

# Clinical Evaluation of a New-Formula Shampoo for Scalp Seborrheic Dermatitis Containing Extract of *Rosa centifolia* Petals and Epigallocatechin Gallate: A Randomized, Double-Blind, Controlled Study

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**Background:** Scalp seborrheic dermatitis is a chronic type of inflammatory dermatosis that is associated with sebum secretion and proliferation of *Malassezia* species. Ketoconazole or zinc-pyrithione shampoos are common treatments for scalp seborrheic dermatitis. However, shampoos comprising different compounds are required to provide patients with a wider range of treatment options. **Objective:** This study was designed to evaluate a new-formula shampoo that contains natural ingredients-including extract of *Rosa centifolia* petals and epigallocatechin gallate (EGCG)-that exert antioxidative, anti-inflammatory, and sebum secretion inhibitory effects, and antifungal agents for the treatment of scalp seborrheic dermatitis. **Methods:** Seventy-five patients were randomized into three treatment groups; new-formula shampoo, 2% ketoconazole shampoo, and 1% zinc-pyrithione shampoo. The clinical severity scores and sebum levels were assessed by the same dermatologists at baseline (week 0), and at 2 and 4 weeks after using the shampoo. User satisfaction and irritation were also assessed with the aid of a questionnaire. **Results:** The efficacy of the new-formula shampoo was comparable to that of both the 1% zinc-pyrithione shampoo and the 2% ketoconazole shampoo.

Furthermore, it was found to provide a more rapid response than the 1% zinc-pyrithione shampoo for mild erythema lesions and was associated with greater user satisfaction compared with the 2% ketoconazole shampoo. However, the new-formula shampoo did not exhibit the previously reported sebum inhibitory effect. **Conclusion:** Extract of *R. centifolia* petals or EGCG could be useful ingredients in the treatment of scalp seborrheic dermatitis. (**Ann Dermatol 26(6) 733~738, 2014**)

## -Keywords-

Ellagitannins, Epigallocatechin gallate, Ketoconazole, Seborrheic dermatitis, Zinc pyrithione

## INTRODUCTION

The scalp hosts a high density of large follicular structures, including the sebaceous glands, which contribute to a high level of sebum production. This makes the scalp vulnerable to irritation arising from the change in sebum quantity or quality and to infection with microorganisms that proliferate by taking nutrients from the sebum. Scalp seborrheic dermatitis is a chronic type of inflammatory dermatosis that is associated with sebum secretion and proliferation of *Malassezia* species; however, the exact cause is unknown. Antifungal therapies against *Malassezia* species with sebum control properties are thus expected to be helpful for the treatment of this condition. Ketoconazole and zinc-pyrithione shampoos are common treatments for scalp seborrheic dermatitis; however, a new shampoo comprising different compounds is required to provide patients with a wider range of treatment options.

Received January 24, 2014, Revised March 7, 2014, Accepted for publication March 24, 2014

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Therefore, we evaluated a new-formula shampoo that contains natural ingredients that exert antioxidative, anti-inflammatory, and sebum secretion inhibitory effects, as well as antifungal agents against *Malassezia* species. This randomized, double-blind, controlled study was designed to compare the efficacy and user satisfaction of the new shampoo with those of 2% ketoconazole shampoo and 1% zinc-pyrithione shampoo.

## MATERIALS AND METHODS

### Patients

Among patients who visited Konkuk University Medical Center for scalp seborrheic dermatitis between March and May 2013, those with a clinical severity score of  $\geq 3$  with faint pink or more severe erythema, and scraped or more severe dandruff were included in this study. All patients provided informed consent to participate (IRB No. KUH 1120033). Patients with skin diseases other than scalp seborrheic dermatitis, those who had been taking any oral agent for skin diseases in the previous month, and those who had used an external preparation for scalp in the last 2 weeks were excluded from the study. In total, 75 patients were randomized into three treatment groups: new-formula shampoo (n=25), 2% ketoconazole shampoo (n=25), and 1% zinc-pyrithione shampoo (n=25). This study has a double-blind design.

### Test products

The new-formula shampoo contained 0.01% extract of *Rosa centifolia* petals (TOYO HAKKO, Osaka, Japan), 0.005% epigallocatechin gallate (EGCG; BioGenics, Daejeon, Korea), 0.3% zinc pyrithione (Kolon Industries, Gwacheon, Korea), and 0.45% climbazole (Guangzhou Tinci Materials Technology, Guangzhou, China). Two widely available commercial shampoos, Nizoral (Janssen Korea, Hwaseong, Korea) and Head & Shoulders (Hankook P&G, Seoul, Korea), were used as the 2% ketoconazole and 1% zinc-pyrithione shampoos, respectively.

All patients were instructed to massage their scalps for at least 5 minutes with the assigned shampoo and then rinse with water three times a week for 4 weeks. Other drugs or external preparations for skin diseases were not allowed during the study period.

### Evaluation

The clinical severity score and sebum level were assessed by the same dermatologists at baseline and at 2 and 4 weeks after using the shampoo. User satisfaction and irritation were assessed with the aid of a questionnaire. Photographs were taken with a folliscope (LeadM, Seoul,

**Table 1.** Criteria for clinical severity scores

Score	Erythema	Dandruff	Lesion extent
0	No erythema	No dandruff	No lesion
1	Faint pink color	Only scraped	1% ~ 30% of scalp area
2	Pink color	Obvious scaling	31% ~ 70% of scalp area
3	Red color	Obvious sheets	71% ~ 100% of scalp area

Korea) at each evaluation.

### 1) Clinical severity score

The clinical features of erythema, dandruff, and lesion extent were measured according to their severity on a four-point scale (Table 1). The clinical severity score was calculated by summing the scores of each item.

### 2) Sebum level

Sebum secretion levels were measured in the frontal, temporal, and vertex areas by using a sebumeter (Courage and Khazaka Electronic, Cologne, Germany), and the mean of these three values was used as the final data.

### 3) Patient questionnaire

Subjective improvement was assessed on a five-point scale (1, much better; 2, somewhat better; 3, no change; 4, somewhat worse; and 5, much worse). For user satisfaction, patients assessed foam richness and hair smoothness while rinsing and after drying on a five-point scale (1, excellent; 2, good; 3, moderate; 4, poor; and 5, very bad), and answered a question about the presence of irritation while using the shampoo.

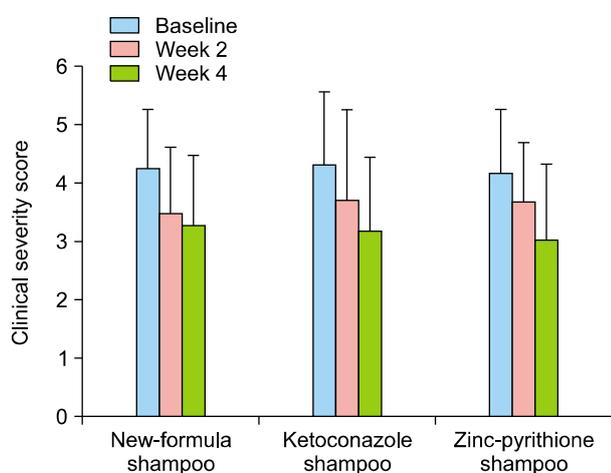
### Statistical methods

The therapeutic efficacy in each group was evaluated with the paired t-test for reductions in the clinical severity score and the sebum secretion level. The differences in baseline characteristics, efficacy, and user satisfaction among the three treatment groups were analyzed with analysis of variance (ANOVA). The Tukey-Kramer test was applied to items showing a significant difference on ANOVA, and the chi-square test was performed to detect whether the presence of irritation differed between the three treatment groups. The Kruskal-Wallis test was used to determine differences in sebum secretion according to scalp location. For the analysis, SAS software, version 9.3 (SAS Institute, Cary, NC, USA) was used. The cutoff for statistical significance was set at  $p < 0.05$ .

**Table 2.** Characteristics of the patients in the three experimental groups

	New-formula shampoo	Ketoconazole shampoo	Zinc-pyrithione shampoo
Initial enrolled number of patients	25	25	25
Lost to follow-up	1	0	2
No. of patients completed	24	25	23
Males	4	7	9
Females	20	18	14
Age (yr)	38.4±8.7	37.7±9.2	36.0±9.0
Sebum secretion ( $\mu\text{g}/\text{cm}^2$ )	88.2±43.3	95.5±44.0	111.1±45.5
Clinical severity score	4.2±1.0	4.3±1.2	4.1±1.1

Values are presented as number only or mean±standard error.



**Fig. 1.** Change in clinical severity score. Values are mean±standard error.

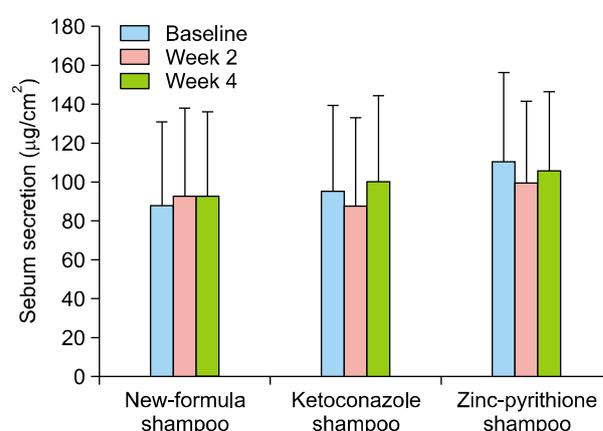
## RESULTS

### Enrolled patients

Seventy-two of the 75 enrolled patients completed the clinical study (Table 2). The clinical severity score, sebum secretion, and age at baseline did not differ significantly between the three treatment groups ( $p=0.90$ ,  $0.20$ , and  $0.65$ , respectively). One patient in the new-formula shampoo group did not use the product properly, and two patients in the zinc-pyrithione shampoo group were lost to follow-up because of personal reasons.

### Change in clinical severity score

The clinical severity score improved significantly relative to baseline at weeks 2 and 4 in all groups ( $p<0.05$ ); however, the changes in clinical severity score at weeks 2 and 4 did not differ significantly between the three groups ( $p=0.39$  and  $0.63$ , respectively; Fig. 1). The changes in clinical severity subscores (i.e., for erythema, dandruff, and lesion extent) at weeks 2 and 4 did not significantly differ between the three groups ( $p=0.55$ ,  $0.53$ , and  $0.18$ , respec-



**Fig. 2.** Change in sebum secretion.

tively, at week 2; and  $p=0.68$ ,  $0.57$ , and  $0.83$  at week 4).

### Change in sebum secretion

Sebum secretion did not change significantly at weeks 2 and 4 in the new-formula, ketoconazole, and zinc pyrithione groups ( $p=0.43$ ,  $0.30$ , and  $0.23$ , respectively, at week 2; and  $p=0.42$ ,  $0.52$ , and  $0.50$  at week 4; Fig. 2). Moreover, the changes in sebum secretion did not differ significantly between the three groups at weeks 2 and 4 ( $p=0.29$  and  $0.53$ , respectively).

### Sebum secretion according to scalp location

Sebum secretion differed significantly according to the scalp location ( $p<0.0001$ ; Table 3), with it being greatest in the frontal area and lowest in the temporal area.

### Subjective improvement score

The patients' subjective improvement score did not differ significantly between the three groups at weeks 2 ( $p=0.17$ ) and 4 ( $p=0.83$ ; Table 4).

### User satisfaction and irritation

Concerning user satisfaction, foam richness and smoo-

**Table 3.** Difference in sebum secretion according to scalp location at baseline

	Frontal	Temporal	Vertex
Sebum secretion ( $\mu\text{g}/\text{cm}^2$ )	123.4 $\pm$ 59.3	75.8 $\pm$ 44.3	94.4 $\pm$ 51.4

Values are presented as mean $\pm$ standard error.

**Table 5.** User satisfaction scores\* with shampoo after 4 weeks

	New-formula shampoo	Ketoconazole shampoo	Zinc-pyriithione shampoo
Foam richness	2.50 $\pm$ 0.18	3.24 $\pm$ 0.17	2.86 $\pm$ 0.18
Hair smoothness while rinsing	3.12 $\pm$ 0.20	3.60 $\pm$ 0.20	2.73 $\pm$ 0.20
Hair smoothness after drying	2.87 $\pm$ 0.18	3.28 $\pm$ 0.18	2.73 $\pm$ 0.19

Values are presented as mean $\pm$ standard error. \*1: excellent, 2: good, 3: moderate, 4: poor, 5: very bad.

thness while rinsing differed significantly between the three groups ( $p=0.019$  and  $0.015$ , respectively; Table 5). Foam richness was superior in the new-formula group compared with the ketoconazole group ( $p=0.013$ ), and smoothness while rinsing was superior in the zinc pyriithione group compared with the ketoconazole group ( $p=0.011$ ). Irritation did not differ significantly between the three groups ( $p=0.63$ ). Of the 11 patients who complained of irritation, 9 reported pruritus and 4 reported erythema, which are mild symptoms commonly present in patients with seborrheic dermatitis.

## DISCUSSION

Despite being commonly used as a first-line treatment for scalp seborrheic dermatitis, external preparations have several limitations; because the thick skin and high level of sebum of the scalp play a barrier function, drugs of lower potency may not provide sufficient efficacy and daily use of external preparations interferes with hair styling. The advantages of using shampoo products for treating seborrheic dermatitis are as follows: (i) the detergent eliminates irritants and antigens, such as fungal elements and oxidized sebum; (ii) contact between active ingredients and the scalp can be increased by eliminating waste matter; (iii) water and surfactants loosen the skin barrier, increasing the penetration of active ingredients; and (iv) as the product is rinsed off, the hair does not appear greasy, causing no discomfort in daily life.

Sebum secretion differed according to scalp location (Table 3). Given that seborrheic dermatitis is more prevalent on the scalp, face, and chest where the sebum secretion level is high, it can be speculated that the frequency

**Table 4.** Patients' subjective improvement scores\* of scalp symptoms

	New-formula shampoo	Ketoconazole shampoo	Zinc-pyriithione shampoo
Week 2	2.62 $\pm$ 0.13	2.28 $\pm$ 0.12	2.43 $\pm$ 0.13
Week 4	2.41 $\pm$ 0.17	2.44 $\pm$ 0.16	2.30 $\pm$ 0.17

Values are presented as mean $\pm$ standard error. \*1: much better, 2: somewhat better, 3: no change, 4: somewhat worse, 5: much worse.

of seborrheic dermatitis also varies with the scalp location. The manifestation of symptoms is affected by the composition and quality of sebum, as well as its quantity. Sebum consists of various compounds, including glycerides, wax esters, squalene, cholesterol, cholesterol esters, and free fatty acids, and their composition and quality can readily change during exposure to the external environment. Sebum consequently transformed by microorganisms or peroxides and lipids with altered composition can be cytotoxic, irritant, or immunogenic etiologies of skin diseases<sup>1</sup>. As for seborrheic dermatitis, an oleic acid and a free fatty acid derived from triglycerides by lipases of *Malassezia* is an irritant<sup>2</sup>. Also, a significant decrease in squalene and increases in cholesterol and cholesterol esters have been reported in skin with seborrheic dermatitis, indicating altered sebum composition<sup>3</sup>. Furthermore, seborrheic dermatitis seems to be associated with activation of Toll-like receptor 2 and interleukins, which are directly induced by *Malassezia* species<sup>4</sup>. The individual susceptibility to abnormal immune responses (e.g., allergic reactions) against *Malassezia* yeasts is also considered to play a role in seborrheic dermatitis<sup>5</sup>. These findings demonstrate that the aim of seborrheic dermatitis treatment should be to control sebum secretion and to provide anti-microorganism, antioxidant, and anti-inflammatory therapies. In addition, the chronic nature of the disease should be taken into account, as this means that long-term use of the product is inevitable. Bioactive ingredients are noteworthy in this context because they are derived from plants that provide a number of antioxidants, antimicrobials, vitamins, flavonoids, proteins, essential oils, sterols, enzymes, and alkaloids, and are perceived by the public as being safer than synthetic products. In the present study, the bioactive extract of *R.*

*centifolia* (pink rose) petals and EGCG were added to the new-formula shampoo. White-rose-petal extract was found to possess outstanding antioxidant and antiallergic properties<sup>6</sup>. Moreover, white-rose-petal extract was shown to markedly reduce intracellular lipids and protein oxidation, and to reduce systemic anaphylactic reactions and scratching behaviors after histamine injection in mice<sup>7</sup>. The pink-rose-petal extract used in the new-formula shampoo in this study has been shown to suppress triacylglycerol (TAG) synthesis in cultured cells and to inhibit diacylglycerol acyltransferase (DGAT) in a dose-dependent manner<sup>8</sup>. DGAT catalyzes the final step of TAG synthesis and is considered a target for controlling triglyceride production. Fractionation of the rose extract revealed that the DGAT inhibitory substances in the rose extract were mostly ellagitannins. As DGAT is present in the sebaceous glands of human skin, as well as in the liver and small bowel<sup>9</sup>, it was expected to decrease sebum secretion from sebaceous glands when used as an external preparation. Therefore, it might be effective in reducing the etiological causes of seborrheic dermatitis, such as pro-inflammatory oxidated molecules and *Malassezia*, which take nutrients from the sebum. In addition, the expression level of DGAT in psoriatic skin was found to be one-third of that in normal skin<sup>9</sup>. This suggests the presence of changed DGAT expression in seborrheic dermatitis, which would make DGAT inhibitors useful for the treatment of seborrheic dermatitis.

The mechanism underlying the action of EGCG, another bioactive ingredient, involves antisebum secretion, anti-inflammation, and antioxidation effects<sup>10</sup>. In SEB-1 sebocytes, EGCG reduced sebum and inflammation by modulating the AMP-activated protein kinase-sterol regulatory element-binding protein-1 signaling pathway and suppressing the nuclear factor kappa B and AP-1 pathways, respectively<sup>11</sup>. It has also been reported that EGCG exerts a positive effect on hair growth<sup>12</sup>. Previous hair restorers have focused on the antiandrogenic effect; however, a recent discovery suggesting that microinflammation is the cause of hair loss supports the hair-growth effect by anti-inflammatory materials such as EGCG. The etiology of seborrheic dermatitis also includes inflammation, which induces hair loss as it progresses, indicating that seborrheic dermatitis and hair loss in part share the same therapeutic mechanism.

The numerous synthetic materials that have been used to reduce scalp inflammation include steroids. However, and as for seborrheic dermatitis, they are not appropriate for long-term and prophylactic use that would be necessary owing to the relapsing nature of the disease. Previous studies have found that the response to steroids was more

rapid than that to zinc pyrithione; however, but steroids further aggravated the symptoms after the cessation of treatment<sup>13</sup>. The onset of the anti-inflammatory effect of steroids may be earlier than that of the inhibitory effect against *Malassezia* by zinc pyrithione; however, steroids are not effective for the inhibition of *Malassezia* growth or sebum secretion, which are the fundamental causes of seborrheic dermatitis, ultimately resulting in earlier relapse than with zinc pyrithione.

Therapeutic improvement requires the development of products other than steroids that exhibit a more rapid response than the currently available products. In this study, mild erythema lesions responded significantly more rapidly to the new-formula shampoo than to the zinc-pyrithione shampoo ( $p=0.03$ ). Because there was no significant difference in response time between the ketoconazole and zinc-pyrithione shampoo groups ( $p=0.10$ ), climbazole and zinc pyrithione could be excluded as causes of the different responses among the ingredients of the new shampoo. The antisebum secretion, anti-inflammatory, and antioxidative effects of EGCG, and the antisebum secretion effect of rose-petal extract (ellagitannin) were suspected to be the main candidates inducing the rapid response. However, sebum secretion did not change significantly in the new-formula shampoo group, and no sebum inhibitory effect exerted by EGCG and ellagitannin was observed in this study. In conclusion, although the anti-inflammatory and antioxidative effects of EGCG did not yield a rapid response in every lesion, they might induce a rapid response in mild erythema lesions.

Climbazole used in the new-formula shampoo is a widely available antifungal agent that is the most commonly used in cosmetic products. This compound is an imidazole antifungal and, as with other azoles, prevents the synthesis of ergosterol by inhibiting cytochrome P450, inhibits the morphogenetic transformation of yeasts to the mycelial form, decreases fungal adherence, and exerts direct toxic effects on membrane phospholipids<sup>14</sup>.

Zinc pyrithione, another synthetic material of the new-formula shampoo, also exerts an antifungal effect, possibly by importing copper into cells and by damaging iron-sulfur proteins<sup>15</sup>. The scalp follicular infundibulum has recently been receiving attention as a site of action and reservoir of zinc pyrithione. This is because the target *Malassezia* yeasts are found primarily in the follicular infundibula, and it has been reported that particles were retained in hair follicles for up to 10 days<sup>16</sup>. It is important to adjust the particle size to enhance the penetration and retention of zinc pyrithione in follicles.

Compliance is as important as clinical efficacy in the treatment of chronic diseases such as seborrheic dermatitis.

This means that user satisfaction can be an important factor in determining treatment options, especially when there is no difference in the therapeutic effect. This study found zinc-pyrithione shampoo to be smoother than ketoconazole shampoo when rinsing, and foam richness was better for the new-formula shampoo than for the ketoconazole shampoo. Mild erythema and pruritus were the only adverse events reported, with no reports of serious adverse events in any of the groups.

In conclusion, although the new-formula shampoo did not exhibit the previously reported sebum inhibitory effect, it was as effective as both the 1% zinc pyrithione and the 2% ketoconazole shampoos for treating scalp seborrheic dermatitis, and especially for mild erythema lesions. These data support the implementation of this new-formula shampoo as an alternative treatment option.

## ACKNOWLEDGMENT

This study was supported by Konkuk University.

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