pISSN 1226-2587
J. Soc. Cosmet. Sci. Korea eISSN 2288-9507
Vol. 44, No. 2, June 2018, 161-170 http://dx.doi.org/10.15230/SCSK.2018.44.2.161

레스베라트릴 트라이아세테이트(RTA)를 함유한 크림의 피부 노화 완화 효과

최 고 운 · 정 현 진 · 석 진 경* · 백 지 훈 · 김 영 미** · 부 용 출*†

(주)더마프로 피부과학연구소, *경북대학교 의과대학 분자의학교실 세포기질연구소, **(주)루비크라운
(2018년 4월 12일 접수, 2018년 5월 4일 수정, 2018년 5월 21일 채택)

Skin Anti-aging Effects of a Cream Containing Resveratryl Triacetate (RTA)

Go Woon Choi, Hyun Jin Jeong, Jin Kyung Seok*, Ji Hwoon Baek, Young Mi Kim, and Yong Chool Boo*†**

Dermapro Skin Research Center, Dermapro Ltd., Seoul, Korea
*Department of Molecular Medicine, CMRI, BK21 Plus KNU, School of Medicine, Kyungpook National University, Daegu, Korea
**Ruby Crown Co., Ltd., Daegu, Korea
(Received April 12, 2018; Revised May 4, 2018; Accepted May 21; 2018)

요 약: 피부 노화의 정도는 기기 분석을 통해 객관적으로 측정 할 수 있다. 본 연구의 목적은 인체 적용 시험을 통해 8000 PPM의 레스베라트릴 트라이아세테이트(RTA)를 함유한 크림의 피부 노화 완화 효과를 평가하는 것이다. 여성 피험자 20명에게 시험 제품을 얼굴에 매일 2회 8주 동안 바르고, 4주마다 기기 분석을 통해 주름, 처짐, 탄력, 진피치밀도, 수분 및 밝기 등을 측정하였다. 시험 제품을 4 주 및 8 주 동안 사용한 결과 총 주름 면적이 감소하고(5.12%, 4.86%), 총 주름 용적이 감소하고(10.53%, 8.41%), 탄력성이 증가하고(2.84%, 3.98%), 진피치밀도가 증가하고(15.65%, 20.80%), 수분이 증가하고(5.83%, 7.37%), 밝기(L* 값)가 증가하고(0.79%, 1.07%), 피부색(individual typology angle, ITA°)이 밝아졌으며(5.43%, 4.95%), 이들 변화는 통계적으로 유의하였다($p < 0.05$). 시험 기간 동안 모든 참가자에게서 부정적인 피부 반응이 관찰되지 않았다. 본 연구는 시험 제품의 피부 노화 완화 효과를 뒷받침한다.

Abstract: Skin aging degree can be objectively measured using the instrumental analysis. The purpose of this study was to evaluate the anti-aging effects of a cream containing 8000 PPM of resveratryl triacetate (RTA) in the human skin test. Twenty female subjects were given test products twice a day for 8 weeks on the face, and wrinkles, sagging, elasticity, dermis denseness, moisture and brightness were measured every 4 weeks by instrument analysis. After 4 and 8 week-use of the test product, total wrinkle area decreased (5.12%, 4.86%), total wrinkle volume decreased (10.53%, 8.41%), sagging decreased (4.69%, 5.91%), elasticity increased (2.84%, 3.98%), dermis denseness increased (15.65%, 20.80%), water content increased (5.83%, 7.37%), lightness (L* value) increased (0.79%, 1.07%), and individual typology angle (ITA°) increased (5.43%, 4.95%)compared with the baseline values before treatments, and all these changes were statistically significant ($p < 0.05$). No adverse skin reactions were observed in all participants during the study period. This study supports the anti-aging effects of the test product.

Keywords: *resveratrol, resveratryl triacetate, anti-aging effect, human skin, cream*

† 주 저자 (e-mail: ycboo@knu.ac.kr)
call: 053)420-4946

1. Introduction

Skin is a protective organ with various physiological functions, and it is also an important organ for obtaining beauty appeal from other people. It is reported that elderly people with skin that looks younger than age are more satisfied with life[1]. In recent years, various skin care products have been developed as consumers are increasingly demanding products that have the effect of delaying or preventing skin aging[2,3].

Skin aging is accompanied by various dysfunctions with visible and invisible changes[4,5]. As the skin aging progresses, the thickness of the epidermis becomes thinner and the boundary of the dermis becomes flat, so that the adhesion is weakened. In aging skin, the production of matrix components decreases while the production of enzymes that degrade them increases, eventually decreasing the thickness. Decreased dermal thickness and changes in its matrix components cause skin elasticity to decrease, making it appear as a sagging or wrinkled skin[6]. In addition, the skin becomes dry, resulting in fine keratin[7]. Although the number of melanocytes responsible for skin pigment decreases every year, the activity of the cells is abnormally increased, resulting in occurrence of spots of low pigmentation and hyperpigmentation of the skin[8].

Resveratrol is a polyphenolic compound contained in various plants such as *Vitis vinifera* L. Resveratrol has biochemical properties that can contribute to prevention of skin aging[9,10]. Resveratrol attenuates UV-induced skin damage, atopic dermatitis and acne vulgaris[11-14]. Resveratrol has also been reported to inhibit melanin production in melanocytes[15,16]. In cosmetics, however, safety and stability as well as the efficacy of the active ingredient are important considerations. Resveratrol itself has a disadvantage that it is easily discolored by oxidation and its stability is poor. In previous studies, we developed resveratryl triacetate (RTA), which is intended to apply resveratrol to cosmetics effectively[17-19].

The purpose of the present is to evaluate the anti-aging effects of a cosmetic product containing RTA in human studies, monitoring skin parameters such as skin wrinkles, sagging, elasticity, dermal denseness, moisture and brightness/color.

2. Materials and Methods

2.1. Cosmetic Products

The test cream contained 8000 PPM of RTA as the active ingredient (Ruby Crown, Daegu, Korea). All ingredients of this product, in decreasing order of their concentrations, are as follows; water, dicaprylyl carbonate, cetyl ethylhexanoate, glycerin, methylpropanediol, pentaerythrityl tetraethylhexanoate, cetearyl alcohol, glyceryl stearate, polyglyceryl-3 methylglucose distearate, 1,2-hexanediol, coconut oil, dimethicone, RTA, PEG-100 stearate, sodium polyacrylate, isotridecyl isononanoate, acrylates/C10-30 alkyl acrylate crosspolymer, butylene glycol, PEG-75 stearate, tromethamine, ethylhexylglycerin, dipotassium glycyrrhizate, ceteth-20, steareth-20, trideceth-6, dextrin, caprylyl glycol, cetyl alcohol, disodium EDTA, phenoxyethanol, fragrance.

2.2. Human Study

The human study was approved by the local ethics committee of Dermapro Ltd. (Approval number, 1-220777-A-N-02-DICN16145)and it was conducted in accordance with good clinical practice guidelines. The participants were clearly informed, verbally and in writing, regarding the nature of the study, the timetable, possible risks and constraints. The researcher screened the participation form of the volunteers and the selection of participants was based on the fulfillment of the following inclusion and exclusion criteria.

2.2.1. Inclusion Criteria

1) Volunteers aged from 30 to 60.
2) Signed and informed consent after the purpose and the protocol of the study were explained to subjects.
3) Cooperative volunteers available for follow-up during the study period.

2.2.2. Exclusion Criteria

1) Pregnancy or nursing or pregnancy plan.
2) Immunotherapy within 1 month.
3) Inadequate time intervals from the previously participating studies (at least one month break required).
4) Sensitivity or hypersensitivity of the skin.
5) Skin damage, including sunburn, tattoos, scars or other deformations, on or around the test site.
6) Similar treatments over the last 3 months.
7) Have experience with test sites (skin decortications, botox and other skin treatment).
8) Chronic diseases (diabetes, asthma, hypertension).
9) Atopic dermatitis.
10) Any difficulty that could interfere with the research purpose at the discretion of the investigator.

After admission to the study, the participants were not allowed to use any functional cosmetics or pharmaceutical products other than the test products.

In total, 23 female participants were recruited. Among them, 3 participants were dropped out (participants #05, #08, and #17, voluntary withdrawal), and the study was completed with 20 participants (average age 43.95 ± 3.82 yr). The participants used the test product on face twice daily (morning and evening) for 8 weeks after skin toner and lotion. The participants visited the research center every 2 weeks. After cleansing the face with a foaming cleanser, the participants rested for 20 min in the laboratory (22 ± 2 ℃ and 50 ± 5% relative humidity) and were then subjected to instrumental analyses of the skin.

2.3. Instrumental Measurement of Skin Parameters

The skin wrinkle parameters were evaluated on crow's feet by 3D skin image analyzing system (PRIMOS®Premium, GFMesstechnik GmbH, Germany)[20]. To evaluate the sagging of cheek, Moire pattern image on cheek was taken by F-ray® (Beyoung, Korea) and analyzed using Image-pro®plus (MediaCybernetics, USA)[21]. Skin elasticity on cheek was measured by a suction method using Cutometer® MPA580 (Courage & Khazaka, Germany)[22]. Dermis denseness of cheek was evaluated using the ultrasound images generated by DermaLab® Series SkinLab Combo (Cortex, Denmark)[23,24]. Skin moisture on cheek was measured by Corneometer®CM825 (Courage & Khazaka, Germany)[25]. The skin lightness and skin color on cheek were evaluated using Spectrophotometer®CM-2500d (Minolta, Japan)[18,26,27]. The color was expressed using the Commission Internationale de l'Eclairage Lab color space, in which L* indicates lightness, a* is the green/red coordinate, and b* is the blue/yellow coordinate. The individual typology angles (ITA°) is defined as follows: ITA° = [Arc Tangent ((L* - 50) / b*)] 180 / 3.14159.

2.4. Self-survey for Efficacy

Self-survey for efficacy was conducted at 4 and 8 weeks after treatment of test product. The participant replied to the questionnaires regarding the efficacy of the test product on a scale of one to five (1, strongly disagree; ~ 5, strongly agree).

2.5. Assessment of Adverse Skin Reactions

Adverse skin reaction was defined as any unusual events occurred on the skin applied with the test product. The researcher recorded the subjective signs reported by the participants as well as the objective signs noted by the researcher.

2.6. Statistical Analysis

Statistical analysis was conducted using the SPSS® software program (IBM, USA). The normality assumption was checked by Shapiro-Wilks test, and analysis of Kurtosis and Skewness. Parametric statistical analysis was conducted using the Repeated Measures ANOVA. When the normality assumptions is rejected, non-parametric statistical analysis was performed using Post-hoc Wilcoxon signed-rank test with Bonferroni correction. The statistical significance level was set at $p < 0.05$. Change rate (%) was defined that; (values after treatments - baseline values before treatments) / baseline values before treatments × 100. Data are presented as Mean ± SD (standard deviation).

Table 1. Classified Skin Characteristics of The Participants (n = 20)

Item	Classification	Frequency (N)	Percentage (%)
Skin type	Dry	9	45.00
	Normal	6	30.00
	Oily	0	0.00
	Dry and oily	5	25.00
	Problematic	0	0.00
Skin hydration	Sufficient	0	0.00
	Normal	10	50.00
	Deficient	10	50.00
Skin sebum	Glossy	1	5.00
	Normal	12	60.00
	Deficient	7	35.00
Skin surface	Smooth	8	40.00
	Normal	11	55.00
	Rough	1	5.00
Skin thickness	Thin	6	30.00
	Normal	14	70.00
	Thick	0	0.00
Daily UV exposure	< 1 h	5	25.00
	1-3 h	15	75.00
	> 3 h	0	0.00
Sleep time a day	< 5 h	1	5.00
	5-8 h	18	90.00
	> 8 h	1	5.00
Smoking	No	20	100.00
	< 10 pieces	0	0.00
	> 10 pieces	0	0.00
Irritation due to any cosmetics	Yes	0	0.00
	No	20	100.00
Stinging due to any cosmetics	Yes	0	0.00
	No	20	100.00
Adverse reactions due to any cosmetics	Yes	0	0.00
	No	20	100.00

3. Results

Comprehensive questionnaire surveys for personal information, life style, and skin characteristics were undertaken for all participants, and data are shown **Tables 1** and **2.**

The skin wrinkle parameters evaluated by 3D skin image analysis are shown in **Table 3.** The analysis system allowed the quantitative description of skin wrinkle in terms of average depth of wrinkles, mean depth of the biggest wrinkle, maximum depth of biggest wrinkle, total wrinkle area, total wrinkle volume, arithmetic average of

Table 2. Individual Skin Characteristics of The Participants

No.	Name	Age	Skin type	Hydration	Sebum	Surface	Thickness	UV exposure	Sleep time
1	M*S	48	1	3	3	2	2	1	1
2	K*S	41	4	3	3	2	2	2	2
3	G*S	42	2	2	2	1	1	1	2
4	H*K	44	2	2	2	2	2	1	2
6	J*J	45	1	3	2	1	2	2	2
7	J*Y	37	1	2	2	2	2	2	2
9	R*J	44	1	3	3	2	1	2	2
10	K*Y	47	1	2	3	2	2	1	2
11	C*M	49	1	3	2	1	2	2	2
12	C*W	52	4	3	2	3	2	2	2
13	O*H	39	1	3	2	1	1	2	2
14	P*M	45	2	2	2	2	2	2	2
15	N*J	43	4	3	1	2	2	2	2
16	J*H	36	2	2	2	2	2	2	2
18	K*J	45	2	2	2	2	2	2	2
19	K*A	45	4	2	2	1	2	2	2
20	K*R	42	2	2	2	1	1	2	2
21	K*M	45	1	3	3	2	1	2	3
22	G*Y	45	1	3	3	1	1	1	2
23	K*Y	45	4	2	3	1	2	2	2

Skin type: 1, Dry; 2, Normal; 3, Oily; 4, Dry and oily; 5, Problematic.
Skin hydration: 1, Sufficient; 2, Normal; 3, Dry
Skin sebum: 1, Glossy; 2, Normal; 3, Deficient
Skin surface: 1, Smooth; 2, Normal; 3, Rough
Skin thickness: 1, Thin; 2, Normal; 3, Thick
Daily UV exposure: 1, < 1 h; 2, 1~3 h; 3, > 3 h
Sleep time a day: 1, < 5 h; 2, 5~8 h; 3, > 8 h

profile peaks within the total measuring length (Ra) and average maximum height of the profile (Rz). Compared to the baseline values before treatment, average depth of wrinkles, Ra and Rz parameters decreased at 4 weeks ($p < 0.05$). The total wrinkle area and total wrinkle volume decreased at 4 and 8 weeks ($p < 0.05$). The decrement rates were 4.86%~10.53%.

Instrumental analysis results of other skin parameters are shown in **Table 4.** The images of 3D-curved skin surface were obtained with the light passed through a specially designed grating window inclined by 30° toward the object. The resulting Moire pattern (contour line) was used to determine angle of cheek deflection. Facial sagging decreased by 4.69% and 5.91% ($p < 0.05$) at 4 and 8 weeks, respectively.

Skin elasticity was measured based on the suction and release of skin. Elasticity was defined as to how close the released skin is to its original vertical position. Skin elasticity increased at 4 and 8 weeks ($p < 0.05$) by 2.84% and 3.98% respectively.

Dermis Denseness was measured by ultrasonic method. Dermis denseness increased at 4 and 8 weeks ($p < 0.05$) by 15.65% and 20.80%, respectively.

Skin hydration was measured based on the different dielectric constant of water and other substances. Skin moisture increased at 4 and 8 weeks ($p < 0.05$) by 5.83 % and

Table 3. Effects of The Test Product on The Skin Wrinkle Parameters

Parameters	Week	N	Mean	SD	*p*-value	Change rate (%)
Average depth of wrinkles	Baseline	20	39.14	8.68	-	-
	4W	20	37.17	8.71	0.026*	-5.03
	8W	20	37.84	7.91	0.217	-3.33
Mean depth biggest wrinkle	Baseline	20	51.82	13.10	-	-
	4W	20	49.73	13.48	0.053	-4.04
	8W	20	48.83	12.44	0.062	-5.77
Max. depth biggest wrinkle	Baseline	20	142.07	50.55	-	-
	4W	20	138.36	47.57	0.523	-2.61
	8W	20	130.31	44.55	0.226	-8.28
Total wrinkle area	Baseline	20	52.22	5.09	-	-
	4W	20	49.54	4.81	0.000*†	-5.12
	8W	20	49.68	4.76	0.000*†	-4.86
Total wrinkle volume	Baseline	20	2.03	0.41	-	-
	4W	20	1.81	0.33	0.000*	-10.53
	8W	20	1.86	0.33	0.007*	-8.41
Ra	Baseline	20	20.48	4.39	-	-
	4W	20	19.35	4.29	0.012*	-5.52
	8W	20	19.77	3.89	0.207	-3.47
Rz	Baseline	20	244.74	46.21	-	-
	4W	20	229.83	42.13	0.003*	-6.09
	8W	20	240.49	54.33	0.635	-1.74

*p < 0.05 versus baseline values before treatments.
†Post-Hoc Wilcoxon signed-rank test (Bonferroni correction)
Ra, Arithmetic average of profile peaks within the total measuring length
Rz, Average maximum height of the profile

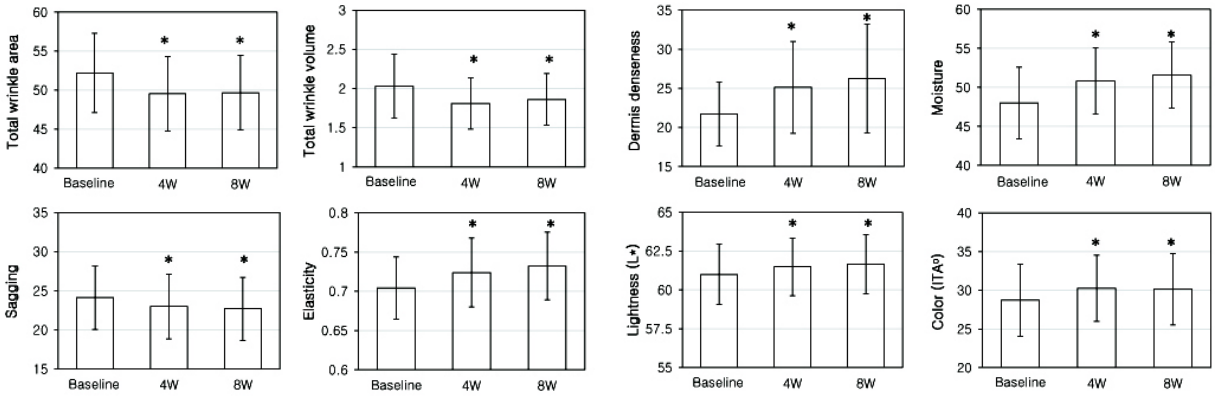

Figure 1. Effects of the test product on total skin wrinkle area and volume, sagging, elasticity, dermis denseness, moisture, and the heavily pigmented sites'lightness and color. The skin parameters were measured before and after treatments of the test product for 4 and 8 weeks. Data are presented as Mean ± SD (N = 20). *p < 0.05 versus baseline values before treatments.

Table 4. Effects of The Test Product on The Various Skin Parameters

Parameters	Week	N	Mean	SD	*p*-value	Change rate(%)
Skin sagging	Baseline	20	24.12	4.07	-	-
	4W	20	22.98	4.14	0.001*	-4.69
	8W	20	22.69	4.04	0.000*	-5.91
Skin elasticity	Baseline	20	0.7042	0.0396	-	-
	4W	20	0.7239	0.0439	0.000*	+2.84
	8W	20	0.7322	0.0431	0.000*	+3.98
Dermis denseness	Baseline	20	21.73	4.11	-	-
	4W	20	25.13	5.88	0.000*	+15.65
	8W	20	26.25	6.96	0.000*	+20.80
Skin moisture	Baseline	20	48.03	4.58	-	-
	4W	20	50.83	4.25	0.000*	+5.83
	8W	20	51.57	4.26	0.000*	+7.37
L* value of heavily pigmented site	Baseline	20	61.01	1.94	-	-
	4W	20	61.49	1.85	0.000*	+0.79
	8W	20	61.66	1.89	0.000*	+1.07
L* value of moderately pigmented site	Baseline	20	63.77	1.97	-	-
	4W	20	64.12	1.94	0.000*	+0.55
	8W	20	64.29	1.75	0.000*	+0.82
ITA°of heavily pigmented site	Baseline	20	28.71	4.66	-	-
	4W	20	30.27	4.28	0.000*	+5.43
	8W	20	30.13	4.60	0.000*	+4.95
ITA°of moderately pigmented site	Baseline	20	36.49	4.43	-	-
	4W	20	36.72	4.10	0.596	+0.63
	8W	20	36.64	4.48	0.769	+0.41

*$p < 0.05$ versus baseline values before treatments.

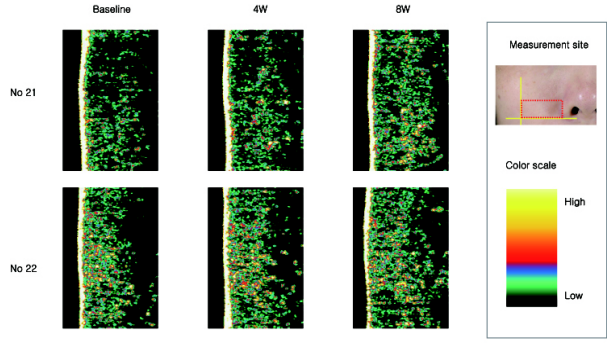

Figure 2. Effect of the test product on dermis denseness. Insets show the measurement sites and a color scale corresponding to the intensity of ultrasonic echo. The ultrasonic images were captured before and after treatments of the test product for 4 and 8 weeks. The representative images from participants No. 21 and 22 are shown.

7.37%, respectively.

The skin lightness and color were evaluated using spectrophotometric method. The skin lightness (L* value) of heavily pigmented sites increased at 4 and 8 weeks ($p < 0.05$) by 0.79 and 1.07%, respectively. The L* value of moderately pigmented sites increased at 4 and 8 weeks ($p < 0.05$) by 0.55 and 0.82%, respectively. The higher the ITA°, the lighter the skin. The ITA° of heavily pigmented site increased at 4 and 8 weeks ($p < 0.05$) by 5.43% and 4.95%, respectively. The ITA° of moderately pigmented site did not change significantly.

Changes in total wrinkle area and volume, sagging, elasticity, dermis denseness, moisture, and the heavily pigmented sites' lightness and color during the use of the

Table 5. Self-survey Results for The Efficacy of The Test Product (n = 20)

Questionnaires	4W		8W	
	Mean	SD	Mean	SD
Decrease of skin wrinkle	3.30	0.470	3.65	0.489
Decrease of skin sagging	3.35	0.587	3.50	0.607
Increase of skin elasticity	3.50	0.607	3.75	0.550
Increase of skin moisture	4.00	0.562	4.20	0.523
Increase of skin brightness	3.65	0.587	3.70	0.571
Improvement of skin condition	3.70	0.571	4.00	0.324

The participants rated the efficacy of the test product on a scale of one to five (1, strongly disagree; ~ 5, strongly agree).

Table 6. Effects of The Test Product on The Adverse Skin Reactions (n = 20)

Classification	Symptom	4W	8W
Subjective signs reported by the participants	Itching	0	0
	Prickling	0	0
	Burning	0	0
	Stinging	0	0
	Stiffness	0	0
	Tightening	0	0
	Burning of eyes	0	0
	Weeping	0	0
	etc.	0	0
Objective signs observed by the researcher	Erythema	0	0
	Edema	0	0
	Scale	0	0
	Papule	0	0
	etc.	0	0

The participants rated the efficacy of the test product on a scale of one to five (1, strongly disagree; ~ 5, strongly agree).

test product are also shown in **Figure 1**. Among these measurement parameters, dermis denseness monitored by ultrasonic images showed the most remarkable changes, and representative images are shown in **Figure 2**.

Self-survey results are shown in **Table 5**. The participants agreed that the test product gradually improved skin condition.

No subjective and objective adverse skin reactions were reported during the study (**Table 6**).

4. Discussion

The Ministry of Food and Drug Safety of Korea has issued guidelines for human skin testing for the anti-aging effects of cosmetics, involving instrumental analyses of facial skin wrinkle, sagging, elasticity, dermis denseness, moisture, and brightness/color. Thus, the current study complies with the guideline.

Skin aging is usually divided into the intrinsic and extrinsic types[2,3]. Intrinsic skin aging inevitably occurs as a natural consequence of physiological changes over time, and it is largely dependent on individual genetics. The factors related to intrinsic skin aging include ethnicity, anatomic variations, and hormonal changes. Extrinsic skin aging is due to external factors such as solar exposure, drugs, smoking, diet, lifestyle, and overall health, and thus it is more controllable than intrinsic skin aging.

There are several strategies for treatments of aging skin[2,3]. The first approach aims at preventing photo-

aging using sunscreens with chemical or physical UV filters. The second strategy uses active substances to postpone or even reduce the signs of skin aging. The third strategy uses more invasive mechanisms, such as chemical peeling, use of lasers, injection of fillers and botulinum toxin, and so forth.

Resveratrol has bioactivities useful for the prevention of skin aging[9,10], as the second strategy mentioned above. RTA is a prodrug form of resveratrol. RTA was more stable in cosmetic formulations than resveratrol, and shows a high level of melanin inhibition efficacy and safety at the cellular level[17]. In addition, its human skin depigmenting effects of cosmetics containing RTA have been reported previously[18,19].

The present demonstrated the human skin anti-aging effects of a cosmetic product containing 8000 PPM of RTA. In 4 to 8 weeks, the test product reduced wrinkles and sagging, while increasing skin elasticity, dermis denseness, moisture, and brightness. Some of these changes were perceived by the participants. No adverse skin reactions were reported during the use of the test product. Because the control product without RTA was not examined in the current study, the anti-aging effect of the test cream may not be attributed solely to RTA. Other ingredients of the test cream could also contribute to the anti-aging effects.

5. Conclusion

In conclusion, this study demonstrates the human skin anti-aging effects of a cosmetic product containing RTA.

Acknowledgments

This study was supported by the Korea Health Technology R&D Project of the Ministry of Health & Welfare (HN12C0051), and the Technological Innovation R&D Program (No. S2486152) of the Ministry of SMEs (Small and Medium-Sized Enterprises) and Startups, Republic of Korea. Parts of this study were presented as a poster at IFSCC 2017 Conference in Seoul, Korea, 2017.

References

1. R. Honigman and D. J. Castle, Aging and cosmetic enhancement, *Clin. Interv Aging*. **1**(2), 115 (2006).
2. R. Ganceviciene, A. I. Liakou, A. Theodoridis, E. Makrantonaki, and C. C. Zouboulis, Skin anti-aging strategies, *Dermatoendocrinol*., **4**(3), 308 (2012).
3. M. Ramos-e-Silva, L. R. Celem, S. Ramos-e-Silva, and A. P. Fucci-da-Costa, Anti-aging cosmetics: facts and controversies, *Clin. Dermatol*., **31**(6), 750 (2013).
4. Y. R. Helfrich, D. L. Sachs, and J. J. Voorhees, Overview of skin aging and photoaging, *Dermatol. Nurs*., **20**(3), 177 (2008).
5. K. P. Wilhelm, A. B. Cua, and H. I. Maibach, Skin aging. Effect on transepidermal water loss, stratum corneum hydration, skin surface pH, and casual sebum content, *Arch. Dermatol*., **127**(12), 1806 (1991).
6. K. Tsukahara, K. Sugata, O. Osanai, A. Ohuchi, Y. Miyauchi, M. Takizawa, M. Hotta, and T. Kitahara, Comparison of age-related changes in facial wrinkles and sagging in the skin of Japanese, Chinese and Thai women, *J. Dermatol. Sci*., **47**(1), 19 (2007).
7. M. Engelke, J. M. Jensen, S. Ekanayake-Mudiyanselage, and E. Proksch, Effects of xerosis and ageing on epidermal proliferation and differentiation, *Br. J. Dermatol*., **137**(2), 219 (1997).
8. J. P. Ortonne, Pigmentary changes of the ageing skin, *Br. J. Dermatol*., **122**(Suppl 35), 21 (1990).
9. P. Farris, J. Krutmann, Y. H. Li, D. McDaniel, and Y. Krol, Resveratrol: a unique antioxidant offering a multi-mechanistic approach for treating aging skin, *J. Drugs Dermatol*., **12**(12), 1389 (2013).
10. R. A. Baxter, Anti-aging properties of resveratrol: review and report of a potent new antioxidant skin care formulation, *J. Cosmet. Dermatol*., **7**(1), 2 (2008).
11. R. Yutani, R. Teraoka, and S. Kitagawa, Microemulsion using polyoxyethylene sorbitan trioleate and its usage for skin delivery of resveratrol to protect skin against UV-induced damage, *Chem. Pharm. Bull. (Tokyo),* **63**(9), 741 (2015).
12. G. Fabbrocini, S. Staibano, G. De Rosa, V.

Battimiello, N. Fardella, G. Ilardi, M. I. La Rotonda, A. Longobardi, M. Mazzella, M. Siano, F. Pastore, V. De Vita, M. L. Vecchione, and F. Ayala, Resveratrol-containing gel for the treatment of acne vulgaris: a single-blind, vehicle-controlled, pilot study, *Am. J. Clin. Dermatol*., **12**(2), 133 (2011).

13. V. Karuppagounder, S. Arumugam, R. A. Thandavarayan, V. Pitchaimani, R. Sreedhar, R. Afrin, M. Harima, H. Suzuki, M. Nomoto, S. Miyashita, K. Suzuki, and K. Watanabe, Resveratrol attenuates HMGB1 signaling and inflammation in house dust mite-induced atopic dermatitis in mice, *Int. Immunopharmacol*., **23**(2), 617 (2014).
14. S. Caglayan Sozmen, M. Karaman, S. Cilaker Micili, S. Isik, Z. Arikan Ayyildiz, A. Bagriyanik, N. Uzuner, and O. Karaman, Resveratrol ameliorates 2,4-dinitrofluorobenzene-induced atopic dermatitis-like lesions through effects on the epithelium, *Peer J*., **4**, 1 (2016).
15. J. Park, and Y. C. Boo, Isolation of resveratrol from vitis viniferae caulis and its potent inhibition of human tyrosinase, *Evid. Based Complement. Alternat. Med*., **2013**, 1 (2013).
16. C. B. Lin, L. Babiarz, F. Liebel, E. Roydon Price, M. Kizoulis, G. J. Gendimenico, D. E. Fisher, and M. Seiberg, Modulation of microphthalmia-associated transcription factor gene expression alters skin pigmentation, *J. Invest. Dermatol*., **119**(6), 1330 (2002).
17. J. Park, J. H. Park, H. J. Suh, I. C. Lee, J. Koh, and Y. C. Boo, Effects of resveratrol, oxyresveratrol, and their acetylated derivatives on cellular melanogenesis, *Arch. Dermatol. Res*., **306**(5), 475 (2014).
18. J. H. Ryu, J. K. Seok, S. M. An, J. H. Baek, J. S. Koh, and Y. C. Boo, A study of the human skin-whitening effects of resveratryl triacetate, *Arch. Dermatol. Res*., **307**(3), 239 (2015).
19. Y. C. Boo, Clinical evaluation of skin whitening effect of a cream containing resveratryl triacetate, *Fragrance J. Korea*, **2016**(3), 72 (2016).
20. P. M. Friedman, G. R. Skover, G. Payonk, A. N. Kauvar, and R. G. Geronemus, 3D in-vivo optical skin imaging for topographical quantitative assessment of non-ablative laser technology, *Dermatol. Surg*., **28**(3), 199 (2002).
21. N. Saito, T. Nishijima, T. Fujimura, S. Moriwaki, and Y. Takema, Development of a new evaluation method for cheek sagging using a Moire 3D analysis system, *Skin Res. Technol*., **14**(3), 287 (2008).
22. H. S. Ryu, Y. H. Joo, S. O. Kim, K. C. Park, and S. W. Youn, Influence of age and regional differences on skin elasticity as measured by the Cutometer, *Skin Res. Technol*., **14**(3), 354 (2008).
23. H. J. Hahn, H. J. Jung, M. C. Schrammek-Drusios, S. N. Lee, J. H. Kim, S. B. Kwon, I. S. An, S. An, and K. J. Ahn, Instrumental evaluation of anti-aging effects of cosmetic formulations containing palmitoyl peptides, Silybum marianum seed oil, vitamin E and other functional ingredients on aged human skin, *Exp. Ther. Med*., **12**(2), 1171 (2016).
24. A. Taub, V. Bucay, G. Keller, J. Williams, and D. Mehregan, Multi-center, double-blind, vehicle-controlled clinical trial of an alpha and beta defensin-containing anti-aging skin care regimen with clinical, histopathologic, immunohistochemical, photographic, and ultrasound evaluation, *J. Drugs Dermatol*., **17**(4), 426 (2018).
25. H. Tagami, M. Ohi, K. Iwatsuki, Y. Kanamaru, M. Yamada, and B. Ichijo, Evaluation of the skin surface hydration *in vivo* by electrical measurement, *J. Invest. Dermatol*., **75**(6), 500 (1980).
26. G. E. Pierard, EEMCO guidance for the assessment of skin colour, *J. Eur. Acad. Dermatol. Venereol*., **10**(1), 1 (1998).
27. Y. K. Seo, S. J. Kim, Y. C. Boo, J. H. Baek, S. H. Lee, and J. S. Koh, Effects of p-coumaric acid on erythema and pigmentation of human skin exposed to ultraviolet radiation, *Clin. Exp. Dermatol*., **36**(3), 260 (2011).