Integrative Medicine Research 11 (2022) 100752

Contents lists available at ScienceDirect

Integrative Medicine Research

journal homepage: www.elsevier.com/locate/imr

Original Article

Wrinkle reduction using a Sasang constitutional medicine-based topical herbal cream in So-eum subjects: A split-face randomized double-blind placebo-controlled study

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ARTICLE INFO

Article history:
Received 7 July 2020
Revised 27 May 2021
Accepted 30 May 2021
Available online 23 June 2021

Keywords:
Anti-wrinkle
Herbal medicine
Sasang constitutional medicine
So-eum type

ABSTRACT

Background: Skin aging is caused by exogenous and endogenous factors and is commonly manifested as wrinkling, sagging, and looseness of the skin. The herbal extract including *Zingiber officinale* Roscoe, *Atractylodes chinensis* (Bunge) Kodiz, *Curcuma longa* L., and *Cinnamomum cassia* (L.) J.Presl (ZACC extract), is widely used for So-eum (SE) Sasang constitutional type individuals. This study aimed to examine the protective effects of the ZACC extract against skin aging in 21 SE type subjects.

Methods: The safety and clinical efficacy of herbal cream were evaluated after application on human skin in a split-face randomized, double-blind, placebo-controlled study. The Sasang Constitution Analysis Tool (SCAT) was used to select 21 SE type subjects, who applied herbal cream and placebo cream for 12 weeks. Visual assessment, wrinkle parameters, questionnaires, and skin safety were evaluated.

Results: The visual assessment score was decreased by using of the herbal cream, but there were no significant differences between groups. Among the wrinkle parameters, R1 (skin roughness) and R4 (smoothness depth) values were significantly improved after the application of the herbal cream compared to those observed after application of the placebo cream for 12 weeks. No significant differences were observed in evaluation of the product efficacy and usability by questionnaires. There were no adverse dermatologic reactions in the SE type subjects during the evaluation period.

Conclusion: The ZACC herbal cream may be used to prevent or slow skin aging, including wrinkle formation, in SE type individuals.

1. Introduction

In the Korean system of Sasang constitutional medicine (SCM), individuals are classified into four Sasang constitutional (SC) types: Tae-eum (TE), So-eum (SE), Tae-yang (TY), or So-yang (SY). This SCM classification is based on the temperament, physical characteristics, such as body and face shapes, voice, skin characteristics, and visceral organ functions of an individual. [1,2] The skin characteristics of each SC type are different: TY type individuals typically have thin and white skin; SY type individuals have thin, smooth, and resilient skin; TE type individuals have thick and rough skin with large pores; and SE type individuals have soft and delicate skin.[3] Perspiration is an important factor that is used to distinguish between the different SC types, especially the TE and SE types.[4] Deep wrinkles are associated with the skin of TE type individuals, whereas fine wrinkles that develop at a relatively young age

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https://doi.org/10.1016/j.imr.2021.100752

are associated with the skin of SE type individuals.[2,5,6] Additionally, skin diseases disrupt the health status of different SC types through distinct mechanisms.[7]

Skin wrinkle is related with extrinsic factor like ultraviolet (UV). Repeated and chronic exposure of skin to UV radiation induces changes in the clinical, histological, and functional characteristics of skin including the breakdown of collagen fibers in the skin due to the increase in expression of matrix metalloproteinase (MMP) enzymes such as MMP-1.[8] These processes lead to changes in structural integrity in the dermis, resulting in wrinkle formation.[9]

The herbal formulation known as ZACC is a used herbal medicine that is especially beneficial for SE type skin. ZACC contains "*Zingiber officinale* Roscoe", "*Atractylodes Chinensis* (Bunge) Kodiz", "*Curcuma longa* L.", and "*Cinnamomum cassia* (L.) J.Presl". Topical application of *Zingiber officinale* extract at a suberythemal dose on the skin of rats or hairless mice significantly inhibited chronic UVB-induced wrinkle formation and prevented the loss of skin elasticity.[10] *Atractylodes chinensis* is a well-studied herb reported to contain polyacetylenic compounds, sesquiterpenoids, triterpenoids, steroids, and coumarin.[11] *Curcuma longa* extract changes skin thickness, decreases pigmentation and wrinkles, increases elasticity, and inhibits MMP-2 expression in chronic UVB-induced hairless mice.[12] *Cinnamomum cassia* has anti-inflammatory and anti-oxidant activities.[13] However, in spite of the information available about the individual herbal components of ZACC, the herbal formulation containing all four herbs has not been studied in terms of clinical trial. Thus, this study aimed to evaluate the safety and protective effects of a topical application of ZACC on wrinkle formation in the skin of SE type subjects.

2. Methods

2.1. Participants

The detailed methodology of this study has been described in our previous reports.[14–16] For determination of SE type before the study, the subjects were asked to fill out the Sasang Constitution Diagnostic Survey, their body mass index (using Inbody® 330; Biospace, Korea) and body circumference were measured, and they were photographed. The SE subjects were selected by using a Sasang Constitution Diagnosis Program (SCAT, Sasang Constitutional Analysis Tool) developed by the Korea Institute of Oriental Medicine.[17]

2.1.1. Inclusion criteria

(1) Adult males and females aged 30 to 65 and who have wrinkles on the test site according to the judgment of the main examiner.
(2) Subjects who are SE type
(3) Healthy persons without major or chronic physical diseases including skin diseases.
(4) Applicants who voluntarily sign a written consent form after being sufficiently explained about the purpose and content of the test before the test.
(5) Those who can follow up during the test period.

2.1.2. Exclusion criteria

(1) Pregnant, lactating, or planning to become pregnant within 6 months.
(2) In the case of using a skin cosmetic product containing steroids for more than 1 month for the treatment of skin diseases.
(3) Six months have not passed since participating in the same experiment.
(4) In the case of having sensitive or irritable skin.
(5) In case of skin abnormalities such as spots, acne, erythema, and expansion of capillaries on the test site.
(6) If the same or similar cosmetics or medicines are used on the test site within 3 months of starting the test.
(7) In the case of having a procedure (skin dermabrasion, botox, other skin care, etc.) on the test site or having a plan within 6 months.
(8) In the case of having chronic diseases (asthma, diabetes, high blood pressure, etc.).
(9) When the test is judged to be difficult by the main tester's judgment.

2.2. Randomization and blinding

Using block randomization, subjects are randomized within the blocks such that an equal number are assigned to each treatment. For example, given a block size of 4, we followed six possible ways to evenly assign subjects to blocks (AABB, ABAB, BBAA, BABA, BAAB, ABBA). The products blinding and labeling were performed by manufacture after delivered to the investigative sites. So, investigator and subjects did not realize about test product and placebo. Until completion of the study, the product information (whether ZACC herbal cream or placebo cream) was replaced with "Product A" or "Product B" as blind codes, and the group information was represented with "Group 1″ or "Group 2″.

2.3. Intervention

2.3.1. Preparation of ZACC extract and ZACC cream (herbal cream)

The preparation of herbal extracts and cream has been described previously.[14,15] Briefly, dried *Zingiber officinale* Roscoe, *Atractylodes chinensis* (Bunge) Koidz., *Curcuma longa* L., and *Cinnamomum cassia* (L.) J.Presl (ZACC) were mixed in a ratio of 1:6:3:1. The ZACC mixture was extracted under reflux for 3 h with 15 × the volume of distilled water. The ZACC extract was then filtered and lyophilized to obtain ZACC powder. The cream base contained water, butylene glycol, glycerin, cyclohexasiloxane, cyclopentasiloxane, cetearyl alcohol, cetearylglucoside, cetyl ethylhexanoate, betaine, 1,2-hexanediol, sodium acrylate/sodium acryloydimethyl taurate copolymer, isohexadecane, polysorbate 80, β-glucan, sodium hyaluronate, polysorbate 60, glyceryl stearate, PEG-100 stearate, tocopheryl acetate, lavender oil, allantoine, xanthan gum, and disodium EDTA. The cream without ZACC extract (placebo cream) and the cream with 1% ZACC extract (herbal cream) were used in the study as control and test groups, respectively.

2.3.2. Procedures

The subjects had 2 weeks wash-out period before start of the study. During this period, the use of functional products that can affect testing was prohibited. The subjects were divided into two groups for a split-face, randomized, double-blinded, placebo-controlled study. Group 1 had to apply the ZACC cream on the right side of the face and the placebo cream on the left side of the face. Group 2 had to apply the placebo cream on the right side of the face and the ZACC cream on the left side of the face. The subjects had to cleanse their faces using a toner and then apply the ZACC cream product A; test group) and the placebo cream (product B; control group) to the area around their eyes twice daily for 12 weeks. At every visit (baseline, 4 weeks, 8 weeks, and 12 weeks), all subjects were to be examined for wrinkles after washing the test area of their face and then resting for 30 min in a room with controlled temperature (22 ± 2 °C) and humidity (50 ± 5%). Primary outcome measurement was skin wrinkle parameters and visual assessment and secondary outcome measurement was use of evaluation questionnaires.

2.4. Primary outcomes measures

2.4.1. Evaluation of skin wrinkle parameters

The evaluation of skin wrinkle parameters has been described previously.[14,15] Skin wrinkle parameters were determined in each assessment session after analyzing images of skin replicas fabricated by using the Skin Visiometer® SV600 (C + K, Koln, Germany). The images of the replicas were obtained by illuminating the replicas at an angle of 35°, and the shadows produced were automatically quantified. Five wrinkle parameters were defined: skin roughness (R1), maximum roughness (R2), average roughness (R3), smoothness depth (R4), and arithmetic average roughness (R5).

2.5. Secondary outcomes measures

2.5.1. Visual assessment of skin wrinkles

Visual assessment was performed as described previously.[14,15] Briefly, wrinkles around the eyes were independently evaluated under controlled lighting conditions—820 lm, 22 W, and Dayglow color. Visual assessment was performed by two evaluators according to the Ministry of Food and Drug Safety (MFDS). Wrinkles were recorded in 10 stratified grades (in 0.5-point increments) in each assessment. Mean values were calculated from the assessment of both evaluators for statistical analysis. The average was used for the analysis if there is a statistical significance in intraclass Correlation Coefficient (ICC) value between 2 researchers over 0.8.

2.5.2. Use of evaluation questionnaires by subjects

Evaluation questionnaires were used as described previously.[14,15] Briefly, all subjects completed the questionnaire about product efficacy after using the product for 4, 8, and 12 weeks by selecting the most appropriate option from the following options: 1. I do not agree at all, 2. I do not agree, 3. There is no difference, 4. I agree, 5. I strongly agree. All the subjects also completed a questionnaire about product usability at 12 weeks with the following options: 1. It is not good at all, 2. It is not good, 3. It is normal, 4. It is good, 5. It is very good. We analyzed the questionnaires about product usability to determine the number of positive answers (options 4 or 5).

2.6. Evaluation of skin safety

The detailed method for evaluation of skin safety has been described previously.[14,15] Briefly, the safety of the product was assessed by clinical observation for subjective and objective signs by the investigators and the subjects after using the product for 4, 8, and 12 weeks.

2.7. Sample size calculation

According to the guideline for evaluating the effectiveness of functional cosmetics that help improve skin wrinkles established by the MFDS, we recruited over 20 subjects aged between 30 and 65.

2.8. Ethical approval

This research has been approved by Korea Institute of Oriental Medicine and was performed in accordance with the standard operating procedures of the DERMAPRO Ltd (Approval number: 1–220,777-A-N-02-DICN14051). DERMAPRO Ltd. is a clinical research center and operates an independent IRB. In addition, the IRB consists of members who are independent of the test, including outside member. All members prepare a COI (Conflict of interest) before the review. Written informed consent was obtained from all eligible participants prior to the beginning of the study. All procedures for recruitment, selection, and inclusion of subjects in this study were established to provide the participants with clear and precise information, as well as allowing them to appreciate the aims of the project and the consequences of their consent.

2.9. Statistical analysis

Statistical analysis was conducted as described previously,[14,15] using the SPSS® software program version 20 (IBM, USA). Normality distribution was determined by Shapiro-Wilk test and Kurtosis & Skewness (between +2 and −2), and we used paired *t*-test for homogeneity test. All data were analyzed by PP (Per protocol) method. To compare between time points (baseline vs. 4, 8, and 12 weeks), we used repeated measures ANOVA (RM ANOVA) for parametric variables and Wilcoxon signed-ranks test (with Bonferroni correction) for non-parametric variables. To compare between groups, RM ANOVA or repeated measures ANCOVA(RM ANCOVA) was used. If normality is not satisfied, the covariate is set to baseline (0 weeks), the between-subjects variable is set to weeks (4, 8, and 12 weeks), and the between-subjects factor is set to group (test = 1 and control = 2). On visual assessment, the average was used for the analysis if there is statistical significance in Intraclass Correlation Coefficient (ICC) value between 2 investigators over 0.8. Results of self-questionnaires for efficacy were statistically analyzed by Mann-Whitney U test. Self-questionnaires for usability were statistically analyzed by Chi-Square test (or Fisher's exact test). A statistically significant difference was set at $p < 0.05$(*).

3. Results

3.1. Participants flow

Twenty-two SE type women were selected by the Sasang Constitution Diagnosis Program (SCAT, Sasang Constitutional Analysis Toos) developed by the Korea Institute of Oriental Medicine. Among the 22 SE type subjects, one subject was dropped out before starting this study for personal reasons. Hence, we allocated the 21 SE type subjects into two groups (Group 1; $n = 9$, Group 2; $n = 12$) and all subjects completed the follow-up (Fig. 1).

3.2. Baseline characteristics

The ages of 21 SE type subjects were ranged from 35 to 54 years, and their mean age was 45.2 ± 5.2 years. All 21 SE subjects were examined, and their skin characteristics and condition were recorded (Table 1).

3.3. Primary outcomes

3.3.1. Wrinkle parameters in SE subjects

The R1 and R4 values for skin wrinkle was significantly decreased in test group compared to control group (R1; $p = 0.000$, R4; $p = 0.024$) for 12weeks. Compared to before treatment, the decrement rate of R1 was 4.24% and that of R4 was 11.11% at 12weeks. The R2, R3, R5 values for skin wrinkles were no significant differences in both groups (R2; $p = 0.215$, R3; $p = 0.149$, and R5; $p = 0.052$ at 12 weeks) (Fig. 2A–E, Supplementary Table 1–4).

3.4. Secondary outcomes

3.4.1. Visual assessment of skin wrinkles

The visual assessment score showed tendency to decreased slightly in test group (before; 5.55, after 12 weeks; 5.50) and control group (before; 5.48, after 12 weeks; 5.45) for 12 weeks. There was no difference between both groups ($p = 0.329$) (Fig. 3A, Supplementary Table 5).

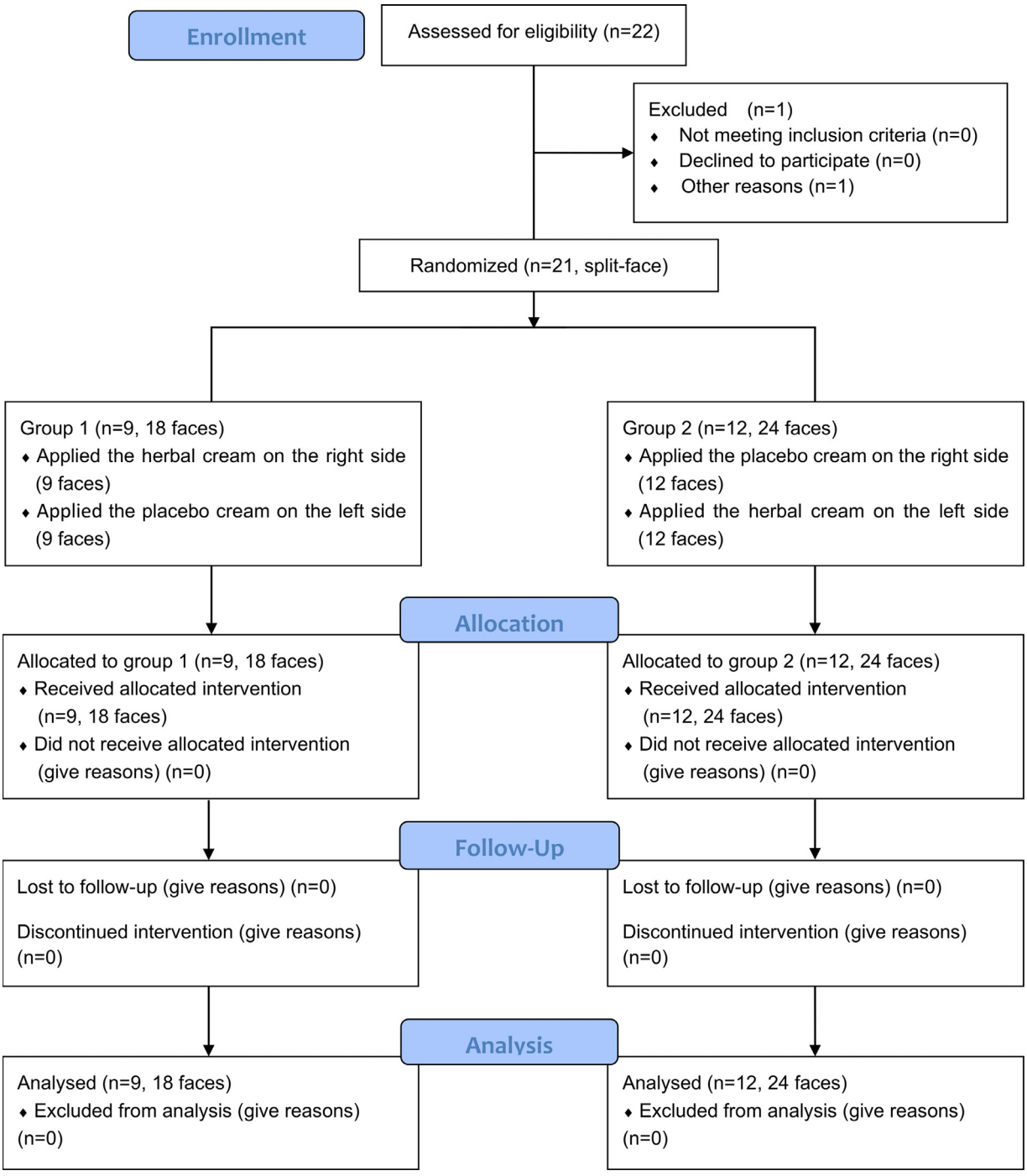

Fig. 1. The participants flow.

3.4.2. Analysis of efficacy questionnaire

After application of the placebo cream and herbal cream for 12 weeks, 71.43–90.48% of the 21 SE subjects responded positively to items such as "Increase in skin moisture ($p = 0.796$)", "Improvement in skin smoothness ($p = 0.824$)", "Increase in skin gloss ($p = 0.641$)", "Improvement in skin elasticity around crow's feet ($p = 0.621$)", and "Decrease in (fine) wrinkles ($p = 1.000$)" (Fig. 3B). However, no significant difference could be observed between the control (placebo cream) and test (herbal cream) groups.

3.4.3. Analysis of product usability questionnaire

Among the 21 SE subjects, 61.90–80.95% of the subjects responded positively to the parameters of "Color ($p = 0.735$)", "Scent ($p = 0.676$)", "Viscosity ($p = 0.896$)", "Absorption ($p = 0.906$)", and "Satisfaction ($p = 1.000$)" in both the test (herbal cream) and control (placebo cream) groups (Fig. 3C). However, there were no significant differences between the control (placebo cream) and test (herbal cream) groups.

3.5. Adverse events

No adverse dermatologic reactions were observed in the 21 SE subjects during the evaluation period (Supplementary Table 6).

Table 1
Skin characteristics and condition of volunteers ($n = 21$).

Item	Classification	Frequency (N)	Percentage
Age	30′s	4	19.05
	40′s	13	61.90
	50′s	4	19.05
Skin type	Dry	10	47.62
	Normal	6	28.57
	Oily	2	9.52
	Dry and oily	3	14.29
	Problematic	0	0.00
Hydration	Sufficient	0	0.00
	Normal	11	52.38
	Deficient	10	47.62
Sebum	Glossy	1	4.76
	Normal	11	52.38
	Deficient	9	42.86
Surface	Smooth	5	23.81
	Normal	13	61.90
	Rough	3	14.29
Thickness	Thin	8	38.10
	Normal	12	57.14
	Thick	1	4.76
Duration of UV exposure (hours)	Less than 1	6	28.57
	1–3	10	47.62
	More than 3	5	23.81
Sleeping hours	Less than 5	1	4.76
	5–8	18	85.71
	More than 8	2	9.52
Smoking	No	21	100.00
	Less than 10 pieces	0	0.00
	More than 10 pieces	0	0.00
Irritability	Yes	3	14.29
	No	18	85.71
Stinging	Yes	2	9.52
	No	19	90.48
Adverse reaction	Yes	0	0.00
	No	21	100.00

4. Discussion

The ZACC herbal cream decreased the visual assessment score, but no significant differences were observed between groups. In the wrinkle parameters, the ZACC herbal cream significantly improved the value of skin roughness and smoothness depth. The evaluation of product efficacy and usability was showed no significant differences. And no adverse dermatologic reactions were observed during the evaluation period.

In ideological viewpoint of the SCM, there have been several attempts to differently treat the same diseases according to their SC types.[18–20] However, evidence for the treatment of appropriate prescriptions against to the suitable SC types is not fully studied yet. In our previous studies, wrinkle formation was reduced in 20 TE subjects by treatment with *Scutellaria baicalensis* and *Raphanus sativus* (SR) extract, which is a well-known component of “Cheongpyesagan-tang”, a formulation used for TE type individuals.[14] Treatment with *Coptis teeta* and *Trichosanthes rosthornii* (CT) extract, a component of “Hwangryeonjiwhang-tang”, a formulation used exclusively for SY type individuals, reduced wrinkle formulation in 21 SY subjects.[15] Likewise, our results showed that treatment with ZACC extract reduced wrinkle formation of 21 SE type subjects.

Skin rejuvenation activity of ZACC is possibly related with the components of ZACC. There are many beneficial reports regarding human health in terms of clinical trials. Among the components of ZACC, ginger is reported to have clinical benefits based on randomized clinical trials (RCTs) like muscle pain, nausea, vomiting, diabetes, cancer, digestive function, and irritable bowel syndrome. More than 100 chemical compounds were isolated from ginger, especially gingerol is considered to possess bioactivities based on antioxidant, antimicrobial, and anti-inflammation.[27] The potential of curcumin from *Curcuma longa* in skin disorders also contributes its role of ZACC. Curcumin is used for the treatment of inflammatory skin diseases, psoriasis, atopic dermatitis, and skin aging from ancient to present.[21,22] *Cinnamomum cassia* also has various activities due to chemical constituents such as terpenoids, phenylpropanoids, glycosides, etc. Recent studies have confirmed that it has a wide range of pharmacological effects, including tumor, inflammation, diabetes, obesity, and other activities.[23] Finally, Atractylenolide I, a bioactive compound isolated from *Atractylodes chinensis* is reported to control inflammatory disorders.[24] Thus, the potential activity

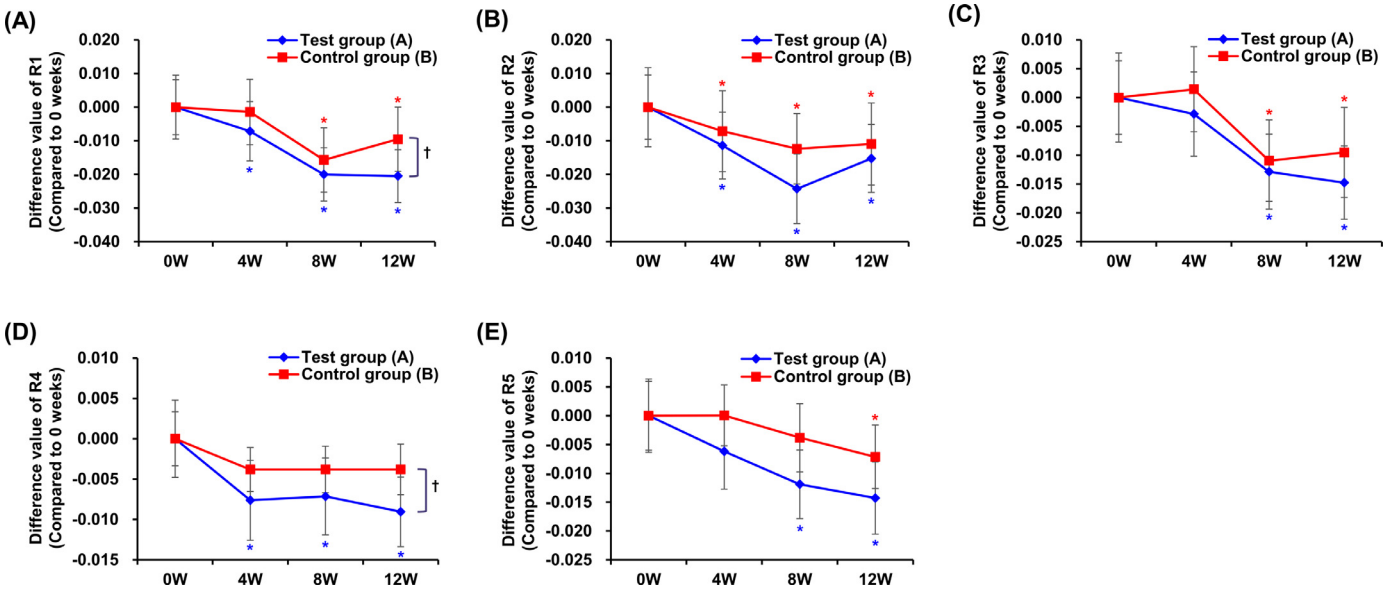

Fig. 2. Evaluation of wrinkle parameters in skin replicas of SE subjects. The SE subjects were treated with the herbal cream (product A, test group) and placebo cream (product B, control group) for 12 consecutive weeks. Wrinkle parameters such as (A) skin roughness (R1), (B) maximum roughness (R2), (C) average roughness (R3), (D) smoothness depth (R4), and (E) arithmetic average roughness (R5) were assessed at 0, 4, 8, and 12 weeks. Data are presented as difference in the values of each parameters' change (mean ± standard error of the mean (SEM)) ($n = 21$, each group). $^{*}p < 0.05$ vs. before treatment (0 W); RM ANOVA, $^{\dagger}p < 0.05$ vs. control group; RM ANOVA. SE, So-eum; ZACC, extract of mixture of *Zingiber officinale, Atractylodes chinensis, Curcuma longa,* and *Cinnamomum cassia.*

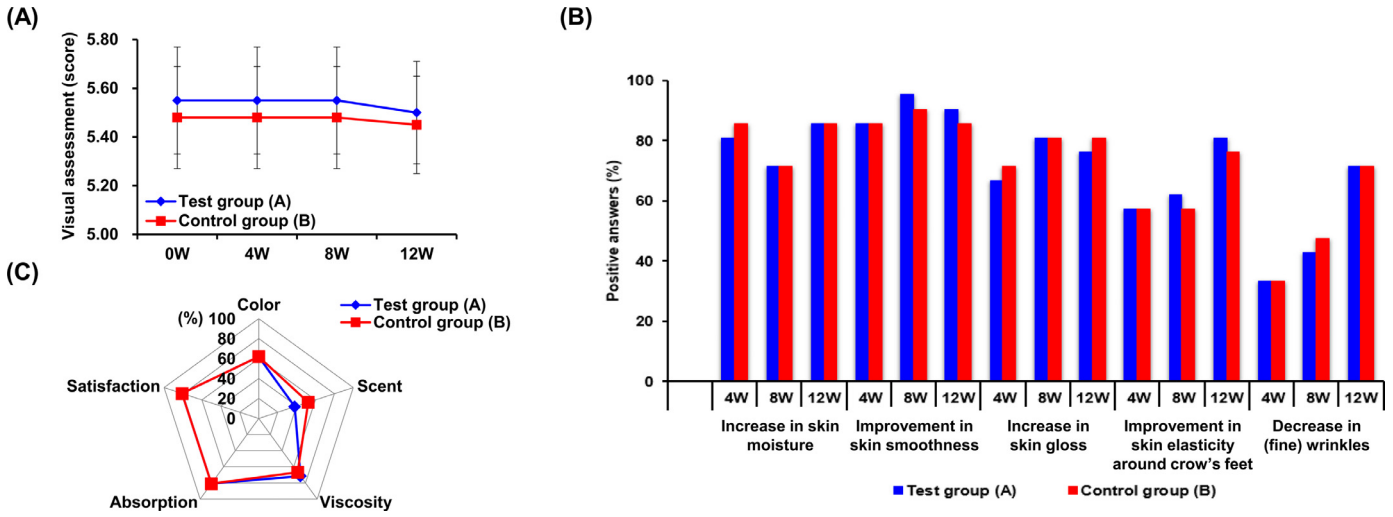

Fig. 3. Evaluation of secondary outcomes in SE subjects. (A) Changes of visual assessment score were analyzed for 12 consecutive weeks, and data are presented as the mean ± standard error of the mean (SEM) ($n = 21$, each group). Comparative sensory profiles of the test and control groups for (B) product efficacy and (C) usability questionnaires (in terms of positive answers%). Test group: herbal cream (product A), Control group: placebo cream (product B). ZACC, extract of mixture of *Zingiber officinale, Atractylodes chinensis, Curcuma longa,* and *Cinnamomum cassia*.

of ZACC might be related with these multi bioactive compounds working in concert.

In recent years, the SCM has increased the interest in various fields including personalized (or customized) medicine and integrative medicine. The SCM inherently categorized the human beings as the SC types and offered important benefits through the specific diagnoses and treatments of one's holistic health status, thus it could be considered a prototype of personalized medicine.[1,2,25,26] This study and our previous studies[14,15] were designed according to SCM, and it showed ameliorating effects of each SC type herbal medicine on skin wrinkle formation in the respective SC type subjects. Thus, we suggest that our findings would be useful information for personalized medicine and integrative medicine field.

In this study, it was difficult to see the results of SE include men because it was conducted only on women. The gender distribution was uneven. In addition, 20 people were tested in accordance with the MFDS guidelines, which met the purpose of evaluating functional cosmetics, but were somewhat insufficient to represent the Sasang constitution. However, if more research is carried out in the future, it seems possible to find out the differences on gender and Sasang constitution, and it apply them to personalized (or customized) cosmetics.

In conclusion, our results indicate that the ZACC extract maybe apply to prevent or slow skin aging including wrinkle formation in SE type individuals. Moreover, this study provides scientific evidence for improving symptoms by the right original prescription according to the SCM, and our findings would be useful information for personalized medicine and integrative medicine field.

CRediT authorship contribution statement

A-Rang Im: Investigation, Writing – original draft. **Kon-Young Ji:** Investigation, Writing – original draft, Writing – review & editing. **Jiho Nam:** Investigation. **Jiwon Yoon:** Investigation. **Seongwon Cha:** Investigation. **Young Kyoung Seo:** Investigation, Data curation. **Sungwook Chae:** Conceptualization, Writing – review & editing, Supervision. **Jong Yeol Kim:** Conceptualization, Project administration.

Conflict of interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

Funding

This study was supported by the Korea Institute of Oriental Medicine (grant number K15301); the National Research Foundation of Korea (NRF) funded by the Ministry of Science, ICT & Future Planning (No. 2006–2005173, NRF-2012–0009830, and NRF-2009–0090900); and the Bio & Medical Technology Development Program of the NRF funded by the Korean government, MSIP (NRF-2015M3A9B6027139).

Ethical statement

This research was conducted under Good Clinical Practices (GCP) regulations according to the Helsinki Declaration. The ethical and scientific validity of this study was reviewed from DERMAPRO Ltd. Institutional Review Board. Furthermore, this study protocol followed the functional cosmetic guidelines of the Ministry of Food and Drug Safety (MFDS) in Korea. The purpose and procedure of this study were explained to the subjects and informed them of potential adverse events (such as erythema, temporary itching, and prickling sensation) and expected efficacy (reduction in wrinkles) of the treatment. In addition, this study was carried out with the voluntary consent of the subjects.

Data availability

The data used to support the findings of this study are available from the corresponding author on reasonable request.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.imr.2021.100752.

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