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The efficacy of a bioactive moisturizer in mitigating side effects of acne therapies: a randomized, investigator-blind, split-face trial

Jidapa Triwatcharikorn, Supanee Techamontrikul, Natnicha Ngamdumrongkiat, Pawinee Rerknimitr

Division of Dermatology, Department of Medicine, Faculty of Medicine, Center of Excellence for Skin and Allergy Research, Chulalongkorn University, Bangkok, Thailand

Correspondence: Pawinee Rerknimitr, MD, MSc, Division of Dermatology, Department of Medicine, Faculty of Medicine, Center of Excellence for Skin and Allergy Research, Chulalongkorn University, Bangkok, Thailand. E-mail: pawinee.r@chula.ac.th. Tel.: +66816291862

Key words: bioactive moisturizer; Eucerin® Adjunctive Soothing Care; mucocutaneous side effects; acne vulgaris.

Contributions: Pawinee Rerknimitr: study design, supervision, critical review of the manuscript; Jidapa Triwatcharikorn: experiments; Jidapa Triwatcharikorn, Supanee Techamontrikul, Natnicha Ngamdumrongkiat: manuscript writing. All authors have read and approved the final version of the manuscript and agreed to be accountable for all aspects of the work.

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Availability of data and materials: all data generated or analyzed during this study are included in this article. Further inquiries can be directed to the corresponding author.

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Abstract

Acne treatments often cause mucocutaneous side effects. This study compared a bioactive moisturizer (containing 4-t-butylcyclohexanol, licochalcone A, ceramide, and panthenol) with a traditional moisturizer in Asian patients using adapalene/benzoyl peroxide gel or oral isotretinoin. Forty participants applied each moisturizer to one side of the face. Assessments at weeks 0, 2, and 4 included hydration, trans-epidermal water loss (TEWL), pH, erythema, acne lesion counts, Investigator Global Evaluation of Acne (IGEA), and patient satisfaction. Hydration increased on both sides, with greater improvement from the bioactive moisturizer (p=0.001). TEWL increased more with the traditional moisturizer; skin pH decreased on both sides. Acne lesions decreased equally. Both moisturizers reduced burning sensations, but dryness scores were higher with the traditional product (p=0.021). Patient satisfaction was significantly higher for the bioactive side (p=0.004). The bioactive moisturizer significantly improves hydration and reduces dryness, supporting its role as an adjunct to acne therapy.

Introduction

Acne vulgaris, a chronic inflammatory disorder of the pilosebaceous unit, is common in adolescents.[1] The primary pathogenic mechanisms include follicular hyperkeratinization, excessive sebum production, colonization by *Cutibacterium acnes*, and inflammation.[2] Individuals with acne have compromised skin barriers, which are further aggravated by mucocutaneous side effects of treatment, leading to reduced treatment adherence.[3,4]

Moisturizers contribute to skin barrier strengthening and acne medication tolerability.[5] Advanced skincare formulations incorporate bioactive ingredients to enhance biological effects, such as reducing itch signals and countering inflammation.[6] The bioactive moisturizer assessed in this study (Eucerin® Adjunctive Soothing Care, Beiersdorf AG, Hamburg, Germany) is formulated with key components, including 4-t-butylcyclohexanol (SymSitive®), licochalcone A, ceramide, and panthenol. Notably, 4-t-butylcyclohexanol can mitigate nerve reactions by opposing transient receptor potential channel vanilloid subtype 1 (TRPV1), reducing sensations like burning or stinging.[7] Licochalcone A, derived from the *Glycyrrhiza inflata* root, possesses anti-inflammatory and anti-microbial effects.[8] Thus, this bioactive moisturizer may alleviate mucocutaneous side effects of acne treatments.

This study aimed to compare the effectiveness of a bioactive moisturizer (Eucerin® Adjunctive Soothing Care) *vs.* a traditional hydrophilic cream base (HB, King Chulalongkorn Memorial Hospital in-house formulation) in Asian subjects with varying severities of acne vulgaris undergoing treatment with adapalene 0.1%/benzoyl peroxide 2.5% gel or oral isotretinoin.

Materials and Methods

This randomized, investigator-blind, split-face study was conducted from November 2021 to July 2022 in Bangkok, Thailand. The study protocol received approval from the Institutional Review Board of the Faculty of Medicine, Chulalongkorn University (IRB number 457/64) and was registered in the Thai Clinical Trials Registry under TCTR20230810001. Prior to enrollment, all participants provided written informed consent.

Patient characteristics

Adult participants aged 18 to 60 years with a diagnosis of acne vulgaris, regardless of severity, were eligible for inclusion in the study. Exclusion criteria included recent use of medications known to influence acne, presence of facial skin infections, chronic conditions affecting acne severity, known allergies to the study products, pregnancy or breastfeeding, use of oral contraceptives, and application of topical acne treatments or moisturizers within two weeks prior to study initiation.

Treatment

All patients were assessed by dermatologists and received acne treatment based on their severity level: those with mild to moderate acne were treated with a once-daily application of a fixed-dose adapalene 0.1%/benzoyl peroxide 2.5% gel (Epiduo®, Galderma, Zug, Switzerland), while those with moderate to severe acne were prescribed oral isotretinoin at 10 mg/day, in accordance with established guidelines.[9] Patients were block-randomized to apply both bioactive and traditional moisturizers, with each side of the face receiving a different type. The bioactive moisturizer applied was Eucerin® Adjunctive Soothing Care, containing active ingredients: 4-t-butylcyclohexanol, licochalcone A, ceramide, and panthenol. In contrast, the traditional moisturizer was a hydrophilic cream base (HB), comprising cetyl alcohol, stearic acid, glyceryl monostearate, and propylene glycol. The study duration was four weeks, and patients were instructed to apply topical medication first, wash their hands, and then apply the assigned moisturizer, with the prohibition of other moisturizers during this period.

Clinical evaluation

Patients were examined and followed up at 0, 2, and 4 weeks. The primary outcome measured biophysical skin changes, including hydration, trans-epidermal water loss (TEWL), pH, and erythema, using Corneometer® CM 825, Tewameter® TM 300, Skin-pH-meter PH 900 (MPA 580 Cutometer Dual-Skin Analyzer), and Visia® CR (Canfield Imaging System, NJ, USA), respectively. Patients were instructed to rest for at least 10 minutes in a regulated room with a temperature of 22°C

and a relative humidity of 60% both before and during the measurements. Secondary outcomes included patient-reported scores for redness, itching, burning, dryness, and scaling, graded from 0 (none) to 3 (severe). A physician evaluated acne lesion counts and the Investigator Global Evaluation of Acne (IGEA) at each visit. Patient satisfaction was assessed at the trial's end using a visual analogue scale, ranging from 0 (minimum) to 10 (maximum).

Statistical analysis

Data collected were analyzed using Stata 15.1 software (StataCorp LLC, College Station, TX, USA). Descriptive statistics are reported as mean ± standard deviation (SD), and categorical variables as percentages. Repeated measures data were compared using multilevel mixed-effects regression, with statistical significance set at a p-value less than 0.05.

Results

Demographic and baseline characteristics of the subjects

Forty participants (9 males, 31 females) with a mean age of 30±7.36 years were enrolled. Acne severity was distributed according to the IGEA scale as follows: IGEA 1 (32.5%), IGEA 2 (42.5%), IGEA 3 (15%), IGEA 4 (7.5%), and IGEA 5 (2.5%). Additionally, 18 subjects had recently used various acne treatments (details in Table 1). Post-enrollment, 30 participants were treated with adapalene/benzoyl peroxide gel, and 10 received oral isotretinoin at 10 mg/day.

Clinical outcomes

i) Hydration: Both the bioactive moisturizer and control sides exhibited a statistically significant increase in skin hydration from week 2 onward, as detailed in Table 2 and Figure 1a. The increase in hydration was notably higher on the bioactive moisturizer side throughout the follow-up period ($p=0.001$).

ii) Erythema: No statistically significant changes in erythema scores were observed on either side compared to baseline (Table 2, Figure 1b). The mean erythema score difference between the two sides was not significant over the total follow-up period ($p=0.684$).

iii) TEWL: Significant changes in TEWL were noted on the control side at week 4, with increases observed on the bioactive moisturizer side at week 2 and on the control side at weeks 2 and 4 (Table 2, Figure 1c). However, the mean TEWL difference between the two sides was not statistically significant over the entire period ($p=0.983$).

iv) Skin pH: Both sides showed a statistically significant reduction in skin pH from baseline since week 2 (Table 2, Figure 1d). The mean difference in skin pH between the bioactive and control sides was not statistically significant over the full duration of the study (p=0.628).

Patients' assessment score

A significant reduction in burning scores was observed on both sides between weeks 2 and 4. However, the bioactive moisturizer side demonstrated lower dryness scores compared to the HB side, with a statistically significant difference throughout the study period (p=0.021). No significant differences were observed in other assessment scores, as shown in *Supplementary Table 1* and Figure 1 g,h.

Acne count

Relative to baseline, both sides showed a statistically significant reduction in the absolute change of non-inflammatory acne at week 4, with no significant difference between the sides over the study period (p=0.232) (Figure 1e). For inflammatory acne, significant reductions were observed on both sides at different time points, with no significant difference in the absolute change between the two sides (p=0.094) (Figure 1f).

Patients' satisfaction score

At the end of the study, the mean ± SD of the patient's satisfaction score (ranging from 0 to 10) for the bioactive *vs.* HB sides was 7.93±0.21 and 7.13±0.21, respectively. The difference was statistically significant (p=0.004), favoring the bioactive moisturizer.

Discussion

This study revealed that the bioactive moisturizer group exhibited superior efficacy in enhancing skin hydration compared to the control group, aligning with patient assessments that showed significant differences in dryness scores and higher satisfaction with the bioactive moisturizer. Both treatment and control effectively reduced skin pH, acne counts, and the burning sensation associated with acne treatment.

In acne patients, intrinsic factors may disrupt the skin barrier's integrity. Acne treatments can modify skin structure, potentially increasing TEWL and skin irritation.[10] A study by Grove *et al.* showed that treatment with adapalene 0.1%/benzoyl peroxide 2.5% gel significantly increases skin dryness and TEWL compared to other acne treatments.[11] Concurrent use of moisturizers with adapalene has been shown to reduce skin irritation without compromising therapeutic efficacy, potentially improving

adherence.[12] The reason for the favorable hydration outcome might be attributed to active ingredients, namely ceramides and panthenol, which enhance the skin's barrier function and aid in moisture retention.[13,14]

Both natural and synthetic retinoids activate TRPV1, inducing pain-related reactions that can be alleviated by blocking TRPV1 activity, as demonstrated in *in vivo* experiments.[15] The compound 4-t-butylcyclohexanol counteracts TRPV1, modulating nerve responses in conditions like capsaicin-induced facial stinging, perioral dermatitis, sensitive skin, and facial dermatitis.[7,16] Our study observed a significant reduction in burning scores at weeks 2 and 4, aligning with this mechanism. The absence of differences between the treatment sides may be attributed to the prevalence of only mild burning sensations among patients and the small sample size, explaining the lack of significant differences in redness, itching, and scale scores between the sides.

The acidification of the stratum corneum appears crucial for both the skin barrier's structure and function.[17] As pH levels increase, there is a notable shift in the skin's microbial flora, facilitating the growth of *C. acnes* within a pH range of 6.0-6.5.[18] Prakash *et al.* observed an increase in facial skin pH among individuals with acne, indicating its potential link to the occurrence or recurrence of acne.[19] Our study revealed a significant decrease in skin pH after acne treatment with moisturizers. Ceramides are pivotal in structuring and maintaining the skin barrier, thereby promoting an acidic pH.[14] By administering moisturizers, we may have ameliorated the inflammation process and minimized skin barrier disruption, potentially contributing to the observed decline in pH levels.[3,20] However, it's important to note that skin pH can be influenced by various internal and external factors, including age, gender, oral medication, and sebum activity.[18]

Although no significant differences in acne counts between groups were observed, there was a notable decrease from baseline in both, indicating that the bioactive moisturizer did not impede the effectiveness of acne treatments. While our study has limitations, including a small sample size and a short follow-up period, its strength lies in comparing a bioactive moisturizer with a traditional one, thereby highlighting the added benefits of bioactive ingredients. Future research with larger participant groups and longer observation periods is necessary to confirm our findings and understand the long-term effects of the bioactive moisturizer.

Conclusions

In conclusion, the concurrent use of a bioactive moisturizer containing 4-t-butylcyclohexanol, licochalcone A, ceramide, and panthenol, along with adapalene/benzoyl peroxide gel or oral isotretinoin, substantially enhances skin hydration and effectively reduces adverse mucocutaneous

side effects. This approach has the potential to increase patient adherence and improve the overall effectiveness of acne treatment.

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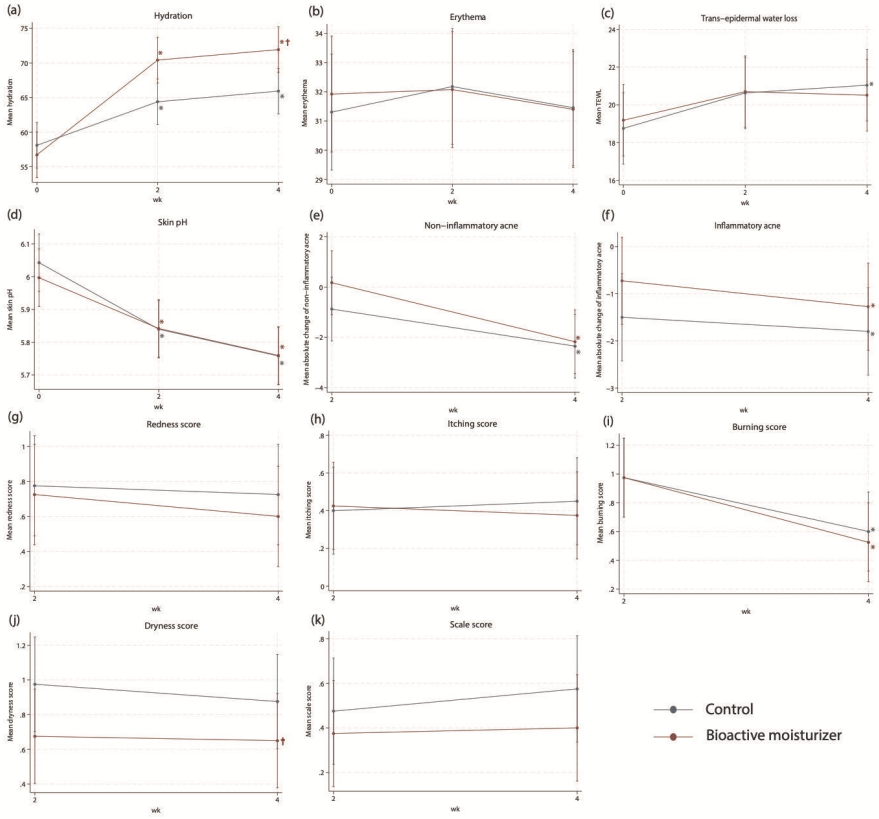
Figure 1. Changes in skin biophysical parameters, acne lesion counts, and patient-reported mucocutaneous adverse events from baseline to week 4, comparing the bioactive moisturizer and control groups. Biophysical measurements include: **a**) skin hydration, **b**) erythema, **c**) TEWL, and **d**) skin pH. Acne outcomes are shown as **e**) non-inflammatory and **f**) inflammatory acne lesion counts. Patient-reported assessments of mucocutaneous adverse events comprise: **g**) redness, **h**) itching, **i**) burning, **j**) dryness, and **k**) scaling scores.



*Statistically significant change compared to baseline ($p<0.05$); †statistically significant change between groups ($p<0.05$).

Table 1. Demographic and baseline characteristic data.

Characteristics	**Values**
Age (years), median ± SD, range	30±7.36, 20-49
Gender, n (%)	
Male	9 (22.5)
Female	31 (77.5)
Underlying disease, n (%)	
Yes	6 (15)
No	34 (85)
History of recently acne treatment, n (%)	
Benzoyl peroxide	8 (20)
Topical retinoids	3 (7.5)
Topical antibiotics	2 (5)
Topical retinoids + topical antibiotics	1 (2.5)
Oral isotretinoin	10 (25)
Miscellaneous	2 (5)
None	22 (55)
IGEA, n (%)	
1	13 (32.5)
2	17 (42.5)
3	6 (15)
4	3 (7.5)
5	1 (2.5)

SD, standard deviation; IGEA, Investigator Global Evaluation of Acne.

Table 2. Outcomes of skin biophysical changes (hydration, erythema, TEWL, skin pH) from baseline through 4-week follow-up visit shown in statistical analysis.

Week	**Bioactive moisturizer**		**Control**		**Between two groups**		
	Estimated mean hydration	**95% CI**	**Estimated mean hydration**	**95% CI**	**Estimated difference hydration**	**95% CI**	**p-value**
0	56.72	53.42-60.02	58.10	54.80-61.40	3.55	1.45-5.65	0.001**
2	70.41*	67.11-73.71	64.39*	61.09-67.69			
4	71.73*	68.63-75.23	65.93*	62.63-69.23			
Week	**Bioactive moisturizer**		**Control**		**Between two groups**		
	Estimated mean erythema	**95% CI**	**Estimated mean erythema**	**95% CI**	**Estimated difference erythema**	**95% CI**	**p-value**
0	31.92	29.94-33.91	31.31	29.32-33.29	0.15	−0.58-0.89	0.684
2	32.08	30.09-34.06	32.18	30.20-34.16			
4	31.40	29.42-33.38	31.46	29.47-33.44			
Week	**Bioactive moisturizer**		**Control**		**Between two groups**		
	Estimated mean TEWL	**95% CI**	**Estimated mean TEWL**	**95% CI**	**Estimated difference TEWL**	**95% CI**	**p-value**
0	19.18	17.29-21.08	18.75	16.86-20.65	−0.01	−1.13-1.11	0.983
2	20.70	18.80-22.60	20.63	18.73-22.53			
4	20.51	18.61-22.41	21.04*	19.14-22.94			
Week	**Bioactive moisturizer**		**Control**		**Between two groups**		
	Estimated mean skin pH	**95% CI**	**Estimated mean skin pH**	**95% CI**	**Estimated difference skin pH**	**95% CI**	**p-value**
0	6.00	5.91-6.09	6.04	5.96-6.13	−0.01	−0.07-0.04	0.628
2	5.84*	5.75-5.93	5.84*	5.75-5.93			
4	5.76*	5.67-5.85	5.76*	5.67-5.85			

CI, confidence interval; TEWL, trans-epidermal water loss; *significant difference ($p<0.05$) between values at baseline and each follow-up visit; **significant difference ($p<0.05$) between the treated side and the control side.

Online Supplementary Material:

Supplementary Table 1. Patients' assessment scores of mucocutaneous adverse events (redness, itching, burning, dryness, and scale) from baseline through 4-week follow-up visit shown in statistical analysis (graded score 0-3).