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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A B S T R A C T

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.

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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 temperamental, 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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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 cellular, 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) Koidiz”, “Curcuma longa L.”, and “Cinnamomum cassia (L.) Presl”.

Topical application of Zingiber officinalis 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 polycyclic aromatic hydrocarbons, sesquiterpenoids, triterpenoids, steroids, and coumarins.\(^11\) 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 Constituitional 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, 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.) 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, butyrene glycol, glycerin, cyclohexsiloxane, cyclopentasiloxane, cetearyl alcohol, cetearlylglycolside, cetyl ethylhexanole, betaine, 1,2-hexanediol, sodium acrylate/sodium acryloyldimethyl tau-rare copolymer, isohexadecane, polysorbate 80, β-glucon, sodium hyaluronate, polysorbate 60, glycerin stearate, PEG-100 stearate, tocopheryl acetate, lavender oil, allantoin, 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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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.\textsuperscript{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 $p < 0.05$(*).
3.4.2. 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          | 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. 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. 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. 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. 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. *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. Finally, Atractylenolide I, a bioactive compound isolated from *Atractylodes chinensis* is reported to control inflammatory disorders. Thus, the potential activity

![Image](image-url)
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. This study and our previous studies 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.

**Conflict of interest**

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

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**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.
References

1. Kim JY, Pham DD, Sasang constitutional medicine as a holistic tailored medicine. *Evid Based Complement Alternat Med*. 2009;6(Suppl 1):11–19.

2. Kim JY, Pham DD, Koh BH. Comparison of Sasang, constitutional medicine, traditional Chinese medicine and Ayurveda. *Evid Based Complement Alternat Med*. 2011:2011.

3. Lee JH, Kim YH, Hwang MW, Kim JY, Lee EJ, Song IB, et al. Survey study about Sasangin’s characteristics of face, voice, skin and pulse diagnosis. *J Sasang Const Med*. 2007;19(3):126–143.

4. Jung SO, Park SJ, Chae H, Park SH, Hwang M, Kim SH, et al. Analysis of skin humidity variation between Sasang types. *Evid Based Complement Alternat Med*. 2009;6(Suppl 1):87–92.

5. Lee SH, Choi SM, Kim HG, Kim JY. Clinical study on the relations of the thickness and the stiffness of back skin of the hand to Sasang constitutions depending on sex and age. *J Physiol Pathol Koreen Med*. 2005;19(2):561–567.

6. Lee SK, Nam KA, Sun BK, Kim SB, Song IB. Correlation between Korean healthy women’s skin condition and Sasang constitution. *J Physiol Pathol Koreen Med*. 2004;25:161–171.

7. Han SJ, Song JM. A case report of Soyangin adult atopic dermatitis patient treatment with Soyangin formulae. *J Sasang Const Med*. 2009;21(3):178–185.

8. Ritté L, Fisher GJ. Natural and sun-induced aging of human skin. *Cold Spring Harb Perspect Med*. 2015;5(1).

9. Quan T, Qin Z, Xia W, Shao Y, Voorhees JJ, Fisher GJ. Matrix-degrading metalloproteinases in photoaging. *J Invest Dermatol Symp Proc*. 2009;14(1):20–24.

10. Tsukahara K, Nakagawa H, Moriwaki S, Takema Y, Fujimura T, Imokawa G. Inhibition of ultraviolet-B-induced wrinkle formation by an elastase-inhibiting herbal extract: implication for the mechanism underlying elastase-associated wrinkles. *Int J Dermatol*. 2006;45(4):460–468.

11. Wang KT, Chen LG, Yang LL, Ke WM, Chang HC, Wang CC. Analysis of the sesquiterpenoids in processed *Atractyloids Rhizoma*. *Chem Pharm Bull (Tokyo)*. 2007;55(1):50–56.

12. Sumiyoshi M, Kimura Y. Effects of a turmeric extract (*Curcuma longa*) on chronic ultraviolet B irradiation-induced skin damage in melanin-possessing hairless mice. *Phytomedicine*. 2009;16(12):1137–1143.

13. Rao PY, Gan SH. Cinnamon: a multifaceted medicinal plant. *Evid Based Complement Alternat Med*. 2014;2014.

14. Im AR, Nam J, Cha S, Seo YK, Chae S, Kim JY. Wrinkle reduction using a topical herbal cream in subjects with greater yin (Tae-eunim)-type: a randomized double-blind placebo-controlled study. *Eur J Integr Med*. 2018;20:173–181.

15. Im AR, Nam J, Ji KY, Cha S, Yoon J, Seo YK, et al. Wrinkle reduction using a topical herbal cream in subjects classified by Sasang constitutional medicine as Soyang type: a randomized double-blind placebo-controlled study. *Eur J Integr Med*. 2020;35.

16. Im AR, Seo YK, Cho SH, O KH, Kim KM, Chae S. Clinical evaluation of the safety and efficacy of a timosaponin AIII-based antiwrinkle agent against skin aging. *J Cosmet Dermatol*. 2020;19(2):423–436.

17. Do JH, Jang E, Ku B, Jang JS, Kim H, Kim JY. Development of an integrated Sasang constitution diagnosis method using face, body shape, voice, and questionnaire information. *BMC Complement Altern Med*. 2012;12:85.

18. Bae J, Kim J, Wei T. A case report of Galgumhaegui-tang applied on erysipelas. *Kor J Ori Med Physiol & Pathol*. 2001;15:571–573.

19. Gu DM. A clinical study based on Sasang, constitutional medicine on the treatment of atopic dermatitis. *J Sasang Const Med*. 2002;14:69–77.

20. Im MK, Song JM. A case study of Taeeumin’s chronic idiopathic urticaria patient. *J Sasang Const Med*. 2008;20(3):190–198.

21. Vollenno I, Falconi M, Gazziano R, Iacovelli F, Dika E, Terracciano C, et al. Potential of curcumin in skin disorders. *Nutrients*. 2019;11(9):2169.

22. Hatcher H, Planalp R, Cho J, Torti FM, Torti SV. Curcumin: from ancient medicine to current clinical trials. *Cell Mol Life Sci*. 2008;65(11):1631–1652.

23. Zhang C, Fan L, Fan S, Wang J, Luo T, Tang Y, et al. *Cinnamomum cassia* Pseud: a review of its traditional uses, photochemistry, pharmacology and toxicology. *Molecules*. 2019;24(19):3473.

24. Hossen MJ, Chou JJ, Li SM, Fu XQ, Yin C, Guo H, et al. An ethanol extract of the rhizome of *Atractylodes Chinese* exerts anti-gastritis activities and inhibits Akt/NF-kB signaling. *J Ethnopharmacol*. 2019;228:18–25.

25. Chae H, Lyoo IK, Lee SJ, Cho S, Bae H, Hong M, et al. An alternative way to individualized medicine: psychological and physical traits of Sasang typology. *J Altern Complement Med*. 2003;9(4):519–528.

26. Song I.B., Sandoval F.E., Gelperin N.R., Society of Sasang constitutional medicine. An introduction to Sasang constitutional medicine. *Jinmoondang: Seoul*. 2005.

27. Anh NH, Kim SJ, Long NP, Min JE, Yoon YC, Lee EG, et al. Ginger on human health: A comprehensive systematic review of 109 randomized controlled trials. *Nutrients*. 2020;12(1):157.