

Original Article

Evaluation of comedogenic potential of a ceramide-based moisturizer (lotion/cream): A prospective, randomized, double-blind, parallel-group comparative study

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ABSTRACT

Objectives: Comedogenicity is a crucial consideration for cosmetic preparations. While most of the ingredients used in moisturizers may have the ability to cause comedones, the study was done to assess the non-comedogenic potential of test products (Venusia CeraPlus Moisturizers). The primary objective of the study was to evaluate the comedogenic potential of the test products using light microscopy.

Materials and Methods: This was a prospective, randomized, double-blinded, positive- and negative-controlled, two-cohort study to evaluate the comedogenic potential of Venusia CeraPlus moisturizers. Thirty female volunteers with follicular orifices in the upper back region were included in the study after obtaining written informed consent. The four sites were marked for the application of each of the two test products and controls occluded by the patch. A follicular biopsy using the cyanoacrylate method was performed for each site. Product application using a patch was done after 2 h of the biopsy on alternate days. Microcomedones grading was done using rating scale (0 = Non comedogenic, 1 = Small microcomedones, 2 = Moderately sized microcomedones, 3 = Large globoid microcomedones over the entire field).

Results: The mean comedogenic grade for the coconut oil (positive control) and glycerine (negative control) was 1.92 and 0.42, respectively. The significant difference ($P = 0.001$) between the positive and negative control validated the method. The mean comedone grade in Venusia CeraPlus Cream ($P = 0.001$) and Venusia CeraPlus Lotion ($P = 0.001$) was significantly less than that of the positive control. No adverse events were reported during the study.

Conclusion: Based on the results, Venusia CeraPlus moisturizers were non-comedogenic, effective, and well tolerated by participants.

Keywords: Ceramides, Comedogenicity, Comedones, Cosmetics, Moisturizers

INTRODUCTION

The cosmetic market is growing widely with moisturizers being the most used. However, it is important to evaluate the ingredients, safety, and efficacy of each product, as well as the patient's skin type, when recommending moisturizers.^[1] However, the most commonly used oils in moisturizers include olive oil, cocoa butter, and linseed oil, which are comedogenic.^[2]

Comedones develop from the obstruction of sebum secretion in a pilosebaceous duct by an excessive proliferation of keratinocytes.^[3] Follicle hyperkeratinization, or the creation of

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microcomedones, is the initial stage in the life cycle of an acne vulgaris lesion, according to the conventional model of acne pathogenesis, which can also be defined as acne lesion development and progression.^[4] Although it can appear at any time together with inflammatory papules and pustules, comedonal acne is more common in young teenagers.^[5]

Comedogenic chemicals such as lanolin, isopropyl myristate, oleic acid, and stearyl alcohol are present in some cosmetics and can exacerbate or cause acne.^[6] When developing cosmetics, topical drugs, and skin care items, comedogenicity has been a crucial factor to take into account.^[7] Skin irritations can happen, and using dermo-cosmetics is advised to avoid retinoid side effects and adhere to therapy.^[8] Owing to their comedolytic and anti-inflammatory properties, topical retinoids and antibiotics are a mainstay of acne treatment.^[9] Today, many dermatologists confront significant issues due to the increasing prevalence of antibiotic resistance and the likelihood of local delayed hypersensitivity reactions.^[10] As an adjuvant therapy, non-comedogenic moisturizers are often administered to reduce cutaneous irritations caused by acne drugs.^[11]

Ceramides play an important role in stratum corneum functioning as they are the main lipid component of the intercellular gaps of the stratum corneum, which comprise the epidermal permeability barrier, along with cholesterol, free fatty acid, and other minor components.^[12,13] It has been claimed that acne patients have a deficiency in total ceramides and free sphingosine.^[14] Thus, ceramide-containing moisturizers (CCMs) have the potential to improve adherence and enhance current acne treatments.^[15] The ingredients derived from *Avena sativa* are used as abrasives, antioxidants, skin conditioning agents, absorbents, and bulking agents in cosmetics.^[16] Products containing *A. sativa* are used as cutaneous moisturizers in dermatology.^[17] According to certain research, moisturizers can help alleviate acne's symptoms on their own.^[18]

The study assessed the comedogenic potential of Venusia moisturizers (lotion and cream) with topical application under occluded skin patches in healthy adults.

MATERIALS AND METHODS

Study design and setting

It was a prospective, randomized, double-blinded, positive- and negative-controlled, two-cohort study to evaluate the comedogenic potential of test products (cream and lotion). The clinical study protocol and related documents were reviewed and approved by the Independent Ethical Committee of C.L.A.I.M.S. (Clinical and Aesthetic Investigative Management Services) (Approval Form No.: CL/033/0524/STU; Date of approval: July 15, 2024). The study was conducted in compliance with the good clinical practice guidelines international council for harmonization (ICH), the Indian Council of Medical Research, and the Declaration of Helsinki

(Taipei 2016). Approval was obtained from the institutional ethics committee before study initiation and written informed consent was obtained from all the participants before any study-related procedures. The study was registered at the clinical trials registry of India (CTRI/2024/07/071597; dt. July 30, 2024).

Study procedure

The study duration was approximately 1 month, with 24 visits. Once the participants signed the informed consent form, they were screened for eligibility in the study. Participants fulfilling the eligibility were enrolled in the study. The four sites (3×3 cm² each) on the upper back were marked using a template for the application of two test products (lotion and cream) and two controls (positive- coconut oil and negative- glycerine). The positive control was coconut oil due to its comedo-causing potential, while the negative control was glycerine, as it is non-comedogenic.^[6] Initially, follicular biopsy of all four sites was performed using 1–2 drops of cyanoacrylate liquid adhesive application on the glass microscope slide. The slide was then applied gently and carefully on the marked zones and the cyanoacrylate was allowed to set for 30–60 s. After that, the slide was gently removed to yield a follicular biopsy specimen. Product application was then carried out as per randomization on 3×3 cm² marked zones, approximately 2 h after the follicular biopsy test. These were occluded using patch chambers (2×2 cm² patches). Each subject had a patch placed on their upper back, covering the corresponding sites with 0.025 g or mL of the test and control materials, applied by clinical research associates (CRAs). Figure 1 shows the diagrammatic representation of the procedure for the study.

Study participants

Healthy women aged between 18 and 55 years with prominent follicular orifices on the upper region of the back were enrolled. Those who were ready to avoid the intense ultraviolet (UV) exposure as well as contact with water were considered for inclusion. Participants having healthy skin test areas and were ready to wear loose cotton clothes were enrolled in the study. Volunteers with regular dermatological infections and scars/tattoos on the area to be studied were excluded. Pregnant or lactating women, prone to hypersensitivity, cutaneous or systemic disease were not included. Those participants who were receiving any medical treatment either systemic/hormonal or topical which might interfere with the performance of the study treatment were an exclusion.

Randomization and blinding

Randomization was done based on the sites on which the test products and controls were applied. Products were coded by C.L.A.I.M.S. Pvt. Ltd. Block randomization was carried out by C.L.A.I.M.S. Pvt. Ltd.'s QA Department. A randomization

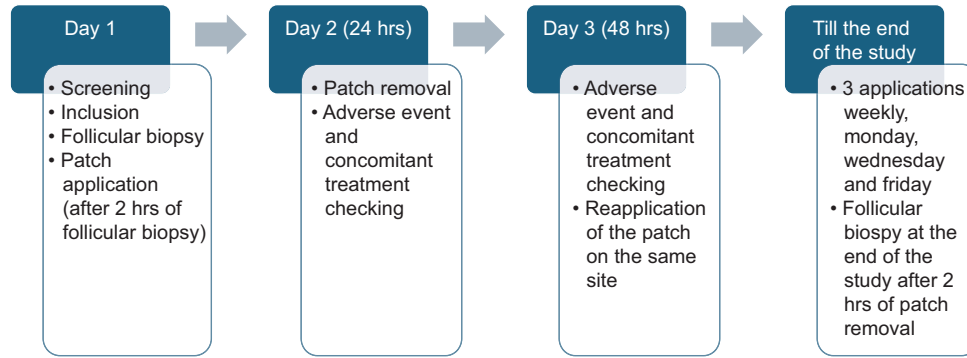


Figure 1: Diagrammatic representation of study procedure.

sheet was generated by the QA Department, which randomly allocated test products and controls to any of the marked test sites. Blinding was ensured with respect to different sites (site 1, site 2, site 3, site 4). Product application was carried out as per randomization by the CRA and evaluation was done by the investigator. It was ensured that the participants and the investigator were blinded to the four treatments.

Test product

Venusia CeraPlus Cream (Ceramide 1,2,3,4,6 II, *Butyrospermum Parkii*, *A. sativa* [Oat], Kernel Oil, *A. sativa* Kernel Extract, Sodium Hyaluronate, Glycerin, Light Liquid, Paraffin, Dimethicone 200, Cetyl Alcohol, *Laminaria digitata* Extract) and Venusia CeraPlus lotion (Ceramide 1,2,3,4,6II, *B. Parkii*, *A. sativa* [Oat], Kernel Oil, *A. sativa* Kernel Extract, Sodium Hyaluronate, Glycerin, Light Liquid, Paraffin, Dimethicone 200, Cetyl Alcohol, *Laminaria digitata* Extract) commercially available as ceramide 1,2,3,4,6II containing moisturizers (manufactured by: Dr. Reddy's Laboratories, India). The formulation provides deep hydration while repairing the skin barrier, skin's barrier restoration, and delivers more soothing and skin relief. Coconut oil and glycerine as controls and the test moisturizers were applied on marked zones and occluded under the patch on the upper back. Patch application/removal was done 12 times during the study.

Study outcome

The primary outcome was the grading of micro-comedones using light microscopy by evaluating the biopsy slides.

Study assessment

Study parameters

Grading of micro-comedones using light microscopy.

Methods and timing for assessing study parameters

The Principal Investigator (Dermatologist) evaluated the biopsy slides and graded the comedones using the below-mentioned scale.

Scale for grading

0	No comedones
1	Small microcomedones
2	Moderately sized microcomedones over most of the field
3	Large globoid microcomedones over the entire field

Sample size

No formal sample size calculation was done. However, 30 participants were enrolled in the study, out of which 26 were analyzed (total drop-out of 4 patients).

Statistical methods and data analysis

All scores were averaged and recorded. Statistical analysis was carried out using the Statistical Package for the Social Sciences version 10.00. All the *P*-values were reported based on a two-sided significance test and all the statistical test was interpreted at 95% level of significance. Mann-Whitney U-test was used for tests of significance. Statistical comparisons included mean comedone grades of positive control versus negative control for method validation and mean comedone grades between test product and positive control.

RESULTS

Demographic and other baseline characteristics

A total of 30 healthy female volunteers were enrolled in the study. Out of which, 4 participants were drop-outs, hence the data analysis was done for 26 participants. All the participants were of an average age of 38.27 years, with 22.00 years being the minimum and 55.00 years being the maximum.

Individual participant comedone grading data

Table 1 shows the participants' comedone grading data. The large globoid microcomedones were maximum at the site with positive control. A total of 8 (30.8%) and 11 (42.3%) participants were non-comedogenic for Venusia CeraPlus

lotion and cream, respectively. However, there was only one (3.8%) large microcomedone for each of the Venusia CeraPlus lotion and cream.

Statistical comparison of mean comedone grades-positive control (coconut oil). Versus negative control (glycerine) (for method validation)

The positive and negative control method was validated by evaluating the comedogenic potential for both test controls. The mean (Standard deviation [SD]) values were 1.92 (0.80) and 0.42 (0.76) for coconut oil (positive control) and glycerine (negative control), respectively.

Statistical comparison of mean comedone grades between test products - Venusia CeraPlus cream and Venusia CeraPlus lotion versus positive (coconut oil) and negative control (glycerine)

Test products were compared with positive control to conclude on comedogenic potential of the test products. Figure 2 illustrates the average mean (SD) comedone grading value for Venusia CeraPlus cream and lotion being 0.81 (0.85) and 1.00 (0.85), respectively. The average mean (SD) of comedones causing the potential for 26 participants in the coconut oil (positive control) site was 1.92 (0.80) and for the glycerine (negative control) site was 0.42 (0.76).

DISCUSSION

A moisturizer is a topical solution made up of ingredients designed to replenish the skin’s natural protective layer and make it more hydrated.^[19] Many moisturizers claim to be effective in treating acne.^[18] The application of cosmetics, such as moisturizers, may result in delayed horny cell desquamation or comedone hyperkeratinization of the follicular epithelium.^[7]

Due to extreme sensitivity, it has been reported that the substances that are weakly comedogenic in the rabbit are probably safe for human use.^[20] The most common ingredients that are used in cosmetics as vehicles that are proven to be comedogenic in a rabbit study conducted by Nguyen *et al.*, 2007 included isopropyl palmitate, isopropyl myristate,

butyl stearate, isopropyl isostearate, decyl oleate, isostearyl neopentanoate, isocetyl stearate, myristle myristate, cocoa butter, while the products that do not cause comedogenicity in rabbit ear model included cocoa butter, cetyl alcohol, paraffin, stearyl alcohol sodium lauryl Sulfate, and petrolatum.^[21]

The aim of comedogenic testing on human models is to measure the amount of microcomedones that form on the backs of the participant. Acne cosmetica prevalence is rising along with the cosmeceutical industry’s expansion. As a result, comedogenicity is a crucial factor for consumers to decide. Comedones of acne cosmetica are smaller, closed, and exhibit less involution of the sebaceous gland.^[22]

The cornerstone of skin disease treatment now includes moisturizers that are high in ceramides. Dermatologists frequently advise applying such as CCM, to mimic skin moisturization for a variety of skin issues brought on by acne treatment.^[11] Our formulations mainly consisted of *ceramide 1,2,3,4,6II*; in the previous study, ceramide-based ointment

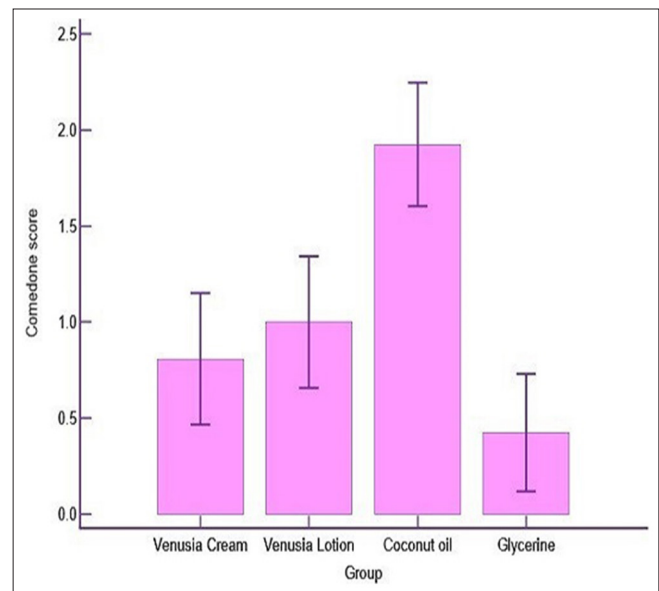


Figure 2: Statistical Comparison of Mean Comedone grades between Test Products- Venusia CeraPlus Cream and Venusia CeraPlus Lotion versus Positive (Coconut Oil) and negative control (Glycerine).

Table 1: Comedone grading with different applications (n=26).

	Venusia-Plus Cream (n=26)	Venusia-Plus Lotion (n=26)	Coconut oil (Positive) (n=26)	Glycerine (Negative) (n=26)
	No. (%)	No. (%)	No. (%)	No. (%)
Non-comedogenic	11 (42.3)	8 (30.8)	0 (0.0)	18 (69.2)
Small microcomedones	10 (38.5)	11 (42.3)	9 (34.6)	6 (23.1)
Moderately sized microcomedones over most of the field	4 (15.4)	6 (23.1)	10 (38.5)	1 (3.8)
Large globoid microcomedones over the entire field	1 (3.8)	1 (3.8)	7 (26.9)	1 (3.8)
"p"*	0.001	0.001		

*P-value: Mann-Whitney U-test versus positive control (Coconut oil), No.: Number of females

has proven to be effective in lack of comedogenicity. According to the results of a previous study, the mean value of ceramide-based ointment was 0.12, while for positive and negative control, it was 0.59 and 0.18, respectively.^[23] With its occlusive and emollient properties, *dimethicone* reduces transepidermal water loss (TEWL) without leaving a greasy aftereffect. It is suitable for those with sensitive skin types and acne because it is non-comedogenic and hypoallergenic. *Glycerine* and *B. parkii* play an important role in hydrating the stratum corneum.^[18,24] To improve the skin's ability to retain water, simple moisturizers blend occlusives with humectants.^[25] Therefore, the ingredients in the Venusia CeraPlus moisturizers provide the benefits of non-comedogenicity and hydrating.

The study conducted by Letawe *et al.*, 1998 for topically applied linoleic acid on acne microcomedones showed about a 25% reduction in their overall size being achieved over a 1-month treatment period.^[26] However, the comedogenicity of Venusia CeraPlus cream and Venusia CeraPlus Lotion was quite low as compared to the positive control (coconut oil), indicating the test products to be non-comedogenic ($P = 0.001$). The previous study results state that coconut oil is a highly comedogenic substance, thus it was used as a positive control.^[27] As glycerin is a humectant and non-occlusive agent, it does not cause comedones and was used as a negative control in the study.^[18] The method validation was done by comparing the mean comedone grades for negative control (glycerine) and positive control (coconut oil). The mean comedone grading for glycerine was significantly less ($P = 0.001$) as compared to coconut oil. Even when applied to vast parts of the body over extended periods of time, moisturizers are rarely linked to health risks. Minor issues like urticaria, cosmetic acne, dermatitis, and skin irritation may occur with moisturizers.^[28] The product has proven to be non-comedogenic, and no skin tolerances or adverse events were reported during the study.

Strengths and future prospects

First, a prospective, randomized, double-blinded study design with both positive and negative controls is the biggest strength of this study. Second, the study being conducted at a single center provides homogeneity to the study participants. Third, all test and control treatment effects were assessed on the same participant making the study design robust. A larger study with multiple centers across India and in diverse study population could be further planned to improve the external validity of the study.

Limitations

A small sample size and short study duration are a possible limitation of this study.

CONCLUSION

Venusia CeraPlus moisturizers (cream and lotion) occluded patch application decreased the number of microcomedones as assessed by light microscopy. The comedogenicity of the positive control (coconut oil) was significantly higher than the test products. The products are proven to be safe for intended use as no adverse events were reported.

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Ethical approval: The clinical study protocol and related documents were reviewed and approved by the Independent Ethical Committee of C.L.A.I.M.S. (Approval Form No.: CL/033/0524/STU; Date of approval: July 15, 2024).

Declaration of patient consent: The authors certify that they have obtained all appropriate patient consent.

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Conflicts of interest: All the authors are the employees of Dr. Reddy's Laboratories Ltd., Hyderabad, Telangana, India.

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