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Research Article

# The Long-Term Efficacy of a Moisturizer Containing 4-t-Butylcyclohexanol and Licochalcone A as Adjunctive Therapy for Facial Seborrheic Dermatitis

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## Abstract

**Background:** Facial seborrheic dermatitis (FSD) is a chronic relapsing skin disease caused by multifactorial factors. Long-term or frequent topical corticosteroid treatment may lead to adverse effects.

**Aims:** To determine the long-term efficacy of a trial moisturizer containing 4-t-butylcyclohexanol and licochalcone A as an adjunctive treatment and its effectiveness in extending the disease-free period in FSD patients.

**Patients/Methods:** Twenty patients with FSD aged ≥ 18 years were enrolled. They individually received a trial moisturizer to apply to their faces twice daily for 20 weeks. Clinical assessment by a physician, patient assessments, and bioengineering measurements were performed periodically.

**Results:** Clinical severity assessment showed a significant improvement after 1 to 2 weeks of treatment compared with the baseline. The trial moisturizer promoted skin hydration and reduced transepidermal water loss. The number of patients with disease exacerbations and frequency of relapses significantly decreased after the first week and during the remainder of the study period. No participants needed rescue by topical corticosteroid therapy.

**Conclusion:** The moisturizer containing 4-t-butylcyclohexanol and licochalcone A showed excellent efficacy without unwanted effects. It is endorsed for use as an adjunctive treatment or maintenance therapy to control the relapse of mild to moderate FSD.

## Background

Seborrheic dermatitis is a common chronic and relapsing inflammatory skin disorder characterized by scaly, itchy erythematous patches, mostly on seborrheic areas such as the face and scalp. The prevalence of seborrheic dermatitis is 1% to 3% of the worldwide population [1,2]. The pathophysiology is not entirely understood. It is possibly associated with Malassezia yeast overgrowth with impaired immune reaction, excessive sebum production, genetics, skin barrier disturbances, and disruption of neurocutaneous transmitters [3]. Facial seborrheic dermatitis (FSD) causes the skin to become easily irritated and sensitive to cosmetic or skincare products, and the condition significantly affects patients' well-being [4]. The mainstay treatments of FSD are mild potency topical corticosteroids (TCSs), topical calcineurin inhibitors, and topical antifungal agents. Patients are usually treated with TCSs due to their excellent efficacy, affordability, and availability. However, the long-term, uncontrolled use of TCS can cause various adverse effects, including skin atrophy, telangiectasia, pigment alteration, steroid acne, hypertrichosis, and perioral dermatitis [5,6]. These skin conditions are frequently found in countries where TCS is freely sold over the counter, such as Thailand.

Technological advancements have led to the development of moisturizers that have anti-inflammatory properties, can repair skin barriers, and can reduce skin irritation. The critical ingredients of the moisturizer tested in this study are 4-t-butylcyclohexanol and licochalcone A. These ingredients have demonstrated the ability to soothe burning sensations and itching by inhibiting the transient receptor potential vanilloid subfamily, member 1 (TRPV1), and by lessening inflammation through the suppression of various pro-inflammatory cytokines [7,8]. Licochalcone A is a phenolic compound extracted from Glycyrrhiza inflata roots. It has demonstrated various pharmacological properties such as anti-inflammation, antioxidant, antibacterial, antifungal, and anticancer properties [9]. Previous studies reported that licochalcone A could inhibit multiple pro-inflammatory mediators and cytokines in vitro, such as prostaglandin E2, nuclear factor kappa B, leukotriene B4, interleukin-6, and tumor necrosis factor α, which are secreted by dermal fibroblasts, keratinocytes, and dendritic cells. [7,8] 4-t-Butylcyclohexanol, a TRPV-1 antagonist, can reduce neuronal activation and decrease neuronal calcitonin gene-related peptide release, significantly relieving stinging and burning sensations [7].

The trial moisturizer containing 4-t-butylcyclohexanol and licochalcone A has been reported to have treatment benefits in several dermatological diseases, such as rosacea [10], atopic dermatitis [11], facial dermatitis [12], and infantile seborrheic dermatitis [13]. Therefore, the moisturizer might benefit FSD treatment due to its anti-inflammatory properties, regulatory effects on neurocutaneous transmitters, and ability to restore the epidermal barrier. However, the moisturizer's long-term efficacy and ability to maintain a disease-free period have never been studied. Our study aimed to investigate the efficacy of moisturizers containing 4-t-butylcyclohexanol and licochalcone A (Eucerin Instant Calming; Beiersdorf, Hamburg, Germany) in the long-term treatment of mild to moderate FSD and their effectiveness in preventing disease flare-ups.

## Materials and Methods

This single-center, open-label, 20-week study was conducted at the Department of Dermatology of the Faculty of Medicine Siriraj Hospital, Mahidol University, Bangkok, Thailand, between November 2020 and March 2022. The Siriraj Institutional Review Board approved the protocol (Si840/2020).

### Study population

Twenty patients aged ≥ 18 years diagnosed with mild to moderate FSD by a dermatologist were enrolled. We excluded patients who had a known contact allergy to the ingredients in the tested products, had a severe uncontrolled facial skin disease, or were pregnant or lactating. Informed consent was obtained from patients before the research commenced.

Each patient was given the trial moisturizer (Eucerin Instant Calming; Beiersdorf, Hamburg, Germany) to apply twice daily to the whole face for 20 weeks. The ingredients of the trial moisturizer were as follows: aqua, glycerin, panthenol, Butyrospermum Parkii butter, cetyl palmitate, olus oil, pentylene glycol, methylpropanediol, sodium polyacrylate, 4-t-butylcyclohexanol (trans-isomer), Glycyrrhiza Inflata root extract, caprylyl glycol. At the study's baseline, 6 patients with an FSD severity that needed TCS were treated with concomitant mild potency TCS twice a day for 1 week or less. Additionally, the study protocol required that TCS was to be employed as rescue therapy should a patient experience an uncontrolled flare-up of facial FSD during the study period. Patient compliance was monitored by measuring the weight of the given product at each return visit. A gentle cleanser (Eucerin pH5 Wash Lotion Perfume Free; Beiersdorf, Hamburg, Germany) was also provided. Any other topical medications, skin care agents, or cosmetic products for the face were disallowed throughout the study.

### Efficacy assessments

The clinical severity of FSD (erythema, scale, and investigator global assessment [IGA] of disease severity) was evaluated by 2 physicians (S.W. and S.P.) using a scale of 0 to 3 (0 = absence, 1 = mild, 2 = moderate, and 3 = severe). The patients were requested to grade their disease severity and symptoms (erythema, scale, and pruritus) using a visual analog scale (0–10) and to record the frequency of disease flare-ups each week during the study period. The physicians and the patients separately assessed the global improvement of severity using 5 score levels. The scores were 0 = no change (not improved or improved by less than 25%); 1 = slight improvement (improved 25%–50%); 2 = moderate improvement (improved 51%–75%); 3 = marked improvement (improved 76%–99%); and 4 = completely clear (no lesions). The various assessments were performed at baseline and weeks 1, 2, 4, 8, 12, and 20.

Digital photographs were taken serially at every visit with the same facial position using a VISIA-CR (Canfield Scientific, NJ, USA). Skin hydration and transepidermal water loss (TEWL) were measured with a Corneometer CM 825 and a Tewameter TM 300 (both from Courage and Khazaka Electronics; Cologne, Germany), respectively. All parameters were measured on the glabellar area and both nasolabial folds in a systematically controlled environment at all visits. The mean value of each parameter was documented.

A satisfaction questionnaire relating to the trial moisturizer was given to patients at the conclusion of the trial. The questionnaire explored difficulty in spreading the moisturizer, irritation, absorption, symptom relief, smell, price, and texture. The physicians and patients rated their satisfaction with the outcomes using the previously mentioned visual analog scale.

### Statistical analysis

Descriptive statistics were used to summarize demographic data and satisfaction scores. Categorical data are shown as numbers and percentages, and continuous data are presented as the mean ± standard deviation or median (minimum, maximum). Repeated measures ANOVA was used to compare efficacy assessment scores, the percentage and frequency of disease flare-ups, and bioengineering data changes in normally distributed outcomes at each time point. Differences were further analyzed using the pairwise comparison method. The analyses were performed using SPSS Statistics version 18.0 (SPSS Inc, Chicago, IL, USA). P values less than 0.05 were considered statistically significant for all tests.

## Results

### Clinical efficacy

A total of 20 patients were enrolled. Their mean age was 38.9 ± 10.4 years, and women predominated (55%). Fifteen patients (75%) had moderate severity of FSD. The illness had run a chronic course in most enrolled patients, whose median duration of having FSD was 10 years. The median frequency of disease flare-up was once per month (range, 0–4 times/month). Six patients (30%) were treated with a 1-week concomitant TCS at the study's baseline. No rescue TCS therapy was needed. The demographic data are detailed in table 1.

**Table 1:** Demographic data of patients with facial seborrheic dermatitis.

| Characteristics | All Patients (N=20) |
|---|---|
| Sex, n (%) | |
| Male | 9 (45.0) |
| Female | 11 (55.0) |
| Age (years), mean ± SD | 38.9±10.4 |
| Age of onset (years), mean ± SD | 26.8±13.5 |
| Disease duration (years), median (min, max) | 10.0 (0.2,38.0) |
| Underlying disease, n (%) | |
| Diabetes mellitus | 4 (20.0) |
| Hypertension | 3 (15.0) |
| Allergic rhinitis | 1 (5.0) |
| Other* | 4 (20.0) |
| Disease severity, n (%) | |
| Moderate | 15 (75.0) |
| Mild | 5 (25.0) |
| Frequency of disease flare-ups (times/month), | 1.0 (0,4.0) |
| Median (min, max) | |
| Previous topical steroid use, n (%) | 10 (50.0) |
| Previous moisturizer use, n (%) | 12 (60.0) |
| Concomitant topical steroid use at baseline, n (%) | 6 (30.0) |

*, antiphospholipid syndrome, breast cancer, cerebrovascular disease, coronary artery disease.

Our physician assessments revealed a statistically significant improvement in erythema, scale, and IGA of disease severity after 1 week of moisturizing product use (Figure 1a). Concurrently, our patients' grading of disease severity and symptoms (erythema, scale, and pruritus) showed substantial decreases after using the moisturizer. The first clinical sign demonstrating a significant decrease was scale (after 1 week of use), followed by erythema and pruritus (after 2 weeks of use; Figure 1b). All parameters maintained significant improvements at every subsequent follow-up relative to the baseline.

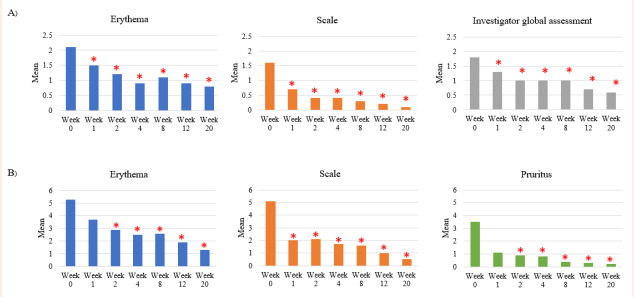


**Figure 1:** Clinical severity scores of patients treated with the test moisturizer as monotherapy assessed by A) physician and B) patients.

*P value < 0.05 compared with baseline.

According to the physicians' and patients' global improvement of severity assessments, the proportion of patients who had a marked improvement or were completely clear of the disease significantly increased after using the trial moisturizer for 12 and 20 weeks (Figure 2). Representative clinical pictures of participants are shown in figure 3. The number of patients with FSD flare-ups and the frequency of disease exacerbation significantly decreased from the end of the first week and during the remainder of the study period (Figure 4). The severity of the flare-ups was mild, and no patient needed TCS rescue therapy.

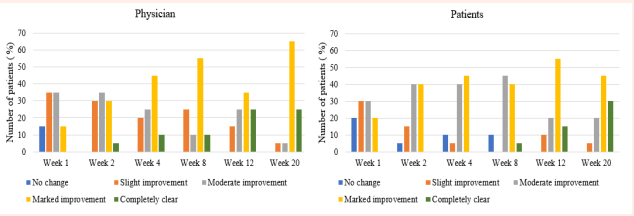


**Figure 2:** Global improvement severity assessment by physician and patients.

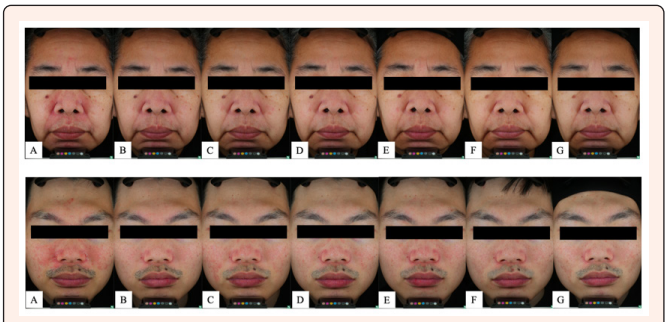


**Figure 3:** Clinical pictures of patients with facial seborrheic dermatitis by VISIA at A) baseline, B) week 1, C) week 2, D) week 4, E) week week 8, F) week 12, and G) week 20.

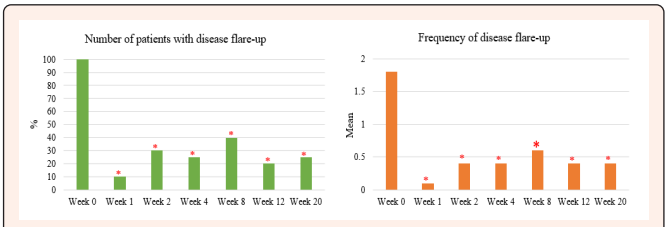


**Figure 4:** Number of patients with disease flare-ups during the study period and mean frequency of disease flare-ups per week.

* P value < 0.05 compared with baseline.

The mean values of skin hydration significantly increased at all follow-up time points. TEWL measured at the nasolabial folds began to decline significantly at the week-4 follow-up. In addition, the mean value of TEWL measured at the nasolabial folds and the glabella was significantly decreased at the study's end (table 2).

**Table 2:** Bioengineering assessment of patients with facial seborrheic dermatitis at week 0, week 1, week 2, week 4, week 8, week 12, and week 20.

| | Mean ± SD | | | | | | | P value |
|---|---|---|---|---|---|---|---|---|
| | Week 0 (N=20) | Week 1 (N=20) | Week 2 (N=20) | Week 4 (N=20) | Week 8 (N=20) | Week 12 (N=20) | Week 20 (N=20) | |
| Skin hydration (mg/cm²) | | | | | | | | |
| Glabella | 42.7±15.1 | 57.3±14.2 | 62.9±11.8 | 58.4±11.9 | 58.3±13.1 | 63.9±11.1 | 62.9±14.3 | <0.001[1,2,3,4,5,6] |
| Nasolabial fold | 27.3±17.8 | 43.0±19.7 | 49.4±15.4 | 45.6±13.1 | 43.4±12.7 | 50.4±15.5 | 51.3±13.8 | <0.001[1,2,3,4,5,6] |
| Mean | 35.0±12.0 | 50.2±13.6 | 56.2±11.3 | 51.9±9.5 | 50.9±8.3 | 57.1±9.9 | 57.1±12.8 | <0.001[1,2,3,4,5,6] |
| TEWL (g/m²/h) | | | | | | | | |
| Glabella | 14.3±7.1 | 13.0±6.8 | 12.8±6.7 | 13.4±8.1 | 13.7±5.8 | 13.2±5.8 | 12.3±6.9 | 0.538 |
| Nasolabial fold | 32.0±14.4 | 25.7±10.1 | 22.4±7.0 | 22.0±8.9 | 22.1±6.8 | 21.6±6.8 | 20.7±7.8 | 0.042[3,4,5,6] |
| Mean | 23.2±10.0 | 19.4±7.5 | 17.6±6.1 | 17.7±7.9 | 17.9±6.0 | 17.4±5.8 | 16.5±6.8 | <0.001[6] |

[1]: Week 0 vs Week 1, [2]: Week 0 vs Week 2, [3]: Week 0 vs Week 4, [4]: Week 0 vs Week 8, [5]: Week 0 vs Week 12, [6]: Week 0 vs Week 20

P value < 0.05 was considered to be statistical significance.

To compare change in normally distributed outcomes among 7 time points, Repeated measure ANOVA was used. Differences were further analyzed using the pairwise comparison method.

Abbreviations: TEWL, transepidermal water loss; SD, standard deviation

A subgroup analysis was carried out on 14 FSD patients who used the trial moisturizer as monotherapy. The physician grading of disease severity, indicated by scale and erythema, significantly improved at week 2, whereas IGA significantly improved at week 12 of the study. Regarding the patients' assessments using the visual analog scale, the severity of scale and erythema significantly decreased at weeks 2 and 4, respectively. The patients also reported that pruritus symptoms tended to decrease after using the moisturizer.

### Safety and satisfaction assessments

All patients tolerated the trial moisturizer well. No adverse events were reported. Regarding product satisfaction, the participants strongly agreed that the moisturizer spread easily on the skin (70%), did not cause allergies or irritation (70%), was well-absorbed (55%), relieved facial rashes (50%), had a pleasant smell (40%), was affordable (35%), and had a light texture (20%). The mean scores for overall product satisfaction among the physicians and participants were 7.9 and 9.0 out of 10, respectively.

## Discussion

This study demonstrated the excellent efficacy of a moisturizer containing 4-t-butylcyclohexanol and licochalcone A as an adjunctive or monotherapeutic treatment for mild to moderate FSD and its prevention. The moisturizer significantly reduced disease severity in terms of erythema, scale, pruritus, and overall severity. Its positive effects were observed as early as the first or second week of use, and its efficacy continued throughout the remainder of the trial period. By the end of the study, most patients demonstrated marked clinical improvements or were completely clear of lesions. The improvements in stratum corneum hydration and TEWL also indicated amelioration of skin barrier function.

As a monotherapy, the moisturizer was also effective for mild to moderate FSD. However, its efficacy was detected as a more gradual onset than for patients given low-potency, 1-week TCS during the first week due to their FSD severity. This result supports a previous study that demonstrated that the test moisturizer could improve the clinical severity of facial dermatitis but had a more gradual onset than TCS [12].

Due to chronic course of disease, the treatment of FSD should aim to control the frequency and severity of exacerbation. Various topical non-pharmacological treatments were reported to speed FSD recovery and prevent flare-ups [14]. The current investigation also established that continuous use of the test moisturizer prevented or reduced the frequency of relapses and decreased the intensity of exacerbation during the long-term management of FSD, which is most desirable for patients with chronic FSD. Our study revealed that the number of patients with disease flare-ups and the frequency of relapses significantly decreased during the study. Moreover, these lower rates were maintained throughout the remainder of the trial. Although the flare-up frequency slightly increased in week 8, this might be because the study was conducted during summer and was accompanied by a rigorous face mask-wearing protocol due to the COVID-19 pandemic. However, the intensity of the FSD exacerbations was mild, and no patients required rescue therapy with TCS during the trial.

In conclusion, the trial moisturizer containing 4-t-butylcyclohexanol and licochalcone A is a safe option as adjunctive therapy for the long-term management of mild to moderate facial FSD. The administration of TCS might be appropriate for initial treatment to alleviate symptoms quickly. However, the moisturizer offers benefits for the long-term treatment of FSD as maintenance therapy and as a preventive measure. Its use would also reduce patients' exposure to TCS and avoid the side effects related to that drug.

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## References

1. Sampaio AL, Mameri AC, Vargas TJ, Ramos SM, Nunes AP, et al. (2011) Seborrheic dermatitis. An Bras Dermatol 86(6): 72-74.
2. Gupta AK, Bluhm R (2004) Seborrheic dermatitis. J Eur Acad Dermatol Venereol 18(1):13-26.
3. Borda LJ, Wikramanayake TC (2015) Seborrheic Dermatitis and Dandruff: A Comprehensive Review. J Clin Investig Dermatol 3(2).
4. Araya M, Kulthanan K, Jiamton S (2015) Clinical Characteristics and Quality of Life of Seborrheic Dermatitis Patients in a Tropical Country. Indian J Dermatol 60(5): 519.
5. Hengge UR, Ruzicka T, Schwartz RA, Cork MJ (2006) Adverse effects of topical glucocorticosteroids. J Am Acad Dermatol 54(1):1-15.
6. Coondoo A, Phiske M, Verma S, Lahiri K (2014) Side-effects of topical steroids: A long overdue revisit. Indian Dermatol Online J 5(4): 416-425.
7. Sulzberger M, Worthmann AC, Holtzmann U, Buck B, Jung KA, et al. (2016) Effective treatment for sensitive skin: 4-t-butylcyclohexanol and licochalcone A. J Eur Acad Dermatol Venereol 30: 1:9-17.
8. Kolbe L, Immeyer J, Batzer J, Wensorra U, Tom DK, et al. (2006) Anti-inflammatory efficacy of Licochalcone A: correlation of clinical potency and *in vitro* effects. Arch Dermatol Res 298(1): 23-30.
9. Li MT, Xie L, Jiang HM, Huang Q, Tong RS, et al. (2022) Role of Licochalcone A in Potential Pharmacological Therapy: A Review. Front Pharmacol 13: 878776.
10. Schoelermann AM, Weber TM, Arrowitz C, Rizer RL, Qian K, et al. (2016) Skin compatibility and efficacy of a cosmetic skin care regimen with licochalcone A and 4-t-butylcyclohexanol in patients with rosacea subtype I. J Eur Acad Dermatol Venereol 30: 1: 21-27.
11. Wananukul S, Chatproedprai S, Chunharas A, Limpongsanuruk W, Singalavanija S, et al. (2013) Randomized, double-blind, split-side, comparison study of moisturizer containing licochalcone A and 1% hydrocortisone in the treatment of childhood atopic dermatitis. J Med Assoc Thai 96(9): 1135-1142.
12. Boonchai W, Varothai S, Winayanuwattikun W, Phaitoonvatanakij S, Chaweekulrat P, et al. (2018) Randomized investigator-blinded comparative study of moisturizer containing 4-t-butylcyclohexanol and licochalcone A versus 0.02% triamcinolone acetonide cream in facial dermatitis. J Cosmet Dermatol 17(6): 1130-1135.
13. Wananukul S, Chatproedprai S, Charutragulchai W (2012) Randomized, double-blind, split-side comparison study of moisturizer containing licochalcone vs. 1% hydrocortisone in the treatment of infantile seborrhoeic dermatitis. J Eur Acad Dermatol Venereol 26(7): 894-897.
14. Piquero CJ, Hexsel D, Mir BJF, Rozas ME (2019) Topical Non-Pharmacological Treatment for Facial Seborrheic Dermatitis. Dermatol Ther (Heidelb) 9(3): 469-477.