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Clinical and Biochemical Assessment of New-formula Shampoo for Scalp Seborrheic Dermatitis

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Background: Scalp seborrheic dermatitis is a common disease characterized by flaking and itching of the scalp. Conventional treatment options, such as the use of topical corticosteroids and antifungal agents, may cause adverse effects and reduce user satisfaction rates; thus, it is important to explore other treatment options for scalp seborrheic dermatitis.

Objective: We aimed to evaluate the efficacy and safety of a new-formula shampoo containing natural ingredients, including the extract of *Rosa centifolia* petals, epigallocatechin gallate, zinc pyrithione, and climbazole.

Methods: A total of 50 patients with scalp seborrheic dermatitis were enrolled and divided into two groups: the new-formula shampoo-treated group and the 1.5% ciclopirox olamine shampoo-treated group. Clinical severity scores, sebum secretion, and inflammatory cytokines were assessed. In addition, patient satisfaction and adverse events were assessed using a questionnaire.

Results: The new-formula shampoo was comparable with ciclopirox in reducing the clinical severity scores and sebum secretion. Patients' improvement scores and user satisfaction rates were higher in the new-formula shampoo group than in the 1.5% ciclopirox olamine shampoo-treated group. The inflammatory cytokine levels considerably changed in both groups during the course of the study.

Conclusion: Thus, the new-formula shampoo can be considered a treatment option for patients with scalp seborrheic dermatitis.

Key Words: *Malassezia*, New-formula shampoo, Scalp, Seborrheic dermatitis

INTRODUCTION

Scalp seborrheic dermatitis (SD) is a chronic inflammatory disease associated with the secretion of sebum and the proliferation of *Malassezia*; however, its exact pathophysiology remains unclear[1]. Treatment of scalp SD focusses upon decreasing inflammation and reducing the amount of *Malassezia* yeasts. Topical corticosteroids and antifungal agents are still the gold standards of treatment of scalp SD. However, continuous and long-term use of topical corticosteroids leads to

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inevitable complications, such as skin atrophy and telangiectasia. Topical antifungal agents, such as ketoconazole and ciclopirox olamine, can reduce the amount of *Malassezia* yeasts, and zinc pyrithione shampoo can inhibit *Malassezia*. However, these antifungal agents are not always effective in the treatment of scalp SD[2], making it important to discover new treatment options. Furthermore, given the chronic and relapsing nature of scalp SD, the safety of long-term daily use of these agents is essential.

Through our previous clinical trial, we demonstrated the comparable efficacy of a new-formula shampoo containing the extract of *Rosa centifolia* petals, epigallocatechin gallate (EGCG), zinc pyrithione, and climbazole against conventional treatments[3]; however, we did not show whether the inhibition of sebum secretion was significant. Here, we improved the formulation of the shampoo and adjusted the amount of surfactant contained. In addition, we measured cytokine levels of the evaluated patients to better understand the pathophysiology of scalp SD.

Th present study aimed to compare our new-formula shampoo with 1.5% ciclopirox olamine, a conventional method, for the treatment of scalp SD. We also measured the inflammatory cytokine (interleukin [IL]-1α, IL-1β, IL-6, IL-8, and IL-10) and tumor necrosis factor-α (TNF-α) levels in the evaluated patients before and after treatment.

MATERIALS AND METHODS

1. Patients

All patients provided written informed consent to participate, and the study protocol was approved by the Institutional Review Board of Konkuk Medical Center. Moreover, the study was conducted in accordance with the principles of Good Clinical Practice and the Declaration of Helsinki. Of the patients who visited Konkuk University Medical Center for the treatment of scalp SD, those with a clinical severity score ≥3 were enrolled. Patients with scalp skin diseases other than scalp SD, those under any oral treatment for skin diseases in the past 4 weeks, and those who used an external preparation for the scalp in the past 2 weeks were excluded. A total of 50 patients were randomized into two treatment groups: the new-formula shampoo (n = 25) group and the 1.5% ciclopirox olamine shampoo-treated (n = 25) group. The new-formula shampoo contained 0.01% extract of *R. centifolia* petals (TOYO HAKKO, Osaka, Japan), 0.005% EGCG (BioGenics, Daejeon, Korea), 0.3% zinc pyrithione (Kolon Industries, Gwacheon, Korea), and 0.45% climbazole (Guangzhou Tinci Materials Technology, Guangzhou, China). All patients were instructed to massage the assigned shampoo onto their scalps for at least 5 min and then rinse it off with water thrice a week for 4 weeks.

2. Assessments

The clinical severity scores of all patients were measured by the same dermatologist. Using the previously reported scoring systems[3], sebum secretion was assessed at baseline and at 2 and 4 weeks after treatment with the shampoo. The patients' improvement scores were determined using a five-point scale (5, much better; 4, somewhat better; 3, no change; 2, somewhat worse; and 1, much worse). User satisfaction was also determined using the five-point scale; the patients assessed foam richness and hair smoothness while rinsing off the shampoo and after drying their hair (5, excellent; 4, good; 3, moderate; 2, poor; and 1, very bad). Using a folliscope (LeadM, Seoul, Korea), photographs were taken at every follow-up.

3. Cytokine profile

Samples were collected from the most flaking lesion on the scalp using D-squame® tape strips. The samples were extracted from the tape using phosphate-buffered saline supplemented with 0.25 M NaCl and a commercially available protease inhibitor cocktail with broad-spectrum inhibitory specificity (Roche Applied Science, Inc., Indianapolis, IN, USA) for 30 min with sonication on ice. The extracts were then centrifuged for 2 min at 10,000 g. The supernatants of these extracts were subsequently analyzed for soluble protein using the BCA™ protein assay kit (Pierce Biotechnology/Thermo Scientific, Rockford, IL, USA) using bovine serum albumin (BSA) as the reference standard. After protein analysis, the extracts were supplemented with 2% BSA, transferred into 96-well polypropylene deep-well plates, and stored at -80℃ until cytokine analysis. Cytokine levels (IL-1α, IL-1β, IL-6, IL-8, IL-10, and TNF-α) were simultaneously quantitated using a Milliplex Human Cytokine Multiplex Kit (Millipore Corp., Billerica, MA, USA).

4. Statistical analyses

The two-sample *t*-test, Mann-Whitney *U*-test, and chi-square test were used for comparisons between the two groups. Each measurement taken at a follow-up visit was compared with the baseline measurements using the paired non-parametric Wilcoxon test. Pearson correlation analysis was used to evaluate the relationships between variables. All statistical analyses were performed using the SPSS software (version 21.0 for

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Table 1. Baseline characteristics

	New-formula shampoo (n = 25)	Ciclopirox shampoo (n = 23)	*p* value
Age, years ± SD	36.2±8.7	34.6±8.2	0.53
Male, n	8	7	0.91
Clinical severity score	4.40±1.08	4.47±1.61	0.79
Sebum secretion (μg/cm^2)	68.33 (8.67~119.00)	50.33 (3.67~190.33)	0.79

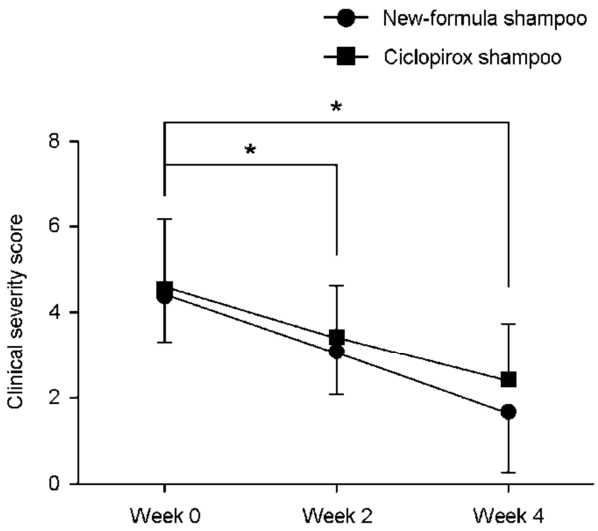

Fig. 1. Change in the clinical severity scores at each follow-up visit. Clinical severity scores at weeks 2 and 4 were improved after treatment in both groups compared with at baseline ($p < 0.01$). The mean changes in clinical severity score at week 4 did not differ between the groups (*$p < 0.01$).

Windows; SPSS, Chicago, IL, USA). $p < 0.05$ was considered statistically significant.

RESULTS

1. Patients

Only 48 of the 50 enrolled patients completed the study; one patient dropped out due to protocol violation (use of a topical corticosteroid on the scalp) and another dropped out due to an adverse event. No age- and sex-related differences were observed between the groups (Table 1). The mean clinical severity scores at baseline did not differ between the groups (4.40 ± 1.08 vs. 4.47 ± 1.61, respectively; $p = 0.79$), and the sebum secretion level did not show any significant differences at baseline (median: 68.33 vs. 50.33, respectively; $p = 0.79$).

2. Changes in the clinical severity scores and sebum secretion levels

The clinical severity scores improved in both groups relative to baseline at weeks 2 and 4 of treatment. The mean changes in the clinical severity scores at weeks 2 and 4 were -1.28 ± 0.8 and -2.72 ± 0.76 ($p < 0.01$) in the new-formula shampoo-treated group versus -1.13 ± 0.76 and -2.13 ± 1.0 ($p < 0.01$) in the 1.5% ciclopirox olamine shampoo-treated group, respectively. The mean changes in the clinical severity scores at week 4 showed no significant differences between the groups ($p = 0.63$, Fig. 1).

The sebum secretion levels decreased in both groups relative to baseline at weeks 2 and 4. In the new-formula shampoo-treated group, the changes in sebum secretion at weeks 2 and 4 were -23.68 (interquartile range [IQR], -45.00 ~ -10.83) and -29.33 μg/cm^2 (IQR, -51.33 ~ -19.33) ($p < 0.01$), respectively. In the ciclopirox olamine shampoo-treated group, the changes in the sebum secretion levels at weeks 2 and 4 were -26.33 (IQR, -57.67 ~ -8.00) and -29.67 μg/cm^2 (IQR, -63.33 ~ -10.67) ($p < 0.01$), respectively. The changes in the sebum secretion levels at week 4 showed no significant differences between the groups ($p = 0.39$, Fig. 2).

3. Patients' subjective improvement scores and user satisfaction

The patients' subjective improvement scores improved after treatment in both groups; most patients responded "much better" or "somewhat better". Significantly greater number of patients responded "much better" in the new-formula shampoo-treated group (56.0% vs. 21.7%, respectively; $p < 0.05$) (Fig. 3).

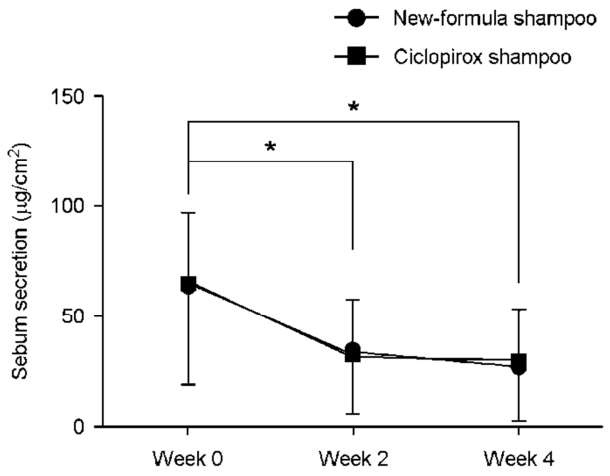

Fig. 2. Change in the sebum secretion levels at each follow-up visit. Sebum secretion was decreased at weeks 2 and 4 after treatment in both groups compared with at baseline ($p < 0.01$). The mean changes in sebum secretion at week 4 did not differ between the groups ($*p < 0.01$).

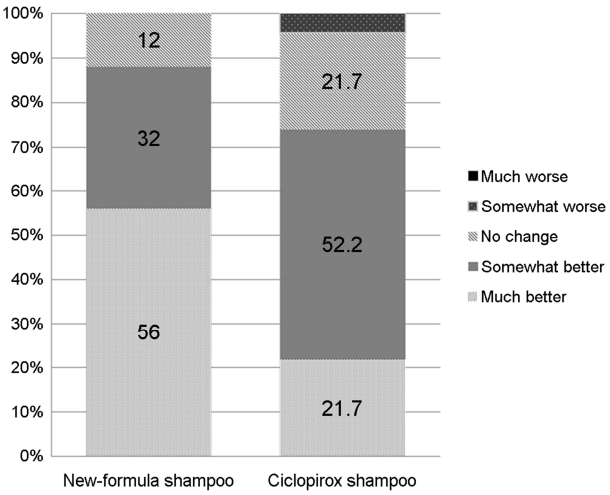

Fig. 3. Changes in patients' subjective improvement scores at week 4. There were more patients who answered "much better" in the new shampoo group.

User satisfaction in terms of foam richness, hair smoothness while rinsing off the shampoo, and hair smoothness after drying were also significantly higher in the new-formula shampoo-treated group (3.13 ± 0.97 vs. 1.88 ± 0.88, 3.13 ± 1.10 vs. 2.04 ± 0.84, and 3.09 ± 0.95 vs. 2.24 ± 1.05, respectively; all $p < 0.05$) (Fig. 4). Three patients in the new-formula shampoo-treated group and seven in the ciclopirox

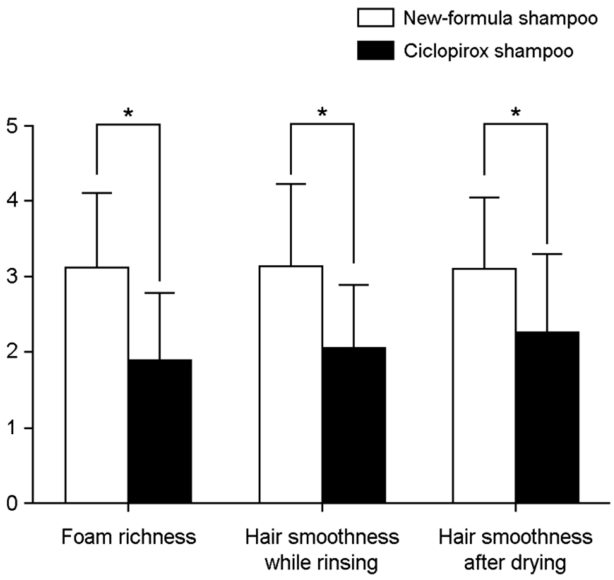

Fig. 4. User satisfaction score after 4 weeks of treatment. User satisfaction in terms of foam richness, hair smoothness while rinsing off the shampoo, and hair smoothness after drying was higher in the new-formula shampoo-treated group ($*p < 0.05$). (5: excellent, 4: good, 3: moderate, 2: poor, 1: very bad)

olamine shampoo-treated group reported discomfort, including mild pruritus and burning sensation, after applying the shampoo. One patient in the new-formula shampoo-treated group developed allergic contact dermatitis on his face. No serious adverse events were reported by the patients in the new-formula shampoo-treated group.

4. Inflammatory cytokine profile

We examined the levels of inflammatory and anti-inflammatory cytokines before and after 4 weeks treatment with the new-formula shampoo. IL-1β and IL-8 were significantly decreased after 4 weeks of treatment (median of percent change from baseline: -63.1 and -83.1; $p < 0.01$ and < 0.01, respectively). In contrast, IL-10 was significantly increased after 4 weeks of treatment (median of percent change form baseline: 77.8, $p < 0.01$) (Table 2, Fig. 5).

DISCUSSION

Scalp SD is a chronic relapsing inflammatory disease; it negatively affects the quality of life of patients. Topical agents, including antifungals and corticosteroids, are the first choice

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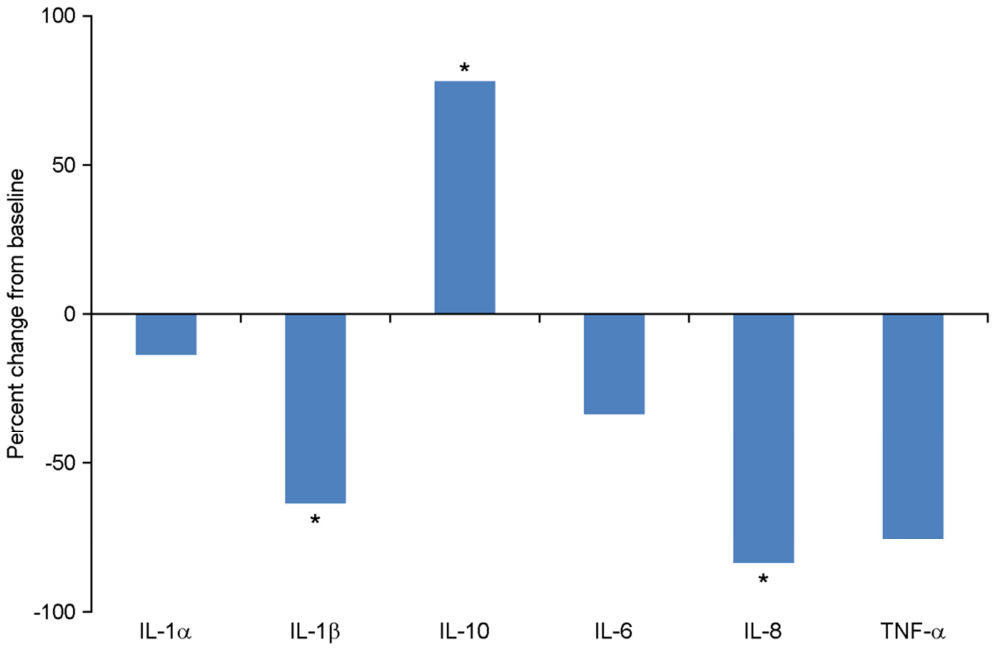

Fig. 5. Changes in the cytokine levels after 4 weeks of treatment with the new-formula shampoo. IL-10 increased after treatment with the new-formula shampoo.

Table 2. Changes in the inflammatory cytokines after 4 weeks of new-formula shampoo treatment

	Differences cytokine level/total protein from baseline (pg/pg)		Percent change from baseline (%)	
	Median (IQR)	*p* value	Median (IQR)	*p* value
IL-1α	-0.58 (-1.68, 0.58)	0.174	-13.9 (-46.3, 21.6)	0.31
IL-1β	-0.35 (-1.22, 0)	<0.01	-63.1 (-93.9, -1.56)	<0.01
IL-10	0.08 (0.03, 0.25)	<0.01	77.8 (16.9, 167.3)	<0.01
IL-6	-0.01 (-0.03, 0)	0.125	-33.3 (-63.3, 0)	0.24
IL-8	-0.54 (-2.70, -0.16)	0.01	-83.1 (-99.5, -32.2)	<0.01
TNF-α	0 (-0.02, 0.02)	0.301	-75.0 (-100.0, 0)	0.24

of treatment for scalp SD and are generally required to be used daily. Daily use of external preparations results in poor patient compliance because it interferes with hair styling and is often impractical for patients who are indifferent to daily skin care. Patient compliance is an important factor for successful long-term treatment of scalp SD; hence, anti-SD shampoos should not only control scalp SD but also offer excellent cosmetic and hair conditioning benefits. Therefore, it is important to discover new and safe treatment options for scalp SD.

An increasing number of studies have identified the pathogenesis of as well as several predisposing factors for scalp SD, including *Malassezia* colonization, sebaceous glands, lipid metabolism, and personal susceptibility. One of the most promising hypotheses underlying scalp SD is the interplay between *Malassezia*, keratinocytes, and immune mechanisms that results in the transformation of *Malassezia* into a pathogen. This change leads to disrupted epidermal barrier function and triggers inflammatory responses. In addition, this change induces keratinocytes to produce proinflammatory cytokines, maintaining inflammation in scalp SD[4-8]. Thus, reducing in-

flammation and inhibiting the activity of *Malassezia* are crucial in the treatment of scalp SD.

The clinical severity scores decreased within 4 weeks in both groups, and the new-formula shampoo demonstrated comparable efficacy with the 1.5% ciclopirox olamine shampoo. Zinc pyrithione and climbazole exert an array of antifungal activities to reduce *Malassezia* proliferation and subsequently reduce inflammatory responses[2]. EGCG is a major polyphenol of green tea and has recently gained interest owing to its anti-inflammatory and anti-microbial activities[9,10]. Yoon et al.[11] reported that EGCG reduced inflammation by inhibiting the NF-κB and AP-1 pathways in an acne model. Moreover, rose extracts have been shown to have potential anti-inflammatory activity[12-14]. Thus, we believe the ingredients contained in the new-formula shampoo have antifungal and anti-inflammatory activities that might be helpful in the treatment of scalp SD.

The sebum secretion levels were also decreased in both groups after 4 weeks of treatment. Scalp SD is strongly associated with sebaceous gland activity. In addition to sebum secretion levels, lipid composition abnormalities may play a role in scalp SD development by creating a favorable microenvironment for *Malassezia* colonization. Previous studies demonstrated that EGCG inhibits adipocyte proliferation and lipogenesis[15,16]. In addition, EGCG reduces the sebum secretion levels by regulating the AMPK-SREBP-1 signaling pathway in an acne model[11]. Rose extracts have also been shown to inhibit lipid metabolism[17]. Our previous study demonstrated the comparable efficacy of a new-formula shampoo and conventional treatments for scalp SD; however, that shampoo did not significantly inhibit sebum secretion[3]. In the present study, we improved the formulation of the shampoo and it consequently inhibited sebum secretion.

The patients in the new-formula shampoo-treated group reported lesser discomfort, such as burning sensation and itching. One patient treated with the new-formula shampoo reported allergic contact dermatitis on his face; however, he had recently used a new cosmetic cream on his face, and it was unlikely that the condition was due to the shampoo.

Furthermore, user satisfaction in terms of foam richness, hair smoothness while rinsing off the shampoo, and hair smoothness after drying was significantly higher in the new-formula shampoo-treated group ($p < 0.05$). Our results suggest that the new-formula shampoo could improve user compliance because it does not ruin patients' hairdos. Therefore, the new-formula shampoo could be a successful treatment option for daily long-term treatment of scalp SD.

Several studies have investigated the pathogenesis of scalp SD; however, the exact pathophysiology still remains unclear. Few previous studies reported that *Malassezia* yeast causes scalp SD and can induce IL-1β, IL-6, and TNF-α production *in vitro*[18-20]. In addition, patients with scalp SD exhibit considerable increases in IL-8 production in their skin[21-23]. In the present study, IL-1β and IL-8 cytokine levels were significantly decreased after treatment with the new-formula shampoo. In their study conducted in a rat model, Kumar et al.[24] observed a significant decrease in the expression of proinflammatory cytokines, including IL-1β and IL-8, after treatment with a rose extract. In addition, EGCG significantly decreased IL-1β and IL-8 levels in an acne model[11]. Clinical trials also revealed that zinc pyrithione-based shampoos decrease IL-8 levels[23]. From these data, we can conclude that the new-formula shampoo decreases proinflammatory cytokine levels, thereby improving the clinical severity of scalp SD.

Interestingly, IL-10 was significantly increased in the new-formula shampoo-treated group after 4 weeks of treatment (difference in the cytokine level/total protein from baseline was 0.08, $p < 0.01$; the percent change from baseline was 77.8%, $p < 0.01$). IL-10 levels were negatively correlated with the clinical severity scores, and patients who had higher IL-10 levels at baseline responded more favorably to the shampoo treatment. IL-10 is a well-known anti-inflammatory cytokine. It modulates the functions of several types of immune cells by inhibiting T-cell proliferation and cytokine synthesis and contributes to regulating inflammation to ensure an equilibrated immune response[25,26]. We hypothesized that the ingredients of the new-formula shampoo contribute to the regulation of IL-10 production. In a mouse model, EGCG upregulated the anti-inflammatory activities of T regulatory cells and suppressed NF-κB, thereby inducing IL-10 expression [27,28]. Based on these data, we concluded that the new-formula shampoo could induce an anti-inflammatory response via IL-10 and that IL-10 might play a role in the pathophysiology of scalp SD. Furthermore, measuring IL-10 levels would help predict which patients will respond to treatment and could be a useful marker for individualizing treatment approaches.

In conclusion, we evaluated a new-formula shampoo for the treatment of scalp SD. After 4 weeks of treatment, the clinical severity scores significantly decreased due to the anti-inflammatory and sebum-reducing activities; further, the treatment was generally well tolerated, with high user satisfaction. The new-formula shampoo decreased proinflammatory cytokine levels and could induce IL-10 expression. These findings indicate that the new shampoo containing zinc pyrithione, climbazole, *R. centifolia* petal extract, and EGCG is useful and tolerable in the treatment of scalp SD.

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CONFLICT OF INTEREST

Hong-Ju Shin and Jeong-Hwan Kim are employed by Amore Pacific Corporation R&D center. Hong-Ju shin involved in data monitoring and Jeong-Hwan Kim was contributed to study design.

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