.4 ± 5.8 (12.6 ± 15.2)
	Delphinol®	53.9 ± 15.8	46.8 ± 10.7 (-7.1 ± 12.9)	54.4 ± 7.5 (0.5 ± 13.5)
Oil content	Placebo	50.4 ± 7.8	43.1 ± 12.7 (-7.3 ± 10.1)	47.0 ± 8.6 (-3.4 ± 9.3)
	Delphinol®	50.5 ± 8.6	46.9 ± 11.0 (-3.8 ± 9.6)	45.9 ± 9.7 (-4.8 ± 8.9)
Water content	Placebo	86.4 ± 16.7	80.4 ± 17.3 (-6.0 ± 5.6)	85.1 ± 13.3 (-1.3 ± 4.3)
	Delphinol®	91.3 ± 8.5	87.1 ± 10.4 (-4.1 ± 8.4)	90.3 ± 10.0 (-1.0 ± 6.4)
TEWL	Placebo	9.9 ± 3.6	13.8 ± 5.5 (3.9 ± 4.2)	11.6 ± 1.7 (1.7 ± 2.4)
	Delphinol®	11.4 ± 5.7	15.4 ± 6.2 (4.0 ± 3.8)	13.4 ± 3.8 (2.0 ± 3.4)
Dermal thickness	Placebo	1313.4 ± 350.3	1152.0 ± 253.1 (-161.4 ± 195.7)	1229.6 ± 315.7 (-83.8 ± 89.6)
	Delphinol®	1382.6 ± 384.3	1219.8 ± 392.3 (-162.9 ± 612.6)	1152.0 ± 348.6 (-230.6 ± 328.4)
Elasticity	Placebo	88.3 ± 6.2	89.4 ± 4.5 (1.1 ± 7.7)	87.1 ± 5.6 (-1.1 ± 10.2)
	Delphinol®	89.4 ± 5.2	91.1 ± 4.2 (1.8 ± 6.1)	90.6 ± 3.8 (1.3 ± 5.9)

Actual scores (upper lines) and changes in the scores (lower lines) are represented as the mean ± SD (n = 8 in both groups).



**Figure 2.** Relationship between collagen score and age of placebo and Delphinol® group. The dotted lines are linear approximation of each group. (A) baseline of placebo, (B) after 4 weeks of placebo, (C) after 8 weeks of placebo, (D) baseline of Delphinol®, (E) after 4 weeks of Delphinol®, (F) after 8 weeks of Delphinol®.

Delphinol® ingestion for four-weeks significantly reduced the degree and area of redness on the face compared with the placebo group. Facial redness is clinically termed facial erythema or rosacea. It is caused by sensitive skin [29], winter xerosis [29], alcohol ingestion [30], and UV radiation [31]. A red face can cause depression or may result in complex social relations [30]. In addition, skin diseases can induce facial redness indirectly. Withdrawal from steroidal ointment in atopic dermatitis patients sometimes causes redness, known as steroid addiction syndrome [32]. To ameliorate facial redness, the use of cosmetics is dominant, including sun protectors [33] [34]. However, alternative care using herbs and nutritional dietary supplements has been examined. These methods are defined as oral photoprotection [35], in addition to the commonly used supplementation of vitamins C and E [36], and carotenoids [37]. For example, dietary supplements containing rosemary and grapefruit extracts were reported to reduce UV-induced skin redness [38]. Moreover, oral treatment with vitamin D has anti-inflammatory effects and improves skin redness [39]. However, although there are many botanical extracts and their constituents that exhibit photoprotective activity by ingestion, especially polyphenols, only the above ingredients have been reported to improve facial redness. So, the suppression of



skin redness by Delphinol® is a novel observation. The anti-oxidant effects are most likely related, in addition to the photoprotective effects of Delphinol® [26] because anthocyanins can suppress allergic inflammatory responses in mast cells [40]. Released histamine induces skin flare [41]. The anti-oxidant effects of Delphinol® are involved because oxidative stress induces skin inflammation [42] and redness. Thus, the anti-oxidant effects of Delphinol® can help to suppress inflammation. Kikuchi *et al.* [43] evaluated the seasonal change in hemoglobin index (one of the indicators of redness) in the face of Japanese women, and reported that facial skin redness increased from autumn to winter. Our present study was conducted from autumn to winter. However, regardless of seasonal factors, improvement of color unevenness due to redness can be expected by Delphinol® supplementation. Kikuchi *et al.* [44] also reported that Caucasian skin becomes more reddish with age than Asian skin. Therefore, Delphinol® is expected to be useful for improving the color unevenness not only Asian women, but also in Caucasian women.

Regarding the collagen score, although there was no significant difference, the Delphinol® group exhibited a slight increase after eight weeks of ingestion compared with before the ingestion. So that, we analyzed the relationship between collagen score and age. As a result, a positive relationship was observed in the Delphinol® group but not in the placebo group. The collagen score analyzed by ultrasound skin images captured by DermaLab is recently used for non-invasive diagnosis [44]. The accuracy of the device has been demonstrated in multiple studies. Peperkamp *et al.* showed a reliable intraclass correlation coefficient (ICC) values. ICC ranged from 0.23 to 0.80, and test-retest ICC ranged from 0.25 to 0.84. Skin thickness was measured with a test-retest ICC ranging from 0.71 to 0.83 and an inter-rater ICC ranging from 0.69 to 0.80 [45]. Anthonissen *et al.* showed good ICC values and rather high SEM values for inter- and intra-observer reproducibility of elasticity measurements. For TEWL measurements, ICC values were good and SEM values were high for inter- and intra-observer reproducibility [46]. Thus, Delphinol® was suggested to possess some ability to maintain collagen in the dermis. Further studies of Delphinol® on collagen production and collagen decomposition are needed to clarify the exact mechanism. Besides this, some limitations exist in this study. First, since the study subjects were small number, they may be healthier than the general population, causing a selection bias. Second, all subjects were Asian women and worked in Oryza Oil & Fat Chemical Co., Ltd. which is another area of potential bias. But in future, we would like to do more experiments with women in different areas to verify the effects.

## 5. Conclusion

In conclusion, we found that ingestion of Delphinol®, anthocyanin-standardized maqui berry extract, increases skin brightness and collagen content, and reduces skin redness. These effects suggest that the maqui berry can maintain a healthy

skin condition.

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## Conflicts of Interest

All authors are employed by Oryza Oil & Fat Chemical Co., Ltd. as research scientists. Oryza Oil & Fat Chemical Company is the developer and manufacturer of Delphinol® used in this study. The authors have not received personal financial gain from the sales of this product. All findings and views expressed in this paper are those of the authors and do not necessarily reflect the views of Oryza Oil & Fat Chemical Co., Ltd.

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