Clinical Study Report

Verification of Acne Vulgaris Improved by Ingestion of Kiwi Seed Extract and Food Containing Rice Derived Ceramide

Protocol Number: HR-2009-OY01
Duration of Study: September 30 2009-November 4 2009
Date of Report: July 20 2011 (1st Version)
August 2 2011 (2nd Version)
September 2 2011 (Final Version)

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1. Summary of Study

Study Title and Protocol Number	Verification of Acne Vulgaris Improved by Ingestion of Kiwi Seed Extract and Food Containing Rice Derived Ceramide
Trial Design	Open label trial (Comparison over time).
Objective	The objective of this study was to evaluate an improved effect on acne by ingesting kiwi seed extract and food containing rice derived ceramide for 4 weeks. To achieve this objective, an open label trial was conducted with Japanese females with facial acne, aged 18-34 years. The clinical trial items were visual evaluation, skin moisture content, sebum capacity, pH measurement, analysis of facial image, questionnaire, biochemical examination of blood, and urinalysis.
Number of Subjects	11 subjects (Number of guaranteed subjects: 10 subjects. The screening test was conducted on 16 subjects).
Inclusion Criteria	• Japanese female 18-34 years old at the time of consent. • Persons with perennial acne and having more than 10 comedones by visual observation (not including catamenial comedones). • Persons who during the test period are able to refrain from intentional sunburn and conduct ultraviolet protection. • Persons who during the test period are able to refrain from ingesting supplements that aim to improve skin condition. • Persons who during the test period are able to refrain from changing or beginning use of cosmetics.
Exclusion Criteria	• Persons who change their life style, e.g. working night shifts or embarking on a long term trip, during the test period. • Persons who have skin diseases such as atopic dermatitis, perioral dermatitis, or rosacea-like dermatitis. • Persons who have allergic symptoms to components of the study supplement. • Persons who are pregnant, potentially pregnant, or lactating. • Persons who have an external injury in the observation region. • Persons who in the past 3 months have used cosmetics for acne care, high-concentrated vitamin compounds, quasi drugs (e.g. Proactiv, Bifnight or Clearasil), drugs (e.g. PAIR A, Highthiol-B, antibiotics, steroid, retinoid or salicylic acid), hormone therapies, or phototherapy. • Persons who in the past 3 months have ingested kiwi seed extract and food containing rice derived ceramide or who currently ingest them. • Persons who are currently participating in another clinical study.
Constraints	• Not to start ingesting new supplements or health foods after the beginning of the trial. • Not to ingest kiwi seed extract and food containing rice derived ceramide other than the test samples. • Not to conduct treatments that improve the skin condition, such as chemical peeling, laser treatment, photo treatment, or hyaluronic acid injections. • Not to have used cosmetics for comedo care, including high concentration vitamin preparations, quasi drugs (e.g. Proactiv, Bifnight or Clearasil), drugs (e.g. antibiotics, steroid, retinoid or salicylic acid), hormone therapies, or phototherapy within the previous 3 months. • Not to engage in activities that leave the subject vulnerable for sunburn, such as sea bathing, climbing, or sun tanning • Not to start using new cosmetics to improve skin condition. • Not to do anything else beyond those specifically stated above that may have an influence on the results of the test.

Precautions	• In case a subject was regularly using supplements not intended for acne care (e.g. the vitamin compounds), the subject was allowed to use it continuously without changing dosage and administration. • Subjects who used cosmetics were asked to use it continuously (except in case of changing by season variation). • Subjects were asked to maintain a regular lifestyle, refraining from irregular patterns and overeat, and to pay attention to their health during the test period.
Selection of Subjects	11 subjects, who were screened through self reporting satisfied the inclusion criteria without satisfying the exclusion criteria, were selected for inclusion in the study. At that time, a visual judgment and a medical interview to the subject by the principal investigator was the primary element of the selection and measurement of skin conditions and questionnaire were the secondary element.
Test Samples	Kiwi Seed Extract and Rice Derived Ceramide-Containing Food
Method of Ingestion	Subjects took 2 capsules of the study supplement once daily at bedtime with a little warm water.
Observing and Evaluating Items	<Primary Items> Visual Judgment by Dermatologist, Analysis of Facial Image (object of evaluation: number of porphyrins), Questionnaire Investigation <Secondary Items> Measurement of skin moisture content, Skin pH Measurement, Sebum Capacity, Analysis of Facial Image (Condition of the Face), Blood Collection and Urine Collection.
Schedule	Total opportunity of visits: Visit-1 (Screening and Baseline), Visit-2 (Week 2), and Visit-3 (Week 4)
Final Report	A final report was made based on the results of compiled data and statistical analysis. Pictorial data was submitted on a CD-ROM.
Ethics	To ensure the safety and to protect the rights of subjects, this study was conducted in accordance with ethical principles grounded in the Declaration of Helsinki and Standards for the Implementation of Clinical Trials on Pharmaceutical Products (MHW Ordinance No. 28 dated March 27, 1997).
Implementation System	See text.

2. Study Title and Protocol Number

1) Study Title

Verification of Acne Vulgaris Improved by Ingestion of Kiwi Seed Extract and Food Containing Rice Derived Ceramide

2) Protocol Number

HR-2009-OY01

3. Implementation System

1) Client

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Person in Charge: Masaki Ishii

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Person in Charge: Toshiyasu Tamura

3) Principal Investigator

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4) Designated Testing Medical Agency
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5) Clinical Research Coordinator
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6) Statistical Analysis Controller
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4. Objective

The objective of this study was to evaluate an improved effect on acne by ingesting kiwi seed extract and food containing rice derived ceramide for 4 weeks. To achieve this objective, an open label trial was conducted with Japanese females with facial acne, aged 18-34 years. The clinical trial items were visual evaluation, skin moisture content, sebum capacity, pH measurement, analysis of facial image, questionnaire, biochemical examination of blood, and urinalysis.

5. Subjects

A questionnaire was administrated during the subject recruitment period. Individuals were screened in self-reporting as to whether they satisfied the inclusion criteria without satisfying the exclusion criteria. 11 subjects were selected for inclusion in the study.

1) Inclusion Criteria

- Japanese female 18-34 years old at the time of consent.
- Persons with perennial acne and having more than 10 comedones by visual observation (not including catamenial comedones).
- Persons who during the test period are able to refrain from intentional sunburn and conduct ultraviolet protection.
- Persons who during the test period are able to refrain from ingesting supplements that aim to improve skin condition.
- Persons who during the test period are able to refrain from changing or beginning use of cosmetics.

2) Exclusion Criteria

- Persons who change their life style, e.g. working night shifts or embarking on a long term trip, during the test period.
- Persons who have skin diseases such as atopic dermatitis, perioral dermatitis, or rosacea-like dermatitis.
- Persons who have allergic symptoms to components of the study supplement.
- Persons who are pregnant, potentially pregnant, or lactating.

- Persons who have an external injury in the observation region.
- Persons who in the past 3 months have used cosmetics for acne care, high-concentrated vitamin compounds, quasi drugs (e.g. Proactiv, Bifnight or Clearasil), drugs (e.g. PAIR A, Highthiol-B, antibiotics, steroid, retinoid or salicylic acid), hormone therapies, or phototherapy.
- Persons who in the past 3 months have ingested kiwi seed extract and food containing rice derived ceramide or who currently ingest them.
- Persons who are currently participating in another clinical study.

3) Selection of Subjects
11 subjects, who were screened through self reporting satisfied the inclusion criteria without satisfying the exclusion criteria, were selected for inclusion in the study. At that time, a visual judgment and a medical interview to the subject by the principal investigator was the primary element of the selection and measurement of skin conditions and questionnaire were the secondary element.

6. Informed Consent
Before the study, the designated testing medical agency explained the operative indications, procedures, as well as possible complications and adverse effects to the subjects and received their informed consent.

7. Outline of Test Samples
Test samples were provided by Oryza Oil & Fat Chemical Co., Ltd. and the duration of ingestion was 4 weeks.

1) Safety and Efficacy Data
<Safety Data 1>
Title of Test: Ames Test of Kiwi Seed Extract Using the Bacteria
Designated Testing Agency: Bozo Research Center Inc
Results: Kiwi seed extract did not have mutagenic potential.

<Safety Data 2>
Title of Test: Acute Toxicity Test
Designated Testing Agency: Oryza Oil & Fat Chemical Co., Ltd.
Results: No death events or weight changes were observed (v.s. Control Group), and no significant macroscopic abnormalities in organ was recognized in autopsy. Therefore the LD_{50} value of oral administration of Kiwi Seed Extract in mice is more than 2000mg/kg for both males and females.

2) Method of Ingestion
Subjects took 2 capsules of the study supplement once daily at bedtime with a little warm water.

3) Test sample Formulations*

Ingredients**	Amount
Kiwi Seed Extract	50mg
Rice Derived Ceramide-Containing Food	20mg

* 2 capsules / day
** Cornstarch and sucrose fatty acid ester were used as an excipient

4) Nutritional Composition of Test Sample

Main components	Test sample
Energy (Kcal)	2.5
Water (g)	0.02
Protein (g)	0.003
Fat (g)	0.004
Carbohydrates (g)	0.61
Sodium (mg)	0.05

5) Preparation and Preservation Method
Preparation: Hard capsule
Preservation Method: Store away from sunlight, heat and moisture

8. Management of the Test Samples

1) Persons in Charge of Controlling Test Samples
Junji Tanaka, Oryza Oil & Fat Chemical Co., Ltd.
Eiji Okamoto, Bokushinkai Medical Corporation

2) Delivery Date of Test Samples
Estimated Delivery Date: Before September 8th 2009
Treatment of Unused Test Samples: Must Return

3) Method of Storage and Preservation for Test Samples
The test samples were stored properly and strictly by the Designated Testing Medical Agency.

4) Delivery of Test Samples
Subjects took the test samples for 4 weeks. The clinical research coordinator explained the method of ingesting the test samples to the subjects before the test samples were delivered to them. An explanation leaflet on the test samples' ingestion and storage was enclosed with the test samples.

9. Methods

1) Study Design
Open label trial (Comparison over time).

2) Number of Subjects
11 subjects (Number of guaranteed subjects: 10 subjects. The screening test was conducted on 16 subjects).

3) Duration of Ingestion
Subjects took the test samples for 4 weeks.

4) Constraints and Precautions
Designated testing medical agency explained the constraints and precautions to the subjects. Details of the constraints and precautions were as follows.

4.1) Constraints

- Not to start ingesting new supplements or health foods after the beginning of the trial.
- Not to ingest kiwi seed extract and food containing rice derived ceramide other than the test samples.
- Not to conduct treatments that improve the skin condition, such as chemical peeling, laser treatment, photo treatment, or hyaluronic acid injections.
- Not to have used cosmetics for acne care, including high concentration vitamin preparations, quasi drugs (e.g. Proactiv, Bifnight or Clearasil), drugs (e.g. antibiotics, steroid, retinoid or salicylic acid), hormone therapies, or phototherapy within the previous 3 months.
- Not to engage in activities that leave the subject vulnerable for sunburn, such as sea bathing, climbing, or sun tanning.
- Not to start using new cosmetics to improve skin condition.
- Not to do anything else beyond those specifically stated above that may have an influence on the results of the test.

4.2) Precautions

- In case a subject was regularly using supplements not intended for acne care (e.g. the vitamin compounds), the subject was allowed to use it continuously without changing dosage and administration.
- Subjects who used cosmetics were asked to use it continuously (except in case of changing by season variation).
- Subjects were asked to maintain a regular lifestyle, refraining from irregular patterns and overeat, and

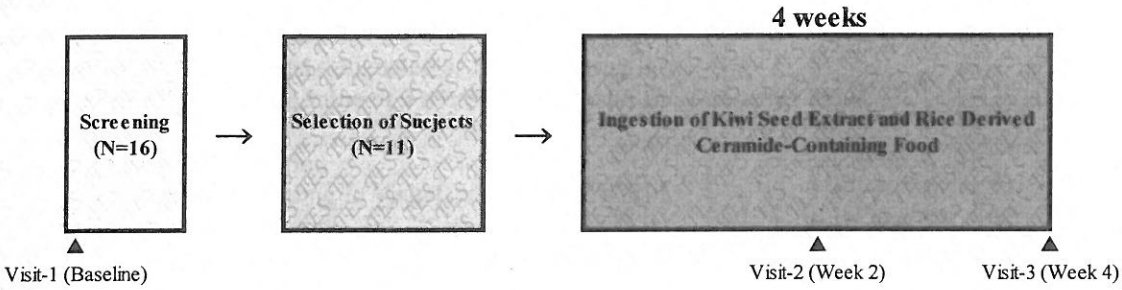
to pay attention to their health during the test period.

5) Schedule

5.1) Test Schedule

Total opportunity of visits: Visit-1 (Screening and Baseline), Visit-2 (Week 2), and Visit-3 (Week 4)

- Trial registration
- Receive informed consent
- Visit-1 (Screening and Baseline Examination)
- Selection of subjects
- Delivery of test samples
- Start of ingestion
- Visit-2 (Week 2 Examination)
- Visit-3 (Week 4 Examination)



5.2) Schedule of Examination

- Explained details of the test and conducted informed consent (only Visit-1).
- Subjects rested for over 15 minutes and then cleansed their faces with a little warm water and a facial wash (prepared by the designated medical test agency).
- The subjects' skin was dried with a paper towel.
- The skin was naturalized for 20 minutes in a temperature controlled chamber. During naturalization, touching of the face was prohibited.
- The skin moisture was measured. This included the skin pH value, and the skin sebum capacity in the lateral position in the temperature controlled chamber.
- The facial image was analyzed as the subject was in a sitting position.
- A visual judgment was conducted and the subject underwent a medical interview by the principal investigator.
- A blood collection and a urine collection were conducted.

6) Condition of the Control Temperature Chamber

In the control temperature chamber, the temperature was set at 22°C±1°C and the humidity was set at 50%±10%.

10. Observation and Evaluation Items

1) Visual Judgment by Dermatologist

Method: The principal investigator categorized the grade of facial acne and counted the total amount of facial acne.

Adopted Value: Number of counts.

2) Analysis of Facial Image

Measuring Equipment: VISIA™ Evolution (Canfield Inc., Fairfield, USA).

Object of Evaluation: Number of porphyrins.

Analyzed Areas: Face of the subject (front side, left side, and right side of subject's face).

3) Measurement of skin moisture content

Measuring Equipment: Corneometer CM825/MPA 580® (Courage+Khazaka Electric GmbH, Cologne, Germany).

Measured Areas: The center of the forehead and the top point of the left cheekbone (If the measuring area was irritated, another area was designated as the measuring area).
Adopted Value: The average value of 5 measurements at the same point, after cutting off maximum and minimum values.

4) Skin pH Measurement
Measuring Equipment: Skin-pH-Meter 905 / MPA 580® (Courage+Khazaka Electric GmbH, Cologne, Germany).
Measured Areas: Center of the forehead and the top point of the left cheekbone (If the measuring area was irritated, another area was designated as the measuring area).
Adopted Value: The average value of 3 measurements made near the measuring areas.

5) Sebum Capacity
Measuring Equipment: Sebumeter SM 815 / MPA 580® (Courage+Khazaka Electric GmbH, Cologne, Germany).
Measuring Areas: The center of the forehead and the top point of the left cheekbone (If the measuring area was irritated, another area was designated as the measuring area).
Adopted Value: The average value of 3 measurements near the measuring areas.

6) Questionnaire Investigation
Investigation Period: Screening & Visit-1, Visit-2, and Visit-3.
Investigation Items: Skinindex-16 (Screening & Visit-1, Visit-2 and Visit-3), Skin Condition Questionnaire (Screening & Visit-1), Lifestyle Questionnaire (Screening & Visit-1), and Usability Questionnaire (Visit-3).
Method: The questionnaire consisted of 16 questions. Q.1-4 were used to create a Symptom Score, Q. 5-11 were used for an Emotion Score, Q. 12-15 were used for a Function Score, and the total points of all 16 questions were used to create a Total Score. Subjects chose one answer from seven possible choices. The raw score of each question was converted to a score on a scale from 0-100, and then the average score was calculated. Subjects wrote the questionnaires during the rest time or during naturalization.

7) Blood Collection
Measuring Period: Screening & Visit-1 and Visit-3
Measuring Items: WBC, RBC, HB, HT, PLT, MCV, MCH, MCHC, TP, BUN, CRE, AST(GOT), ALT(GPT), γ-GT, ALP, CK, TC, TG, HDL-CHO, TB and GLU.

8) Urine Collection
Measuring Period: Screening & Visit-1 and Visit-3
Measuring Items: Urine urobilinogen, Occult blood, Urine bilirubin, Urine ketone bodies, Urine glucose, Urine protein and Urine pH.

9) Subject's Log
Log Period: Every day from the first day of ingestion to the last day of the test.
Logged Items: Conditions of ingestion, bedtime, subjective symptoms, usage of medical drugs, skin care, usage of supplements, menstruation, and bowel movements.

11. Final Report
A final report was made based on the results of compiled data and statistical analysis. Pictorial data was submitted on a CD-ROM.

12. Criteria for Stopping
This study could be stopped according to the event of a medical or ethical judgment by the principal investigator when the following events occurred. Subjects could receive appropriate medical treatment and be guaranteed their own safety in the event of event-1 on the following list. To advocate subjects' rights, the principal investigator stopped the study when the subject claimed to stop the trial.

- When adverse events, e.g. serious side effects or subjective and objective symptoms occurred.
- When the subject could not participate in the study concurrent with an illness or with the aggravation of a coexisting disease.

- When the subject could not sustain the test activities.
- When the subject became pregnant.
- When the test was stopped.
- When the principal investigator judged it necessity to stop the test.

13. Adverse Events

1) Definition of Adverse Events

In this study all adverse medical events that occurred after the ingestion of the study samples were recognized as adverse events. Events occurring before ingestion of the study samples and noticed regularly throughout the study were excluded from the category of adverse events. When these events went into a decline, such events were recognized as adverse events. Generalized events were dealt with as adverse events when causal association of these events could not be denied.

2) Causal Correlation

When adverse events were recognized, the principal investigator wrote down the area affected, the degree, the expression date, the treatment, and the transfer, discussed the correlation between the test sample and the events, and judged the status of the recuperation. As a general rule, follow-up survey of regional adverse events was conducted until the disappearance of the events. Events which were undeniably caused by the test sample were recognized as side effects. The regional adverse events were evaluated in 4 grades. The grade of general adverse events that could not be denied a causal role was evaluated in the same way as the regional adverse events.

14. Exclusive Criteria of Statistical Analysis

When a subject showed signs of the following, the subject would become the object of a clinical conference and excluded as the object of statistical analysis by the review.

- When the subject came in over 7 days late at each visit.
- When the total percentage of uningested days was over 15% of the estimated ingestion schedule.
- When the fact that the subject notably deviated from the constraints during the test period.
- When the reliability of the data was damaged due to trouble during the survey.
- When other problems that should be treated as dropouts occurred.

15. Caution

Subjects filled in the survey with black ink ballpoint pens. All corrections were done with double lines to mark out mistakes.

16. Subject Confidentiality

The contracted research organization maintained subject confidentiality, made subjects in pictures or image data impossible to identify, and received informed consent in the case of providing pictures or data to other parties such as in the presentation of results or in published papers.

17. Treatment of Alters

When measurement was delayed or missed due to health problems or the will of the subject, the subject's condition or will took priority according the spirit of the Declaration of Helsinki. Therefore in cases where collecting data was impossible, such data was treated as a missing value.

18. Ethics

1) Compliance Rule

To ensure the safety and to protect the rights of subjects, this study was conducted in accordance with ethical principles grounded in the Declaration of Helsinki and Standards for the Implementation of Clinical Trials on Pharmaceutical Products (MHW Ordinance No. 28 dated March 27, 1997).

2) Ethical Review Committee

This study was under the supervision of the TES Holdings Ethical Review Committee (Chair: Prof. Dr. Yasuo Watanabe).

19. Results

This study started with 11 subjects. A dropout was occurred during the study and 1 subject showed signs of menoxenia. This subject was excluded from statistical analysis. As a result statistical analysis was conducted to 9 subjects.

1) Backgrounds of Subjects
The backgrounds of subjects were shown in **Table 1**. This study contained 9 subjects (26.8 ± 5.4 years).

2) Visual Judgment by Dermatologist
The Results of visual judgment by a Dermatologist is shown in **Table 2-4, 2-2** and **Figure 1-1, 1-2**. A dermatologist counted comedones, pimples, pustules, abscesses, and tubercles, scoring each instance (comedo: 1 point, pimple: 2 points, pustule: 3 points, abscesses: 4 points, tubercule: 5 points). The result was analyzed using the Wilcoxon singed-rank test. The result of statistical analysis was described when a significant change was recognized.
The baseline value before ingestion was 21.1±1.4 points, 2 weeks after ingestion it was 21.3±4.7 points, and 4 weeks after ingestion it was 16.8±2.3 points. The value of 4 weeks after ingestion significantly decreased from that of the baseline.
The difference from the baseline was 0.2±3.6 points (2 weeks after ingestion) and -4.3±1.4 points (4 weeks after ingestion). The value was significantly decreased for 4-week ingestion as compared with the baseline.

3) Analysis of Facial Image
The results of the analysis of facial image (object of evaluation: number of porphyrins) is shown in **Table 3-1, 3-2** and **Figure 2-1, 2-2**. Results were analyzed using a paired *t*-test. Results of statistical analysis were described when a significant change was recognized.

3.1) Front Side of the Subject
The baseline value before ingestion was 329.1±75.1, 2 weeks after ingestion it was 313.2±84.9, and 4 weeks after ingestion it was 291.7±71.9.
The difference from the baseline was -15.9±44.2 (2 weeks after ingestion) and -37.4±28.6 (4 weeks after ingestion).

3.2) Left Side of the Subject
The baseline value before ingestion was 280.7±73.1, 2 weeks after ingestion it was 274.4±102.2, and 4 weeks after ingestion it was 252.9±66.9.
The difference from the baseline was -6.2±56.9 (2 weeks after ingestion) and -27.8±30.9 (4 weeks after ingestion).

3.3) Side of the Subject
The baseline value before ingestion was 300.3±73.9, 2 weeks after ingestion it was 296.3±110.2, and 4 weeks after ingestion it was 265.7±71.7.
The difference from the baseline was -4.0±61.7 (2 weeks after ingestion) and -34.7±26.2 (4 weeks after ingestion).

4) Questionnaire Investigation (Skindex-16)
Results of Skindex-16 are shown in **Table 4-1, 4-2** and **Figure 3-1~3-8**. Results were analyzed using a Wilcoxon singed-rank test. Results of statistical analysis were described when a significant change was recognized.

4.1) Symptom Score
The baseline score before ingestion was 23.4±8.1, 2 weeks after ingestion it was 20.9±7.6, and 4 weeks after ingestion it was 25.6±8.4.
The difference from the baseline was -2.6±6.5 (2 weeks after ingestion) and 2.1±8.9 (4 weeks after ingestion).

4.2) Emotion Score
The baseline score before ingestion was 66.4±7.0, 2 weeks after ingestion it was 48.8±9.5, and 4 weeks after ingestion it was 42.7±10.5. The score 2 weeks after ingestion significantly decreased from the baseline.

The difference from the baseline was -17.7±6.6 (2 weeks after ingestion) and -23.8±8.6 (4 weeks after ingestion). The difference 2 weeks after ingestion significantly decreased from the baseline.

4.3) Function Score
The baseline score before ingestion was 8.1±4.9, 2 weeks after ingestion it was 8.1±6.6, and 4 weeks after ingestion it was 12.6±12.6.
The difference from the baseline was 0.0±3.1 (2 weeks after ingestion) and 4.5±8.6 (4 weeks after ingestion).

4.4) Total Score
The baseline score before ingestion was 37.4±6.1, 2 weeks after ingestion it was 29.2±7.1, and 4 weeks after ingestion it was 26.9±7.4.
The difference from the baseline was -8.2±4.3 (2 weeks after ingestion) and -10.6±5.4 (4 weeks after ingestion).

5) Measurement of Skin Moisture Content
Results of measurements of skin moisture content are shown in **Table 5-1, 5-2** and **Figure 4-1, 4-2**. Results were analyzed using a paired *t*-test. Results of statistical analysis were described when a significant change was recognized.

5.1) Center of the forehead
The baseline value before ingestion was 54.56±3.00, 2 weeks after ingestion it was 55.79±3.05, and 4 weeks after ingestion it was 55.75±2.79.
The difference from the baseline (100.0%) was 103.4±6.0% (2 weeks after ingestion) and 103.9±6.7% (4 weeks after ingestion).

5.2) Top point of the left cheekbone
The baseline value before ingestion was 59.03±3.45, 2 weeks after ingestion it was 54.79±4.36, and 4 weeks after ingestion it was 59.80±2.52.
The difference from the baseline (100.0%) was 93.0±6.2% (2 weeks after ingestion) and 103.4±6.2% (4 weeks after ingestion).

6) Skin pH Measurement
Results of skin pH measurement t are shown in **Table 6-1, 6-2** and **Figure 5-1, 5-2**. Results were analyzed using a paired *t*-test. Results of statistical analysis were described when a significant change was recognized.

6.1) Center of the forehead
The baseline value before ingestion was 5.46±0.09, 2 weeks after ingestion it was 5.44±0.09, and 4 weeks after ingestion it was 5.49±0.06.
The difference from the baseline (100.0%) was 99.6±1.2% (2 weeks after ingestion) and 100.7±1.2% (4 weeks after ingestion).

6.2) Top point of the left cheekbone
The baseline value before ingestion was 5.63±0.07, 2 weeks after ingestion it was 5.54±0.08, and 4 weeks after ingestion it was 5.61±0.05.
The difference from the baseline (100.0%) was 98.4±1.5% (2 weeks after ingestion) and 99.6±1.0% (4 weeks after ingestion).

7) Sebum Capacity
Results of sebum capacity are shown in **Table 7-1, 7-2** and **Figure 6-1, 6-2**. Results were analyzed using a paired *t*-test. Results of statistical analysis were described when a significant change was recognized.

7.1) Center of the forehead
The baseline value before ingestion was 25.0±2.4μg/cm^2, 2 weeks after ingestion it was 21.4±2.6μg/cm^2, and 4 weeks after ingestion it was 20.6±3.1μg/cm^2.
The difference from the baseline (100.0%) was 91.1±13.5% (2 weeks after ingestion) and 84.0±11.9% (4

weeks after ingestion).

7.2) Top point of the left cheekbone
The baseline value before ingestion was 9.7±1.9μg/cm^2, 2 weeks after ingestion it was 7.3±1.4μg/cm^2, and 4 weeks after ingestion it was 6.4±1.7μg/cm^2.
The difference from the baseline (100.0%) was 130.5±59.2% (2 weeks after ingestion) and 97.2±30.6% (4 weeks after ingestion).

8) Analysis of Facial Image (Condition of the Face)
Results of analysis of facial image (condition of the face) are shown in **Table 3-1**, **3-2** and **Figure 2-3~2-16**. Results were analyzed using a paired t-test. Results of statistical analysis were described when a significant change was recognized.

8.1) Brown Spots
8.1.1) Front Side of the Subject
The baseline value before ingestion was 92.4±14.0, 2 weeks after ingestion it was 85.8±12.0, and 4 weeks after ingestion it was 98.1±10.4.
The difference from the baseline was -6.7±4.4 (2 weeks after ingestion) and 5.7±7.1 (4 weeks after ingestion).

8.1.2) Left Side of the Subject
The baseline value before ingestion was 165.4±12.5, 2 weeks after ingestion it was 161.1±17.9, and 4 weeks after ingestion it was 158.9±12.8.
The difference from the baseline was -4.3±15.4 (2 weeks after ingestion) and -6.6±11.1 (4 weeks after ingestion).

8.1.3) Right Side of the Subject
The baseline value before ingestion was 172.6±17.1, 2 weeks after ingestion it was 160.2±14.9, and 4 weeks after ingestion it was 164.9±13.9.
The difference from the baseline was -12.3±14.6 (2 weeks after ingestion) and -7.7±8.7 (4 weeks after ingestion).

8.2) Pores
8.2.1) Front Side of the Subject
The baseline value before ingestion was 298.8±39.8, 2 weeks after ingestion it was 282.6±38.7, and 4 weeks after ingestion it was 310.1±34.0.
The difference from the baseline was -16.2±12.0 (2 weeks after ingestion) and 11.3±10.2 (4 weeks after ingestion).

8.2.2) Left Side of the Subject
The baseline value before ingestion was 278.4±38.7, 2 weeks after ingestion it was 286.6±45.2, and 4 weeks after ingestion it was 293.0±36.5.
The difference from the baseline was 8.1±13.9 (2 weeks after ingestion) and 14.6±8.4 (4 weeks after ingestion).

8.2.3) Right Side of the Subject
The baseline value before ingestion was 276.0±40.3, 2 weeks after ingestion it was 279.8±42.5, and 4 weeks after ingestion it was 289.3±45.8.
The difference from the baseline was 3.8±14.3 (2 weeks after ingestion) and 13.3±8.1 (4 weeks after ingestion).

8.3) Red Areas
8.3.1) Front Side of the Subject
The baseline value before ingestion was 60.2±4.5, 2 weeks after ingestion it was 58.0±9.7, and 4 weeks after ingestion it was 62.4±8.5.
The difference from the baseline was -2.2±9.1 (2 weeks after ingestion) and 2.2±8.6 (4 weeks after ingestion).

8.3.2) Left Side of the Subject
The baseline value before ingestion was 59.2±14.2, 2 weeks after ingestion it was 68.8±20.9, and 4 weeks after ingestion it was 66.6±17.6.
The difference from the baseline was 9.6±12.0 (2 weeks after ingestion) and 7.3±9.9 (4 weeks after ingestion).

8.3.3) Right Side of the Subject
The baseline value before ingestion was 85.0±21.0, 2 weeks after ingestion it was 57.3±17.2, and 4 weeks after ingestion it was 62.4±17.8.
The difference from the baseline was -27.7±22.5 (2 weeks after ingestion) and -22.6±18.4 (4 weeks after ingestion).

8.4) Spots
8.4.1) Front Side of the Subject
The baseline value before ingestion was 26.0±3.1, 2 weeks after ingestion it was 28.0±4.7, and 4 weeks after ingestion it was 28.4±3.1.
The difference from the baseline was 2.0±2.5 (2 weeks after ingestion) and 2.4±1.5 (4 weeks after ingestion).

8.4.2) .Left Side of the Subject
The baseline value before ingestion was 54.0±9.8, 2 weeks after ingestion it was 54.4±9.1, and 4 weeks after ingestion it was 54.4±9.0.
The difference from the baseline was 0.4±1.4 (2 weeks after ingestion) and 0.4±2.4 (4 weeks after ingestion).

8.4.3) Right Side of the Subject
The baseline value before ingestion was 46.6±8.8, 2 weeks after ingestion it was 47.9±9.1, and 4 weeks after ingestion it was 50.3±10.1.
The difference from the baseline was 1.3±1.2 (2 weeks after ingestion) and 3.8±2.8 (4 weeks after ingestion).

8.5) Texture
8.5.1) Front Side of the Subject
The baseline value before ingestion was 656.2±118.8, 2 weeks after ingestion it was 588.1±95.1, and 4 weeks after ingestion it was 618.0±96.3.
The difference from the baseline was -68.1±47.2 (2 weeks after ingestion) and -38.2±30.0 (4 weeks after ingestion).

8.5.2) Left Side of the Subject
The baseline value before ingestion was 357.7±51.8, 2 weeks after ingestion it was 372.3±55.0, and 4 weeks after ingestion it was 383.1±45.4.
The difference from the baseline was 14.7±32.2 (2 weeks after ingestion) and 25.4±19.4 (4 weeks after ingestion).

8.5.3) Right Side of the Subject
The baseline value before ingestion was 342.3±44.1, 2 weeks after ingestion it was 352.6±41.0, and 4 weeks after ingestion it was 381.7±60.2.
The difference from the baseline was 10.2±28.1 (2 weeks after ingestion) and 39.3±22.8 (4 weeks after ingestion).

8.6) Ultraviolet Spots
8.6.1) Front Side of the Subject
The baseline value before ingestion was 92.7±8.8, 2 weeks after ingestion it was 92.7±8.8, and 4 weeks after ingestion it was 96.8±6.9.
The difference from the baseline was -2.9±3.0 (2 weeks after ingestion) and 4.1±3.5 (4 weeks after ingestion).

8.6.2) Left Side of the Subject
The baseline value before ingestion was 197.0±14.6, 2 weeks after ingestion it was 200.0±11.1, and 4 weeks after ingestion it was 201.1±12.0.
The difference from the baseline was 3.0±4.6 (2 weeks after ingestion) and 4.1±4.6 (4 weeks after ingestion).

8.6.3) Right Side of the Subject
The baseline value before ingestion was 202.6±11.0, 2 weeks after ingestion it was 200.4±11.0, and 4 weeks after ingestion it was 201.1±12.0.
The difference from the baseline was -2.1±2.6 (2 weeks after ingestion) and -1.4±2.9 (4 weeks after ingestion).

8.7) Wrinkles
8.7.1) Front Side of the Subject
The baseline value before ingestion was 3.7±1.5, 2 weeks after ingestion it was 2.0±0.4, and 4 weeks after ingestion it was 3.0±0.6.
The difference from the baseline was -1.7±1.5 (2 weeks after ingestion) and -0.7±1.1 (4 weeks after ingestion).

8.7.2) Left Side of the Subject
The baseline value before ingestion was 3.7±1.0, 2 weeks after ingestion it was 4.1±1.2, and 4 weeks after ingestion it was 4.3±1.1.
The difference from the baseline was 0.4±0.9 (2 weeks after ingestion) and 0.7±1.0 (4 weeks after ingestion).

8.7.3) Right Side of the Subject
The baseline value before ingestion was 5.1±1.7, 2 weeks after ingestion it was 6.0±1.8, and 4 weeks after ingestion it was 5.6±1.4.
The difference from the baseline was 0.9±1.1 (2 weeks after ingestion) and 0.4±0.5 (4 weeks after ingestion).

9) Blood Examination
Results of the blood examination are shown in **Table 8-1** and **8-2**. Results were analyzed using a paired *t*-test. Results of red blood count, hemoglobin content, hematocrit, uric acid, and total bilirubin changed significantly within the criterion value.

10) Urine Examination
Results of the urine examination are shown in **Table 9-1** and **9-2**. Results were analyzed using a paired *t*-test. No significant change was recognized.

11) Subjects' Log
Results of subjects' log are shown in **Table 10~16**.
Results of ingestion rate are shown in **Table 10**. Ingestion rate of all subjects was over 85% and none of their activity conflicted with the criteria for exclusion in statistical analysis.
Results of ingesting conditions, bedtime, subjective symptoms, usage of medical drugs, skin care, usage of supplements, menstruation, and bowel movements are shown in **Table 11~16**. In menstruation, 1 subject showed signs of menoxenia, but other changes were not apparent in subjective symptoms affecting the test result.
Personal data of each subject is shown in **Table 17~24**.

20. Discussion
Acne is a cutaneous inflammation caused by the interaction of hormones, bacillus, or sebum. In particular, dihydrotestosterone, converted from testosterone by 5α- reductase, stimulates sebaceous cell and promotes sebum secretion. Propionibacterium acne is normal bacteria flora inside a human skin hair follicle. It increases in an area where sebum has pooled excessively, and produces bacterial lipase. Lipase decomposes triglyceride in sebum, separates fatty acid, and induces an inflammatory response. As a consequence, acne

develops or gets worse. The test sample consisted of kiwi seed extract and functional food materials like rice derived ceramide. Kiwi seed extract containing polyphenols like flavonol glycoside inhibits activity of 5α- reductase and propionibacterium acnes derived lipase[1)]. Rice derived ceramide is the main component of human skin surface intercellular lipids, functions as a skin barrier, and produces an effect of improvement in keeping skin moisture and smoothness[2)]. Therefore the test sample is assumed to function to improve acne and the overall skin condition.

The objective of this study was to evaluate the level of improvement in acne brought about by ingesting kiwi seed extract and food containing rice derived ceramide for 4 weeks. To achieve this objective, an open label trial was conducted with Japanese females aged 18-34 years, who had acne on their faces. The clinical trial items were visual judgment, skin moisture content, sebum capacity, pH measurement, analysis of facial image, questionnaire, biochemical examination of blood, and urinalysis.

As a result, the condition of acne showed significant improvement in visual judgment by a dermatologist. On the front side of subjects' faces sebum capacity decreased 16% compared with the baseline. However, there was no significant change in the analysis of facial image. The number of porphyrins seen in the analysis of facial image decreased with time. It was inferred that ingesting study samples inhibited the growth of propionibacterium acne. The result of Skindex-16 implied that the function of the study sample was effective not only against acne, but also to improve skin condition.

In general, the term for skin turnover is approximately 28 days. In this study, porphyrins and serum capacity decreased on the 14th day after the start of ingestion and the number of acne decreased on the 28th day after start of ingestion. Therefore, the improvement of acne was implicated as the result of a direct effect on acne. In this study, test samples were a compound of kiwi seed extract and rice derived ceramide. Referring to previous research, sebum production was inhibited by the inhibitory effect of kiwi seed extract on dihydrotestosterone and the skin condition was improved by rice derived ceramide. In a longer study, the inhibitive effect on sebum capacity, the effect on skin turnover in the change of skin condition such as the antioxidative effect, i.e. the wrinkle improving effect, the skin whitening effect, and improvement effect on dark rings, could be examined. Results in subjects' logs show there were other changes occurring as a result of taking the study samples or as a result of subjective symptoms affecting the test result. Some changes were verified in the blood examination, but all changes were within the criterion value.

In conclusion, it is clinically evident that this test sample has an effect, mainly an inhibitive effect on sebum secretion, which improves skin condition and the condition of acne. As a result, this test sample is shown to be a safe and beneficial supplement.

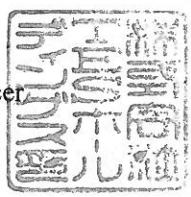
Works Cited

1) Tanaka J, Shan S, Aitani N and Simoda H, *Kiui Shushiekisu no Nikibi, Shiwa oyobi Kuma ni taisuru Yobou/ Kaizenkouka.* Food Style 21, **9**(12): 81-89, 2005.

2) Kajimoto O, Oiso N and Takahashi T, *Komeyurai Seramido Ganyushokuhin ni okeru Bihadakouka no Rinshoteki Kento*. Oryza Oil & Fat Chemical Co., Ltd., 2006.

We certify the above to be true in every particular.

Akio Hayashi
President and Chief Executive Officer
TES Holdings Co., Ltd.



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