ORIGINAL ARTICLE

Effect on Skin Condition by 8-week Ingestion of Standardized Cherry Blossom Flower Extract (Sakura Extract-P)

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ABSTRACT

Edible cherry blossom flowers are cultivated in Japan and China. We have previously confirmed that these flowers contain cinnamoyl glucose derivatives and flavonoid glucosides, which reduce advanced glycation end products (AGEs) in skin cells. However, the influence of cherry blossom flower extract (CBE) on the human skin has not been evaluated. Therefore, we conducted a randomized double-blind placebo-controlled study of CBE supplementation in Japanese subjects to examine the effect of standardized CBE (150 mg daily) containing caffeoyl glucose (3 mg). CBE or placebo capsules were administered for 8 weeks to Japanese women aged 30 to 50 years. Skin condition and skin AGEs were evaluated before and after treatment. Photographs of the facial skin were also analyzed and skin symptoms were evaluated on a visual analog scale (VAS). In the CBE group, skin AGEs showed a significant decrease by approximately 7%. In the placebo group, skin elasticity decreased significantly (13%), while no significant change was observed in the CBE group. Furthermore, analysis of photographs revealed a significant decrease of facial pigmented spots and reddish areas in the CBE group versus no significant changes in the placebo group. Thus, CBE was found to reduce skin AGEs, prevent loss of skin elasticity, and decrease facial pigmentation and reddish areas. These results suggest that daily oral intake of CBE might reduce AGE levels in the skin and improve facial pigmentation and reddening. (*Int J Biomed Sci*** 2018; 14 (1): 12-19**)**

Keywords: cherry blossom; advanced glycation end products; skin; moisture; elasticity; pigmentation; caffeoyl glucose

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INTRODUCTION

The cherry tree (Rosaceae) is a species of *Prunus*, and about 200 species have been identified. The cherry blossom is an iconic Japanese symbol, and approximately 25 species of flowering cherry grow in Japan. *P. yedoensis* is a typical decorative cherry tree, and its flowers are

considered to be edible. In addition, the flowers of *P. lannesiana* soaked in salty plum vinegar are used to make cherry blossom tea, which is served to guests in a special ceremony. We examined the constituents of *P. lannesiana* flowers, isolating 3 cinnamoyl glucose derivatives and 4 flavonol glucosides that have been shown to reduce levels of advanced glycation end products (AGEs). (1) In the skin, AGEs are generated by glycation of the amino groups of proteins and reducing sugars or other reactive carbonyl species, and AGEs are increased by aging and diabetes mellitus (2, 3). Skin AGEs can be detected by assessing fluorescence. (4) The major target protein of AGEs in the skin is collagen (5), where accumulating AGEs induce cross-linking of collagen and reduce skin elasticity and dermal regeneration. (6) Some food ingredients, including *L*-carnitine (7), carnosine (8), and *Akebia quinata* fruit extracts (9), have been reported to reduce skin levels of AGEs. With regard to CBE, a mixture of CBE and lingonberry extract was reported to suppress AGE production (10). Therefore, we evaluated the effect of CBE on AGE production in the skin and on skin condition.

MATERIALS AND METHODS

Participants

To recruit subjects, 30 participants were registered with the monitor bank of TES Holdings Co. Ltd. based on the answers to several questionnaires. The registration criteria were for subjects to be Japanese women aged from 35 to 59 years with mild skin problems (such as difficulty using cosmetics, sagging and dry skin, or skin aging) who could change their daily use of cosmetics or avoid using new cosmetics. Exclusion criteria were as follows:

1) Current use of medications for treatment of chronic diseases.

2) Allergy to the test product.

3) Use or planned use of CBE supplements or dietary supplements effective for the skin.

4) Use of oral or topical medications.

5) Use of cosmetics with strong moisturizing or anti-wrinkle effects.

6) High intake of alcoholic beverages.

7) Previous malignancy, heart failure, or myocardial infarction.

8) Possible changes to daily life, such as going on a trip or shiftwork.

9) Current participation in another clinical trial.

10) Pregnant or breastfeeding women and women wanting to become pregnant.

11) Persons determined to be inappropriate for the study by the attending physician.

Twenty women aged from 35 to 59 years were selected from the results of the screening test (Fig. 1), being chosen from the woman with lowest skin elasticity, moisture, and

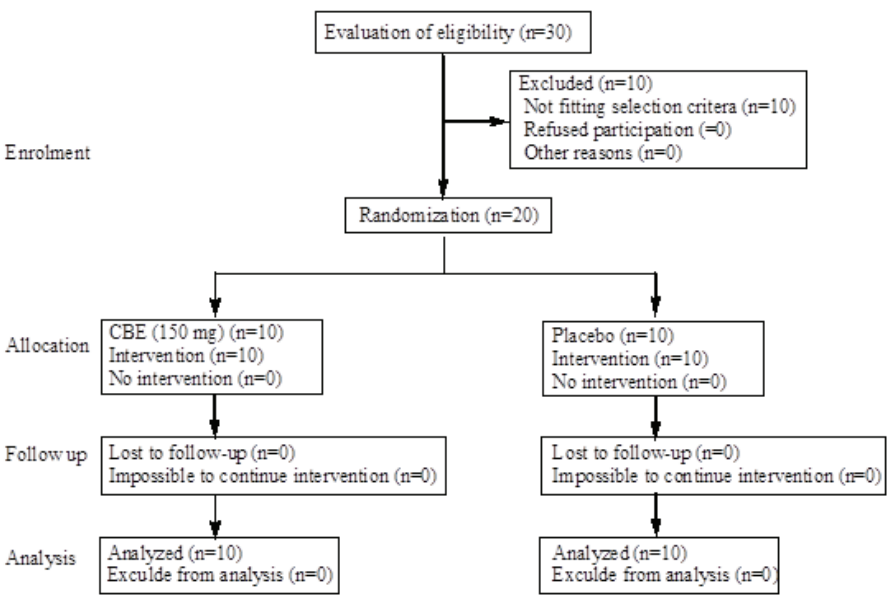

Figure 1. Flowchart showing the disposition of the subjects.

AGE levels. Then 10 subjects were randomly allocated to each of 2 groups. The average age was 48.0 years in the CBE group and 50.6 years in the placebo group. Informed consent was obtained from all subjects prior to the study. After a full explanation of the study, including the purpose, methods, and test product, as well as the voluntary nature of participation and no disadvantages from refusing to participate, signed consent was obtained from all participants.

The subjects were asked to avoid excessive eating, drinking, and exercise, and to obtain sufficient sleep and maintain a regular lifestyle during the study period. Their usual cosmetics were permitted and daily facial care was continued in the same way as before the study.

Preparation and allocation of the test products

The test products (indistinguishable brown capsules containing CBE or placebo) were provided by Oryza Oil & Fat Chemical Co., Ltd. CBE capsules (active) contained 150 mg of Sakura Extract-P (standardized CBE, Oryza Oil & Fat Chemical Co. Ltd.), which comprised 103.5 mg of dextrin, 37.5 mg of CBE, 4.5 mg of ascorbic acid, and 4.5 mg of maleic acid. CBE contained 3 mg of caffeoyl glucose and 0.075 mg of quercetin 3-*O*-glucoside. The placebo capsules contained 150 mg of dextrin. Information about allocation of the test medications was strictly held by the study treatment/allocation controller of TES Holdings Co. Ltd. who was not directly involved in the study, and was not disclosed until the subjects for analysis were determined at a clinical conference after completion of the study.

Study protocol

This study (protocol No. HR-2010-OY04) was a placebo-controlled double-blind comparison of 2 groups treated concurrently and was carried out at Sirogane EXE Clinic (Tokyo). Statistical analysis of the data was done by TES Holding Co. Ltd. (Tokyo, Japan) Subjects in the placebo group and CBE group took one capsule daily (placebo or CBE, respectively) with water after breakfast for 8 weeks and wrote a daily report about capsule intake, lifestyle, and menstruation. The primary outcomes were skin AGEs, skin moisture, transepidermal water loss (TEWL), skin elasticity, skin replica, and facial condition assessed by a face image analyzer (VISIA Evolution, Canfield Scientific, USA). These parameters were assessed before treatment and after 8 weeks of treatment. The secondary outcomes were questionnaires regarding skin condition that the subjects completed before the start of treatment and after 8 weeks of treatment. The subjects also recorded the following information in a diary: adverse events, intake of the test product, medication, use of dietary supplements, and menstrual periods.

Evaluation of skin AGEs and other skin parameters

All skin parameters were measured in an air-conditioned room at 22±1°C and 50±10% RH. Prior to the study, the subject washed her face with warm water and the designated face soap. After wiping the face with a soft paper towel, the subject was acclimated for 20 min. First, skin moisture and TEWL were measured at the left cheek by using a Corneometer (CM825, Courage+Khazaka Electronic GmbH, Germany) and a Tewameter (TM300, Courage+Khazaka Electronic GmbH), respectively. Second, skin elasticity was measured at the mid-point of a line between the left ear and lip border with a Cutometer (MPA580, Courage+Khazaka Electronic GmbH). Then an image of the left side of the face was captured with a VISIA Evolution. The items evaluated were spots, wrinkles, texture, pores, ultraviolet (UV) reactive spots, brown spots, reddish areas, and porphyrin. After that, skin AGEs were measured at the midpoint of the forearm by using an AGE reader (DiagnOptics, Netherlands). Finally, a skin replica was obtained from the cheek at the same site where elasticity was measured and was analyzed by using a reflective 3-dimensional replica analysis system (ASA-03RXD, Asahi BioMed, Japan).

Questionnaire

During the acclimation period before measurement of skin parameters, the subjects answered a questionnaire that covered skin moisture, pores, wrinkles around the eyes, skin texture, skin dryness, nasolabial folds, spreadability of cosmetics, skin resilience and elasticity, skin clearness, sagging cheeks, oily and shiny skin, periorbital dark circles, skin smoothness, fine wrinkles, facial redness, and total skin condition. Each item was evaluated on a 100 mm visual analogue scale (VAS).

Ethics, adherence, and compliance

This study was performed according to the Declaration of Helsinki (2008 revision, Seoul) and was carried out in conformity with ethical considerations. The Ethics Committee of TES Holdings Co. Ltd. was convened to0 assess the ethicality and appropriateness of the study protocol. This 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.

Investigation of adverse events

Each adverse event was evaluated to determine the causal relationship with the test product. Adverse events were defined as clinically significant new physical abnormalities or symptoms that occurred during the study period. If an adverse event occurred, the physician provided appropriate treatment and decided whether the study should be continued. The causal relationship with the test product was judged according to the following criteria.

1. Unrelated. The event was not considered to be related to the test product.

2. Probably unrelated. There was no chronological relationship between the event and use of the test product.

3. Probably related. There was a possible chronological relationship between the event and use of the test product.

4. Related. There was an obvious chronological relationship between the event and use of the test product.

5. Unclear. It was impossible to determine whether the event was caused by the test product.

Statistical analysis

Data are reported as the mean and SD. Student's *t*-test or the Mann-Whitney test was performed to compare values before treatment with those after 8 weeks of treatment and for comparison between the CBE and placebo groups.

RESULTS

Compliance with study treatment

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

AGEs and skin parameters

As shown in Table 1, fluorescence of skin AGEs decreased significantly (-6.6%) in the CBE group. Fluorescence of AGEs also decreased (-2.5%) in the placebo group, but the change was not significant. Skin moisture decreased significantly in both the CBE group and the placebo group (-12.4% and -15.7%, respectively). The relative value of TEWL increased significantly in the CBE group (30.0%), while resilience and elasticity (R5) increased (11.5%) in the placebo group.

Table 1. Changes of skin AGEs and facial skin parameters

	Group	Before	After 8 weeks
AGEs (AU)	CBE	2.08 ± 0.06 (100.0 ± 0.0)	1.94 ± 0.06[a] (93.4 ± 2.0)
	Placebo	2.07 ± 0.08 (100.0 ± 0.0)	2.00 ± 0.03 (97.5 ± 3.5)
Skin moisture (AU)	CBE	67.3 ± 2.4 (100.0 ± 0.0)	58.7 ± 2.2[b] (87.6 ± 2.8[b])
	Placebo	66.2 ± 2.8 (100.0 ± 0.0)	55.3 ± 2.5[b] (84.3 ± 3.7[b])
TEWL (g/h·m^2)	CBE	8.37 ± 1.49 (100.0 ± 0.0)	9.79 ± 0.87 (130.0 ± 11.9[a])
	Placebo	9.04 ± 1.47 (100.0 ± 0.0)	8.37 ± 0.91 (102.2 ± 10.3)
Resilience and elasticity (AU)			
R2	CBE	0.91 ± 0.01 (100.0 ± 0.0)	0.90 ± 0.01 (99.6 ± 1.0)
	Placebo	0.91 ± 0.01 (100.0 ± 0.0)	0.92 ± 0.01 (100.8 ± 0.9)
R5	CBE	1.00 ± 0.06 (100.0 ± 0.0)	0.99 ± 0.05 (100.3 ± 4.1)
	Placebo	1.05 ± 0.07 (100.0 ± 0.0)	1.15 ± 0.06[a] (111.5 ± 3.8[a])
R7	CBE	0.60 ± 0.01 (100.0 ± 0.0)	0.59 ± 0.02 (98.2 ± 2.0)
	Placebo	0.59 ± 0.02 (100.0 ± 0.0)	0.60 ± 0.02 (101.3 ± 1.8)

Data are represented as the mean and SD (n=10). Values in parentheses show the percent change compared with before ingestion. Asterisks indicate significant differences from before ingestion at [a]$p<0.05$, [b]$p<0.01$. No significant differences were observed between the CBE and placebo groups. AU: arbitrary unit.

VISIA and skin replica parameters

As shown in Table 2, the number of facial spots and reddish areas decreased significantly in the CBE group (-0.14 AU and -0.19 AU, respectively), while these parameters did not change significantly in the placebo group (-0.04 AU and -0.13 AU, respectively). In the placebo group, the skin texture and the number of pores increased significantly, but these parameters did not change significantly in the CBE group. UV-reactive spots increased significantly in both groups. The other parameters showed no changes.

Questionnaire results

In the placebo group, the VAS scores for wrinkles around the eyes and "oily and shiny skin" showed a significant increase (Table 3). In contrast, these scores did not increase in the CBE group. The score for facial redness showed a significant increase in the CBE group, but not in the placebo group. The other VAS scores improved significantly in both groups and no significant differences were observed between the 2 groups.

Table 2. Changes of VISIA and skin replica parameters

Parameter	Group	Before	After 8 weeks
VISIA parameter (AU)			
Spots	CBE	2.00 ± 0.32 (0.00 ± 0.00)	1.86 ± 0.32[a] (-0.14 ± 0.06)
	Placebo	2.02 ± 0.23 (0.00 ± 0.00)	1.98 ± 0.24 (-0.04 ± 0.07)
Wrinkles	CBE	1.50 ± 0.50 (0.00 ± 0.00)	1.59 ± 0.46 (0.09 ± 0.20)
	Placebo	1.18 ± 0.27 (0.00 ± 0.00)	1.32 ± 0.31 (0.14 ± 0.16)
Texture	CBE	0.68 ± 0.18 (0.00 ± 0.00)	0.87 ± 0.19 (0.19 ± 0.09)
	Placebo	0.64 ± 0.07 (0.00 ± 0.00)	0.94 ± 0.14[b] (0.30 ± 0.09)
Pores	CBE	0.92 ± 0.16 (0.00 ± 0.00)	1.06 ± 0.21 (0.14 ± 0.08)
	Placebo	0.99 ± 0.12 (0.00 ± 0.00)	1.27 ± 0.17[b] (0.28 ± 0.06)
UV-reactive spots	CBE	2.26 ± 0.42 (0.00 ± 0.00)	2.59 ± 0.47[a] (0.33 ± 0.13)
	Placebo	2.87 ± 0.40 (0.00 ± 0.00)	3.19 ± 0.36[a] (0.31 ± 0.13)
Brown spots	CBE	6.91 ± 0.48 (0.00 ± 0.00)	6.62 ± 0.53 (-0.29 ± 0.19)
	Placebo	7.67 ± 0.48 (0.00 ± 0.00)	7.50 ± 0.50 (-0.17 ± 0.18)
Reddish areas	CBE	1.31 ± 0.27 (0.00 ± 0.00)	1.12 ± 0.27[a] (-0.19 ± 0.06)
	Placebo	1.24 ± 0.17 (0.00 ± 0.00)	1.11 ± 0.12 (-0.13 ± 0.10)
Porphyrin	CBE	0.37 ± 0.15 (0.00 ± 0.00)	0.40 ± 0.22 (0.036 ± 0.131)
	Placebo	0.32 ± 0.13 (0.00 ± 0.00)	0.27 ± 0.10 (-0.049 ± 0.044)
Replica			
Texture volume ratio ($mm^3/mm^2/100$)	CBE	45.1 ± 8.2 (0.00 ± 0.00)	44.0 ± 9.5 (-1.17 ± 4.41)
	Placebo	37.4 ± 6.6 (0.00 ± 0.00)	40.1 ± 6.7 (2.65 ± 4.46)
Texture number ($/mm^3$)	CBE	1.42 ± 0.20 (0.00 ± 0.00)	1.38 ± 0.21 (-0.04 ± 0.18)
	Placebo	1.42 ± 0.19 (0.00 ± 0.00)	1.52 ± 0.19 (0.10 ± 0.16)

Data are represented as the mean and SD (n=10). Values in parentheses are differences from before ingestion. Asterisks indicate significant differences from before ingestion at [a]$p<0.05$, [b]$p<0.01$. No significant differences were observed between the CBE and placebo groups. AU: arbitrary unit.

Table 3. Changes of VAS scores for questions regarding facial condition

Parameter	Group	Before	After 8 weeks
Skin moisture	CBE	3.16 ± 0.51 (0.00 ± 0.00)	6.21 ± 0.70[b] (3.05 ± 0.91)
	Placebo	3.93 ± 0.47 (0.00 ± 0.00)	7.46 ± 0.42[b] (3.53 ± 0.74)
Pore appearance	CBE	3.79 ± 0.55 (0.00 ± 0.00)	5.18 ± 0.57[a] (1.39 ± 0.51)
	Placebo	2.44 ± 0.33 (0.00 ± 0.00)	5.44 ± 0.61[b] (3.00 ± 0.50)
Wrinkles around eyes	CBE	3.16 ± 0.65 (0.00 ± 0.00)	4.73 ± 0.78 (1.57 ± 1.03)
	Placebo	2.49 ± 0.44 (0.00 ± 0.00)	5.75 ± 0.69[b] (3.26 ± 0.79)
Skin texture	CBE	3.37 ± 0.40 (0.00 ± 0.00)	6.17 ± 0.63[b] (2.80 ± 0.63)
	Placebo	2.70 ± 0.38 (0.00 ± 0.00)	6.75 ± 0.52[b] (4.05 ± 0.55)
Skin dryness	CBE	2.77 ± 0.67 (0.00 ± 0.00)	6.14 ± 0.81[b] (3.37 ± 0.69)
	Placebo	3.64 ± 0.65 (0.00 ± 0.00)	7.58 ± 0.46[b] (3.94 ± 0.98)
Appearance of nasolabial folds	CBE	2.19 ± 0.48 (0.00 ± 0.00)	4.82 ± 0.72[b] (2.63 ± 0.64)
	Placebo	1.40 ± 0.39 (0.00 ± 0.00)	5.12 ± 0.53[b] (3.72 ± 0.36)
Cosmetic spreadability	CBE	3.56 ± 0.46 (0.00 ± 0.00)	7.00 ± 0.77[b] (3.44 ± 0.49)
	Placebo	3.35 ± 0.23 (0.00 ± 0.00)	7.96 ± 0.28[b] (4.61 ± 0.35)
Resilience and elasticity	CBE	2.76 ± 0.52 (0.00 ± 0.00)	6.67 ± 0.88[b] (3.91 ± 0.85)
	Placebo	2.93 ± 0.24 (0.00 ± 0.00)	7.57 ± 0.28[b] (4.64 ± 0.45)
Skin clearness	CBE	2.52 ± 0.52 (0.00 ± 0.00)	5.30 ± 0.77[b] (2.78 ± 0.76)
	Placebo	2.66 ± 0.28 (0.00 ± 0.00)	6.47 ± 0.37[b] (3.81 ± 0.54)
Sagging cheeks	CBE	2.29 ± 0.51 (0.00 ± 0.00)	4.82 ± 0.66[b] (2.53 ± 0.55)
	Placebo	1.61 ± 0.36 (0.00 ± 0.00)	6.20 ± 0.44[b] (4.59 ± 0.50)
Oily and shiny skin	CBE	4.44 ± 0.78 (0.00 ± 0.00)	6.17 ± 0.43 (1.73 ± 0.96)
	Placebo	4.54 ± 0.62 (0.00 ± 0.00)	6.51 ± 0.57[a] (1.96 ± 0.76)
Periorbital dark circles	CBE	2.77 ± 0.59 (0.00 ± 0.00)	5.07 ± 0.58[b] (2.30 ± 0.44)
	Placebo	2.74 ± 0.41 (0.00 ± 0.00)	5.69 ± 0.55[b] (2.95 ± 0.56)
Skin smoothness	CBE	3.55 ± 0.70 (0.00 ± 0.00)	7.11 ± 0.69[b] (3.56 ± 0.69)
	Placebo	3.95 ± 0.40 (0.00 ± 0.00)	7.33 ± 0.46[b] (3.38 ± 0.37)
Fine wrinkles	CBE	2.65 ± 0.47 (0.00 ± 0.00)	5.93 ± 0.95[b] (3.28 ± 0.83)
	Placebo	2.53 ± 0.39 (0.00 ± 0.00)	6.31 ± 0.66[b] (3.78 ± 0.54)
Facial redness	CBE	4.15 ± 0.74 (0.00 ± 0.00)	7.44 ± 0.67[b] (3.29 ± 0.90)
	Placebo	4.70 ± 0.53 (0.00 ± 0.00)	6.71 ± 0.84 (2.01 ± 0.96)
Overall skin condition	CBE	2.70 ± 0.42 (0.00 ± 0.00)	6.94 ± 0.74[b] (4.24 ± 0.69)
	Placebo	2.78 ± 0.28 (0.00 ± 0.00)	7.38 ± 0.45[b] (4.60 ± 0.43)

Data are represented as the mean and SD (n=10). Values in parentheses are differences from before ingestion. Asterisks indicate significant differences from before ingestion at [a]$p<0.05$, [b]$p<0.01$. No significant differences were observed between the CBE and placebo groups.

DISCUSSION

In the present study, ingestion of CBE for 8 weeks reduced the skin level of AGEs and improved skin spots and reddish areas on the face, while these parameters did not change significantly in the placebo group. However, no significant differences were observed between the CBE and placebo groups. In a previous study of the effect of CBE on AGEs, Yonei *et al*. (10) found that ingesting a mixture of 37.5 mg of CBE and 300 mg of lingonberry extract for 8 weeks reduced serum levels of carboxymethyl lysine and 3-deoxyglucosone, but there was also no significant difference between the placebo and active groups. It is possible that a larger number of subjects would be required to find significant differences between the placebo and CBE groups because the suppressive effect of CBE on AGEs is not so strong.

Image analysis (VISIA scan) revealed that the skin texture and number of pores did not change in the CBE group in spite of both showing a significant increase in the placebo group. To obtain more definite results, the effect on these skin parameters should be evaluated over a longer period or by using a higher dose of CBE. Intake of CBE did not affect to skin moisture parameters or resilience and elasticity, with the result for resilience elasticity corresponding to the findings reported by Yonei *et al.* (10).

According to subjective evaluation using the questionnaire, VAS scores for "wrinkles around the eyes" and "oily and shiny skin" were maintained in the CBE group, but became worse in the placebo group. However, evaluation of wrinkle parameters by the VISIA and skin replica methods was not correlated with the VAS scores. In conclusion, we demonstrated that intake of standardized CBE (150 mg/day) for 8 weeks decreased skin AGE levels, as well as improving facial skin pores and reddish areas. However, none of these factors showed a significant difference from the placebo group. Further investigation using a longer treatment period or a higher dose of CBE will be required to properly assess the efficacy of this extract.

CONFLICT OF INTEREST

Mitsunori Kikuchi and Hiroshi Shimoda Ph.D. are employed by Oryza Oil & Fat Chemical Co. Ltd. as research scientists. Oryza Oil & Fat Chemical Company is the developer and manufacture of the cherry blossom extract 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 authors and do not necessarily reflect the view of Oryza Oil & Fat Chemical Co. Ltd.

Akiyama Matsuyama M.D. is medical doctor at Shirogane EXE Clinic. The author has not received personal financial gain form sales of this product. All findings and views expressed in this paper are those of authors and do not necessarily reflect the view of Shirogane EXE Clinic.

AUTHORS' CONTRIBUTIONS

Akimasa Matsuyama M.D. and Mitshunori Kikuchi conducted the study. Akimasa Matsuyama M.D. performed the tests. Mitsunori Kikuchi prepared test samples. Hiroshi Shimoda Ph.D. wrote the manuscript.

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CHEMICAL COMPOUNDS

Caffeoyl glucose (PubChem CID: 5281761); quercetin 3-*O*-glucoside (PubChem CID: 5280804).

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