



Efficacy of *Cistanche Tubulosa* and *Laminaria Japonica* Extracts (MK-R7) Supplement in Preventing Patterned Hair Loss and Promoting Scalp Health

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Cistanche tubulosa and *Laminaria japonica* have been reported to have anti-oxidative, anticoagulant, anti-cancer and anti-inflammatory properties. They are expected to be promising candidates for promoting hair growth and treating dandruff and scalp inflammation as a consequence. In this double-blinded, placebo-controlled clinical trial, we investigated the efficacy of *Cistanche tubulosa* extract and *Laminaria japonica* extract complex (MK-R7) in promoting hair health in patients with mild to moderate patterned hair loss. Using phototrichogram (Folliscope 4.0, LeadM, Seoul, Korea), we compared the density and diameter of hairs in patients receiving a placebo or *Cistanche tubulosa* extract and *Laminaria japonica* extract complex (MK-R7) at baseline, 8 and 16 weeks of the study. In order to determine the efficacy of treatment on dandruff and scalp inflammation, investigator's assessment score and patient's subjective score were also performed. We found a statistically significant increase in the hair density of the test group (n = 45, MK-R7 400 mg) after 16 weeks of consuming the MK-R7 (test group: 23.29 n/cm² ± 24.26, control: 10.35 n/cm² ± 20.08, p < 0.05). In addition, we found a statistically significant increase in hair diameter in the test group compared to control group at week 16 (test group: 0.018 mm ± 0.015, control: 0.003 mm ± 0.013, p < 0.05). There were also significant outcomes regarding the investigator's visual assessment and patient's subjective score of dandruff and scalp inflammation in the test group compared to those in control group. Based on the results of this clinical study, we conclude that *Cistanche tubulosa* extract and *Laminaria japonica* extract complex (MK-R7) are promising substances for promoting health of the scalp and hair.

Key Words: *Cistanche tubulosa*, Fucoidan, Hair loss, *Laminaria japonica*, Scalp health, Supplement

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Received March 2, 2015

Revised March 23, 2015

Accepted March 30, 2015

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Introduction

Recently, the occurrence of patterned hair loss has been significantly increased among the middle-aged adults but also among young adults, and has made several hindrances in their social life. This has brought about huge interest in finding a safe and convenient substance that could prevent patterned hair loss and promote the regrowth of hair on the scalp, and it is expected that such a solution would have a correspondingly high market value. Numerous studies has been performed on the treatment of patterned hair loss, but to date, there has not yet been any groundbreaking discovery [1]. As it has been empirically proved applying various treatment methods together is more effective than relying on a single type of treatment in curing patterned hair loss, and many researches in the area of patterned hair loss reflect such an understanding. The existing drug treatments for patients diagnosed with patterned hair loss, a topical agent named Minoxidil [2] and an orally consumed drug named Propecia [3]. However, practical usages of these treatments are limited by adverse reactions of these treatments which include skin irritation, sexual dysfunction, circulatory system issues [4]. Dandruff and scalp inflammation coincided with patterned hair loss are prevalent social health concerns but the topical steroids, most commonly used treatment may have adverse effects if used fin the long term, which necessitates the search for a new treatment.

Fucoidan, a branched sulphated fucan extracted from brown seaweeds and marine plants such as tangleweed (*Laminaria japonica*), wakame (*Undaria pinnatifida Sporophyll*) and limu moui (*Cladosiphon okamuranus*) has been used as an anti-aging remedy in Eastern traditional medicine. Previous studies reported that components of *Laminaria japonica* (LJ) extracts including fucoidan has anti-oxidative, anticoagulant, anti-cancer and anti-inflammatory properties [5,6]. As a result, researchers have focused on determining the efficacy of LJ extract in treating inflammatory diseases, ischemia, decreased immunity and tumors [7,8]. As it has been recently reported that LJ extract has a significant effect in preventing and treating ischemic heart disease due to its thrombolytic properties [9,10], it is hypothesized that fucoidan could be effective in promoting hair growth, improving dandruff and treating inflammation by increasing blood flow to the scalp.

The roots of *Cistanche tubulosa* (CT), a plant that grows in the Taklamakan desert, are also traditionally used as medicine in China. CT has been reported to decrease the generation of TNF- α and IL-4, key cytokines necessary for the release of nitric oxide (NO) from the inflamed cells, and has exhibited pow-

erful anti-inflammatory properties in animal model [11,12]. CT has also been shown to improve blood circulation by lowering blood cholesterol levels [13], and could therefore positively affect in promoting hair growth and treating dandruff and scalp inflammation.

The purpose of this study was to evaluate the effect of CT and LJ extract complex (MK-R7/HGF-R7) on the prevention and treatment of patterned hair loss and the enhancement of scalp and hair health.

Materials and Methods

Study design

In this double-blind, placebo-controlled clinical trial, via using stratified permuted block randomization, a randomization table was composed by a statistician using an allocation code, and MK-R7 and placebo were allocated to the subjects according to a ratio of 1:1 according to the test subject number. Both groups were asked to consume two capsules per day (400 mg/day), one immediately after breakfast and dinner, for a total period of 16 weeks. Participants were forbidden from taking any drugs or supplements related to patterned hair loss improvement throughout the study period. The product used in this study was a complex composed of CT and LJ extract including echinacoside glycosides and fucoidan (MK-R7, Misuba RTech, Asan, Korea), was provided as a hard capsule containing 150mg CT and 50mg LJ, ration of 3:1. In order to compare experimental outcomes according to dosage, capsules containing 200 mg dextrin of the combination product were given to the test group. Placebo capsules consisting of maltodextrin that did not include any CT and LJ were provided in the control group under the same conditions as above.

Subjects

The study was performed with physically and mentally healthy adults ages 20 to 60 diagnosed with mild to moderate patterned hair loss (Males: Type II, IIa, IIv, IIIa or IIIv according to the modified Norwood-Hamilton classification, females: Ludwig classification Type I). Participants who had a history of any skin disorders, endocrine abnormalities, or systemic diseases such as liver function abnormality were excluded from this study. Also individuals who had undergone patterned hair loss treatment, applied topical hair restorer, received surgical treatments for patterned hair loss such as hair transplant and scalp reduction to prevent any influence from other types of treatment were excluded from this study. Pregnant and nurs-

ing women were also excluded from this study. This study was reviewed and approved by the institutional review board of Chung-Ang University hospital C2012223(918) and performed in accordance with the principles of the Declaration of Helsinki and Korean Good Clinical Practice, and with local regulatory requirements. All subjects provided a written informed consent prior to study participation.

Assessment

Hair density and diameter

Prior to initiation of the clinical trial, patients who had hair in the area affected by patterned hair loss shaved to < 2 mm length in the shape of a circle with diameter 1 cm near the crown of the head. An experimental target area at the center of the circle was marked with a 1 mm black dot (tattoo). The density and diameter of their hair were objectively assessed using phototrichogram (Folliscope 4.0, Lead M, Seoul, Korea) before using the product and at 8 and 16 weeks of the product treatment. The density of hair was measured by counting the number of hairs within a 1 cm² of the area. The diameter was measured by calculating the mean value of the diameter of five hairs in the area.

Investigator's assessment score, patient's subjective score

In order to visually assess the improvement of overall patterned hair loss symptoms, dandruff and scalp inflammation, an expert was provided with photographs of the subject's head viewed from above at baseline, and at 8 and 16 weeks of the study. The expert determined the degree of improvement on a 5 point scale (-1: deterioration, 0: no improvement, +1: slight improvement, +2: improvement, +3: remarkable improvement). In order to assess the test subject's perception of improvement in improving patterned hair loss, dandruff and inflammation of the scalp, participants were asked to evaluate the degree of improvement they witnessed on a 5 point scale (-1: unsatisfied, 0: insignificant, +1: somewhat satisfied, +2: satisfied, +3: very satisfied).

Safety

In order to evaluate the safety of the product, the type and frequency of adverse reactions experienced by subjects who consumed the test product or the placebo pill at least one time were assessed. The effects of the product on their physical examination, laboratory examination and vital signs were also assessed.

Statistical analysis

The statistical Analysis tool SPSS (Statistical Package for Social Sciences, SPSS Inc., Chicago, IL, USA) 19.0 was used to assess the efficacy of the test product. Statistically significant differences between the test group and control group from parametric tests, at $p < 0.05$ level, were determined by paired sample t-test. Statistically significant differences before and after use of the product for each group were determined through analysis of variance (ANOVA). For non-parametric tests, the Wilcoxon signed ranks test was used. The values for compliance after use of test product, investigator's visual assessment, the effect of scalp improvement, and user's preference toward the product were assessed and reported as mean and standard deviation.

Results

General characteristics of the subjects

In this study each group had at least 45 subjects which is valid enough to generate 80% power at 5% of significance level and, considering 10% of drop-out, 50 subjects were assigned to each group. Among the 100 persons who participated in the test, 5 persons in the test group and 1 person in the control group were omitted due to resignation and follow up loss, leading to a total of 94 persons participating in the experiment. There were no participants who were omitted due to adverse drug reactions. The percentage of male subjects in the test group were 42.22% (19/45 persons) and the percentage of female subjects were 57.78% (26/45). In the control group, the percentage of male participants was 55.10% (27/49 persons) and female participants was 44.89% (22/49 persons), showing no significant difference between the two groups with regard to gender distribution ($p = 0.2121$). The average of subjects' age was 40.80 ± 9.70 for the test group and 41.39 ± 11.27 for the control group and no significant difference in age was found between the two groups ($p = 0.7879$). There was also no significant difference between the two groups in the number of subjects over the age of 40 ($p = 0.7295$). The demographic information of each group is shown in Table 1, and no statistically significant differences were found between the two groups.

Changes in hair density

The mean hair density of the test group was 159.56 ± 28.34 (n/cm²) prior to product consumption, 168.93 ± 30.92 (n/cm²) after

Table 1. Demographic characteristics of the subjects

Characteristics		Test group	Control	p value
		n = 45	n = 49	
		n (%)	n (%)	
Sex	Male	19 (42.22)	27 (55.10)	0.2121 [†]
	Female	26 (57.78)	22 (44.89)	
Age	Mean ± SD	40.80 ± 9.70	41.39 ± 11.27	0.7879 [*]
	Median	43.00	44.00	
	Min, Max	21.00, 57.00	21.00, 59.00	
Age	20-29	8 (17.78)	9 (18.37)	0.7295 [†]
	30-39	10 (22.22)	11 (22.45)	
	40-49	18 (40.00)	15 (30.61)	
	≥ 50	9 (20.00)	14 (28.57)	

*Unpaired t-test; [†]Chi-square test.

8 weeks of consumption, and 182.84 ± 32.98 (n/cm^2) at 16 weeks of product consumption. The control group showed a mean hair density of 150.18 ± 39.57 (n/cm^2) prior to product consumption, 154.76 ± 38.28 (n/cm^2) after 8 weeks of consumption, and 160.53 ± 37.55 (n/cm^2) after 16 weeks of consumption. Thus, all subjects in this clinical trial experienced an increase in hair density (Figure

1). At week 16, the degree of change in hair density was greater in the test group at 23.29 ± 24.26 , versus 10.35 ± 20.08 in the control group. This increase in hair density experienced by the test group was statistically significant in comparison to the control group ($p = 0.0036$) (Figure 2).

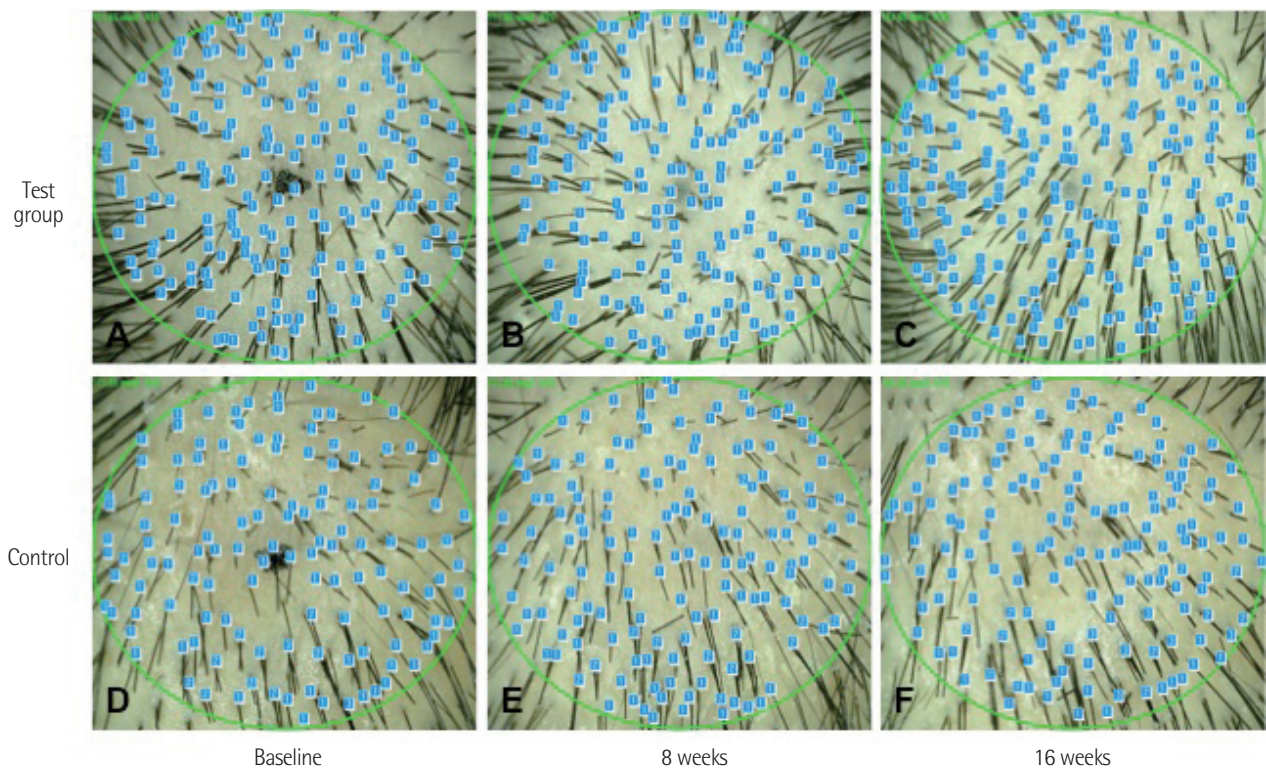


Figure 1. Folliscope of hair density at baseline (A, D), 8 weeks (B, E) and 16 weeks (C, F) after MK-R7 or placebo treatment.

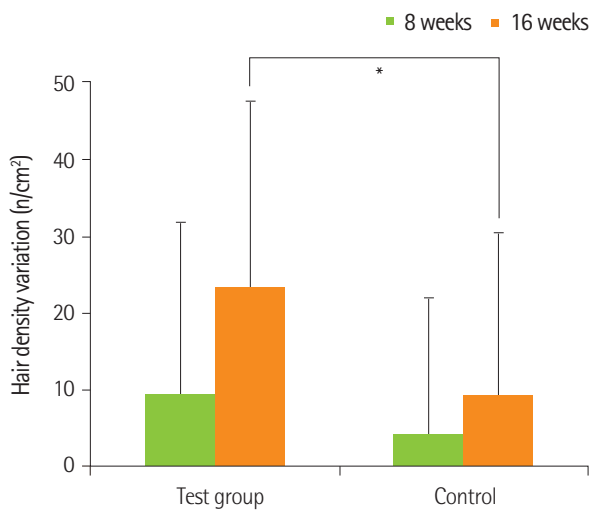


Figure 2. Hair density variation. *Significant differences were detected between groups by Wilcoxon signed ranks test with $p < 0.05$.

Changes in hair diameter

The mean hair diameter of the test group was 0.063 ± 0.014 (mm) prior to product consumption, 0.079 ± 0.045 (mm) after 8 weeks of consumption, and 0.086 ± 0.018 (mm) after 16 weeks of consumption. In contrast, the control group showed

diameters of 0.071 ± 0.029 (mm) prior to consumption, 0.079 ± 0.045 (mm) after 8 weeks of consumption, and 0.077 ± 0.015 (mm) after 16 weeks of consumption. Hence, all groups witnessed an increase in hair thickness after the clinical trial (Figure 3). At 8 weeks, the change in hair diameter was 0.016 ± 0.031 (mm) in the test group and 0.008 ± 0.016 (mm) for the control group, indicating increases of hair diameter in both groups, though the difference between these values was not statistically significant ($p > 0.05$). However, at 16 weeks, the test group showed a statistically significant increase in hair diameter compared to the control group (0.018 ± 0.015 versus 0.003 ± 0.013 , $p = 0.0045$) (Figure 4).

Investigator's assessment score

All patients were assessed by a blinded investigator who assigned visual assessment scores of clinical improvement of patterned hair loss at each time point. At 8 weeks, both groups had shown some improvement in mean scores, as the test group received 0.52 ± 0.66 , and the control group received 0.24 ± 0.63 however the difference between the two groups was not statistically significant ($p > 0.05$). At 16 weeks, both groups showed increases in assessment scores, as the test group received 0.64 ± 0.78 , and the control group 0.51 ± 0.82

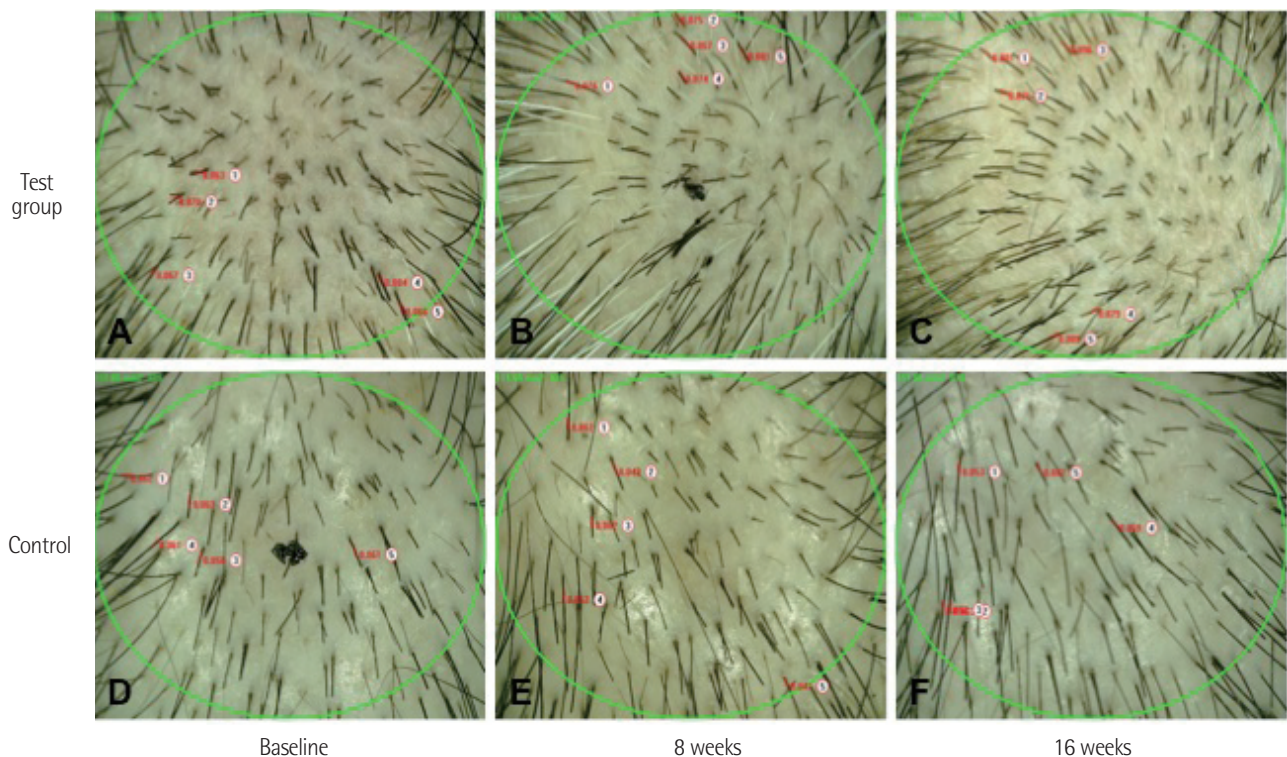


Figure 3. Folliscope of hair thickness at baseline (A, D), 8 weeks (B, E) and 16 weeks (C, F) after MK-R7 or placebo treatment.

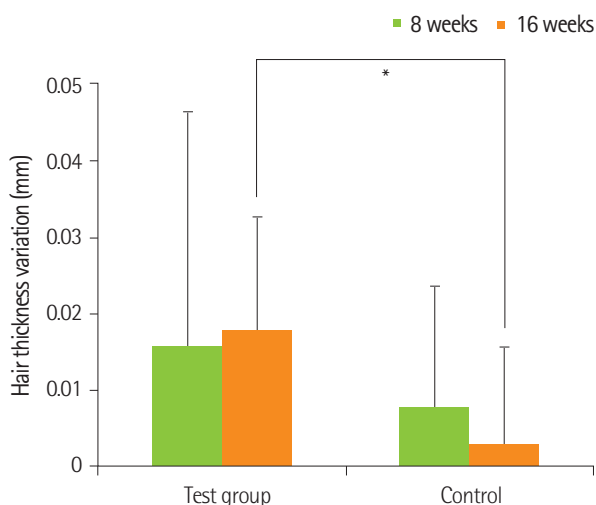


Figure 4. Hair thickness variation. *Significant differences were demonstrated between groups by Wilcoxon signed ranks test at $p < 0.05$.

but the difference between the groups was not statistically significant ($p > 0.05$) (Figure 5A). For the degree of changes in the investigator's assessment score within each group after 16 weeks of consumption, the scores given to test group and the control group did show a statistically significant difference ($p=0.0001$) compared to the scores at baseline within each group.

Regarding the investigator also visually assessed improvements made in dandruff and inflammation. After 8 weeks, the test group received a mean score of 0.48 ± 0.62 and the control group received 0.30 ± 0.60 . While there was a slight improvement in both groups, no statistically significant difference was found between the two groups ($p > 0.05$). After 16 weeks, there were increases in the scores of both groups; the test group received 0.68 ± 0.64 and the control group received 0.35 ± 0.62 , the scores given to test group and the control group did show a difference ($p = 0.038$) (Figure 5B).

Patient's subjective score

Patients provided subjective assessment scores which indicate their satisfaction regarding the improvement of patterned hair loss. At week 8, these scores were 2.55 ± 1.02 for the test group and 2.41 ± 1.04 for the control group. At week 16, scores were 2.82 ± 1.01 for the test group and 2.49 ± 1.06 for the control group, demonstrating that most participants were satisfied or even very satisfied with the treatment. However, there was no significant difference between groups (Figure 6A). Regarding the patient's satisfaction on the improvement of dandruff and inflammation of the scalp, the mean score at week 8 was 2.21 ± 1.02 for the test group, and 2.02 ± 1.07 for the control group ($p > 0.05$), and the scores after 16 weeks of consumption were 2.65 ± 1.04 for the test group and 2.13 ± 1.05 for the control group, the scores given to test group and

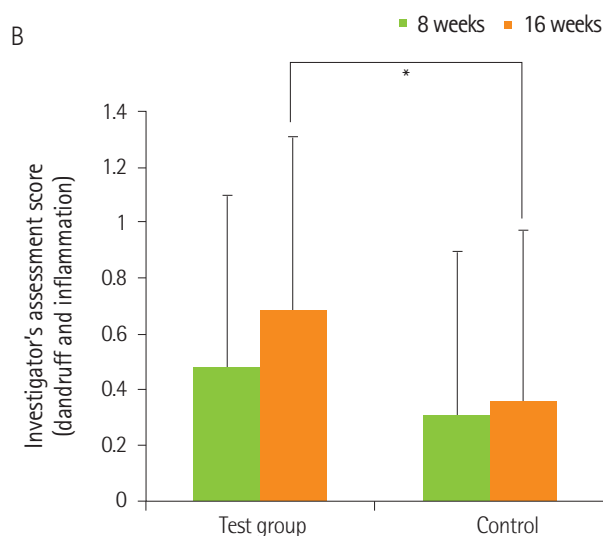
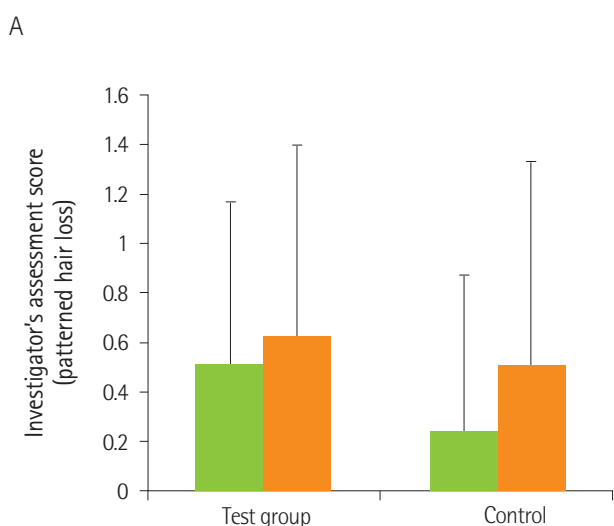


Figure 5. (A) Investigator's assessment score (patterned hair loss). Significant differences were not detected between groups by Wilcoxon signed ranks test. (B) Investigator's assessment score (dandruff and inflammation). *Significant differences were detected between groups by Wilcoxon signed ranks test with $p < 0.05$.

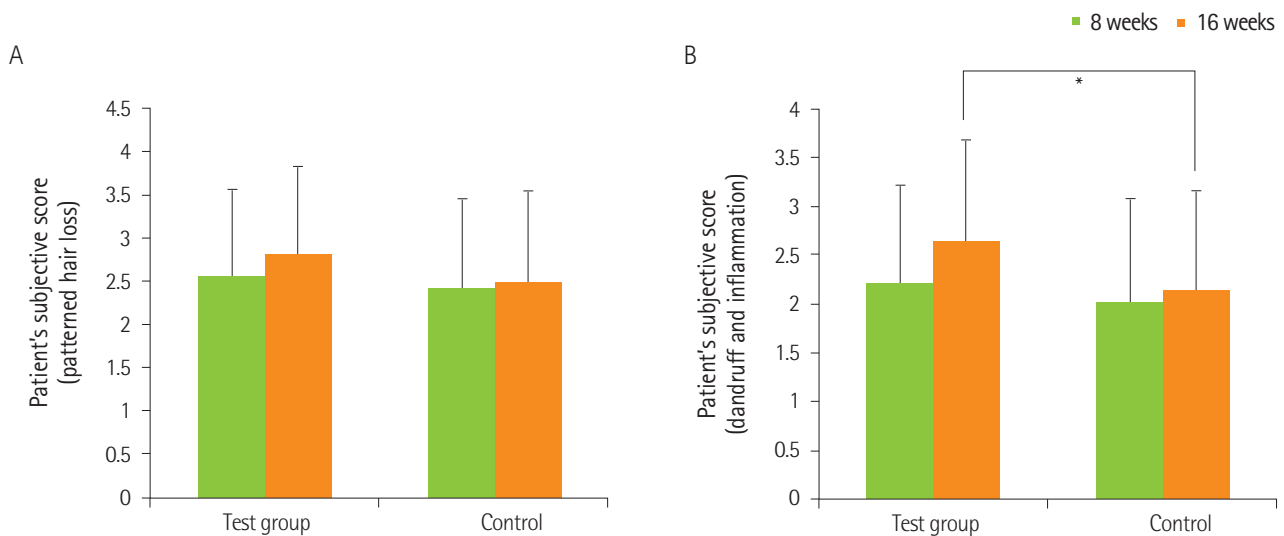


Figure 6. (A) Patient's subjective score (patterned hair loss). Significant differences were not shown between groups by Wilcoxon signed ranks test. (B) Patient's subjective score (dandruff and inflammation). *Significant differences were detected between groups by Wilcoxon signed ranks test with $p < 0.05$.

the control group did show a difference ($p = 0.042$) (Figure 6B).

Safety evaluation

Analysis of safety was performed on patients who had consumed the test product or the placebo pill at least once. As a result, a total of 94 subjects (45 from the test group and 49 from the control group) were assessed for the type and frequency of adverse reactions they experienced and the effect of the product on their physical examination, laboratory findings and vital signs. Adverse events were found in 6 out of 45 persons in the test group (13.33%), and 2 out of 49 persons in the control group (4.08%), and adverse drug reactions were not found. There was no statistically significant difference between the two groups with regard to the percentage of adverse effect occurrence ($p = 0.1467$), and it is also regarded that the statistically significant differences that are found are not actually substantial in the clinical perspectives. The analysis of blood tests and vital signs do not show any indicators of significant change when comparing the values from baseline and 16 week (data not shown). In conclusion, comparison and assessment of the safety of the treatment in the test group and control group, confirmed that the differences between the two groups are negligible in declaring safety issue.

Discussion

In this double-blinded, placebo-controlled clinical trial, we investigated the efficacy of CT and LJ extracts (MK-R7) in promoting hair health in patients with mild to moderate patterned hair loss. In comparing the hair densities of the test and control groups, we found a statistically significant increase in the hair density and hair diameter of the test group compared to that of control group after 16 weeks consumption the product. Our data suggest that CT extract and LJ extract complex assist the increase of hair density and diameter. These findings were more profound at 16 weeks of consumption rather than 8 weeks, suggesting that continuous consumption of the product maximizes its effects. Despite the fact that investigator's assessment score and the patient's subjective score did not reveal a significant outcome for patterned hair loss, not only was there an overall improvement exhibited in the test group in comparison to the control group, an increase in hair diameter and hair density was found as well. As hair diameter and density tend to decrease along with hair loss, it can be determined that CT and LJ extract complex used in this study is effective for treating patterned hair loss. In addition, there were significant outcomes regarding the improvement of investigator's visual assessment and patient's subjective score of dandruff and inflammation with using MK-R7 product.

A LJ extracts including fucoidan, obtained from the brown seaweed *Laminaria japonica*, showed that all fractions pos-

sessed considerable antioxidant activities. This substance inhibited coagulant in aPTT, TT and PT assays [6]. LJ extract has a stimulatory effect on the thrombolytic activity of tissue plasminogen activator as well as dose-dependent antithrombotic activity in an arterial thrombosis model [9]. LJ extract induces the release of tissue factor pathway inhibitor from cultured human umbilical vein endothelial cells, which may contribute to its antithrombotic effect [14]. Furthermore, it has important roles as an antioxidant and anticoagulant. These properties suggest that LJ extract might influence hair growth by improving blood flow to the scalp, which helps normalize hair follicles and induces hair growth [15].

Androgenic alopecia (AGA) patients have been shown to have higher levels of fibrinogen, C-reactive protein and lipoprotein(a) [16]. Sadighha and Zahed [17] also found significant increases in triglyceride levels and the total cholesterol:HDL-C ratio, as well as significantly lower HDL-C levels in men with AGA. CT has been shown to increase the mRNA expression of proteins related to cholesterol transport and metabolism, and CT exhibits hypocholesterolemic activity [13]. As patterned hair loss and blood cholesterol have a strong correlation, it follows that CT could have some role in promoting hair growth.

Previous studies have investigated the anti-inflammatory effects of CT and LJ [12] and found that while fucoidan blocks infiltration of inflammatory cells, CT inhibits activation of the cells, and that the combination of these two independent properties targeting different mechanism into a single treatment could be promising for the relief of various types of inflammatory disease. Specifically, this could be one mechanism whereby these agents reduce dandruff and scalp inflammation.

Conclusion

Based on the results of this clinical study, we conclude that CT extract and LJ extract complex can promote the health of the scalp and hair, specifically by improving patterned hair loss, dandruff, and inflammation. This study lays important groundwork for further studies that use a greater sample size to validate these benefits.

Conflict of Interests

No conflict interests were declared by any of the authors.

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