

Article

Soothing Effect of a Cosmetic Product on Skin Discomforts Induced by a Chemical Irritant (Capsaicin) and UV-Radiation, and after Mosquito Bites and Sunburn in a Real-World Setting

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Abstract: Irritated and itchy skin is a common skin condition. Consumers tend to opt for natural ingredients for irritated skin (e.g., after insect bites or sun exposure). We tested a cosmetic product with 94% of its ingredients being of natural origin, each with its beneficial properties, e.g., nourishing shea butter, cooling menthol, and soothing bisabolol. Skin discomfort was induced either by a chemical irritant (capsaicin) or UV radiation by a solar simulator. In this clinical, prospective, and controlled experimental study, we investigated the soothing effect of the tested product. We observed a soothing effect on the capsaicin-induced itching and stinging sensation with a statistically significant decrease in the discomfort sensations one minute after a single application. The tested product also showed a significant reduction in the UV-induced skin erythema (UVA+B exposure). In a real-world study, these results can be correlated with a decrease of itching and irritation after sunburn or after insect bites.

Keywords: sunburn; insect bite; pruritus; itch; skin irritation; menthol; shea butter; bisabolol; cosmetics; soothing



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1. Introduction

1.1. Skin Barrier

Skin is the largest organ and protects us from environmental injuries, including those resulting from exposure to the ultraviolet radiation (UVR) in sunlight [1] and microbial invasion. In addition, skin is essential for body homeostasis by regulating temperature and maintaining hydration. To fulfil those life preserving capabilities, skin's structure provides the necessary components. Herein, the most superficial layer of the epidermis, stratum corneum (SC), is of special importance, containing natural moisturizing factors (NMF) and intercellular lipids. The primary lipids forming the SC matrix are approximately 20% free fatty acids (FFAs), 20% cholesterol (CHOL), and 60% ceramides (CERs). The proportions of lipids, including CHOL, FFAs, and CERs, are essential to forming an effective skin barrier that prevents transepidermal water loss (TEWL) [2]. Healthy skin retains enough water and acts as a hydrolipid film to function as a first-line defense against outside factors [1].

1.2. Dry Skin and Itching

Dry skin can cause pruritus or worsen pre-existing pruritus associated with other dermal conditions. Current European guidelines for pruritus recommend maintaining an optimal basic skin care with lipid-replenishing, hydrating properties to stabilize the physiological skin barrier [3,4]. The soothing effect of emollients and moisturizers on dry and itchy skin is well documented [3,4]. Natural oils are now being increasingly recognized for their effects on both skin diseases and the restoration of cutaneous homeostasis and are, therefore, important components in cosmetics and pharmaceutical products [5]. Differing ratios of essential fatty acids are major determinants of the barrier repair benefits

of natural oils. Natural components like shea butter also show clinical benefits including anti-inflammatory and antioxidant effects on the skin and promotion of wound healing [5]. There is a close link between barrier damage, dry skin, and itch [6]. Here the clinical benefits of moisturizers have been shown to tackle barrier function disruption as well as inflammation [7].

1.3. Pathophysiology of Sunburn

The ultraviolet (UV) components of sunlight present a considerable health hazard causing various immediate and long-term deleterious effects. Those include acute erythema (sunburn), degradation of collagen and elastin, wrinkled appearance of the skin (photoaging) [8], and direct skin tissue damage by promoting oxidative stress and attacking proteins, lipids, and DNA [1].

Although the precise mechanism has not been clearly identified, sunburn response is induced by acute overexposure to UV radiation, principally ultraviolet B (290–320 nm), and ultraviolet A (320–400 nm) [1]. UVB radiation changes the epidermal permeability barrier [9,10] and reduces SC hydration [9]. After UVB radiations of 0.75 minimal erythema dose, Basal TEWL in human skin increases significantly [11]. The use of cooling agents and of moisturizers for sunburn is broadly recommended [12]. The increased TEWL can be addressed with natural oils and hydrating agents (e.g., shea butter) [2], complemented with compounds with soothing properties (e.g., bisabolol) [13].

1.4. Pathophysiology of Insect Bites and Stings

With their saliva, insects can inject a pruritic and/or pain-inducing substance through the epidermis into the dermis. This triggers a cascade of histamine receptors, inducing neurogenic inflammation, itch, erythema, and oedema [14,15].

The histamine-dependent pruritic pathway is the most prominent and historically acknowledged direct mediator of itch [16]. The amount of histamine contained in the saliva of mosquitoes seems to be enough to induce itch, depending on individual tolerance. Other saliva components are anticoagulant factors, vasodilators, and enzymes that may be involved in the direct elicitation of bite-induced itch. Bites can induce an immediate wheal and flare reaction that peaks after 20 min and/or delayed pruritic indurated papules within 24–36 h. Intense pruritus may accompany all phases of the reaction [17].

Most reactions to insect bites and stings are mild [18]. Itch-reduction is of special importance to prevent secondary infection due to scratching [19] and the so-called itch-scratch vicious cycle. The latter describes the fact that repeated scratching prolongs and aggravates the itch, in the case of mosquito bites and various situations like atopic dermatitis [20]. Cooling is an established and effective temporary remedy for itch [21]. Dermatologists widely recommend applying an anti-itch cream or ice pack to soothe bug bites and stings, and the use of moisturizers is beneficial, too [22]. In addition, in the case of popular urticaria associated with insect bite hypersensitivity, moisturization is recommended in pediatric settings [23].

1.5. Use of Natural Products for Soothing Irritated Skin

Natural ingredients in cosmetics are used to stabilize and repair the skin barrier, and they can show soothing and anti-inflammatory effects on irritated skin, too [3]. In this manuscript, we present three clinical approaches in which we tested a novel soothing cosmetic product with the Formula Code (FC) 16419 intended to be applied after mosquito bites and sunburn (marketed as FeniNatural by GSK Consumer Healthcare GmbH & Co. KG a Haleon company). In one experimental study, we assessed the effect of this cosmetic product on decreasing the skin discomfort induced by a chemical irritant (capsaicin). In this standardized test under dermatological control, capsaicin leads to an irritated, inflamed skin condition. In a second experimental study, we evaluated the effect of the cosmetic product in reducing the skin redness induced by the exposure to UVA+B radiation together with its moisturizing effect. In a third approach, we tested the effects of the cosmetic

product under everyday conditions in a real-world setting. Here, the participants of an in-use test were instructed in product application after mosquito-bites or sunburn.

2. Materials and Methods

2.1. Formulation Approach and Actives Selection

2.1.1. Formulation Approach

The ingredients of the here-tested cosmetic product with Formula Code (FC) 16419 (marketed as FeniNatural by GSK Consumer Healthcare GmbH & Co. KG a Haleon company, Munich, Germany) were chosen according to their beneficial properties for irritated skin. The aim was to combine components which soothe itchy and irritated skin after insect-bites and sunburn. Being used on acute irritated skin, the galenic of the product is a true oil-in-water emulsion (O/W) with a high-water content. This light emulsion itself supports the cooling effect with the water content evaporating slowly. FeniNatural consists of 94% natural-origin ingredients (6% other ingredients to protect and stabilize the formulation), each with its beneficial properties, e.g., nourishing shea butter, cooling menthol, and soothing bisabolol (from the bark of the candeia tree). It has a lightweight cream texture, is dermatologically tested, and smells of fresh menthol. It is suitable for children, due to approval of menthol content starting from 2 years of age and older [24].

2.1.2. Active Ingredients Selection

The active ingredients were chosen for their characteristic nourishing and soothing properties addressing barrier function disruption, dry skin, itch, and inflammation [6,7]. FC 16419 contains emollients, such as shea butter, which are considered a first line topical treatment and are frequently recommended in the management of dry and itchy skin [25]. The addition of ingredients such as menthol (0.5% or 1%) in this lightweight emulsion is also recommended for itch [24]. The ingredient list of FC 16419 is as follows: Aqua (Water), Caprylic/Capric Triglyceride, Ethylhexyl Palmitate, Cetearyl Alcohol, Potassium Cetyl Phosphate, Butyrospermum Parkii (Shea) Butter, Cera Alba (Beeswax), Cetyl Palmitate, Glycerin, Phenoxyethanol, Glycyrrhetic Acid, Menthol, Oleyl Alcohol, Xanthan Gum, Ethylhexylglycerin, Tocopheryl Acetate, Zanthoxylum Bungeanum Fruit Extract, Sodium Phytate, Lecithin, Bisabolol, Tocopherol, Ascorbyl Palmitate, Citric Acid.

The active shea butter (*Butyrospermum parkii*) was selected focusing on its beneficial effects including the repair of skin barrier, its anti-inflammatory and antioxidant effects, and promotion of wound healing. It protects and nourishes the skin by retaining moisture in the skin [5]. Shea butter is a common emollient in skin care and cosmetic product formulations. It contains unusually high levels (5–15%) of non-saponifiable lipid constituents in the fat, which are a potentially rich source of Vitamin E, a natural antioxidant [26]. According to the European Cosmetic Ingredient (CosIng) database, shea butter has a skin conditioning effect [27].

The active menthol was selected for its cooling properties. Menthol is an organic compound that is typically derived from plants. Topically applied, menthol produces a sensation that can be described as “cooling” or “fresh” [28]. Topical menthol dilates blood vessels and, thus, promotes blood flow and induces a fresh and cool sensation which reduces itch and pain [29]. The cooling sensation on the skin results from a physiological action on the nerve endings [30]. Besides the cooling sensation, it has antipruritic effects, too. It was shown to alleviate itch in the conditions where cooling was effective, like atopic dermatitis and psoriasis, or in experimental studies where itch was induced by injections of histamine or hydroxyethyl starch. Topically applied menthol is a chemical activator of cold sensitive A-delta fibres [31]. It elicits the same cool sensation as low temperature. In neurological studies, topical menthol is used to mimic cold pain, by exposing skin to high concentrations of topical menthol and, thus, inducing the typical cold sensation [32]. According to the CosIng database, menthol has a refreshing effect in addition to its soothing effect [33].

The active bisabolol was selected as a skin conditioning agent which is also known to soothe sensitive skin [13]. The natural α -bisabolol of FC 16419 is obtained from candeia oil from the Brazilian tree *Vanillomopsis* (candeia tree). The use of α -bisabolol or bisabolol-rich oil as an anti-inflammatory agent is ubiquitous [34]. According to the CosIng database, bisabolol has a skin conditioning effect in addition to its soothing effect [35].

2.2. Experimental Design and Participants

In three clinical studies, we tested a novel soothing cosmetic product with natural ingredients intended to be applied after mosquito bites and after sunburn (FC 16419). The product was tested prospectively and under controlled conditions in an experimental setting designed to demonstrate the product efficacy in decreasing the skin discomforts induced by a chemical irritant (capsaicin) and by UVA+B radiation by a solar simulator. The third clinical study took place in a prospective real-world setting with accidentally occurring mosquito-bites or sunburn. The participants were healthy volunteers. All the study procedures were carried out in compliance with the ethical principles for medical research (Ethical Principles for Medical Research Involving Human Subjects, adopted by the 18th WMA General Assembly Helsinki, Finland, June 1964 and amendments).

2.2.1. Assessment of the Soothing Effect of a Cosmetic Product on Skin Discomforts Induced by a Chemical Irritant (Capsaicin)

The first study aimed to assess the effect of the cosmetic product in decreasing the skin discomforts induced by a chemical irritant (capsaicin). The randomized, controlled, experimental clinical study was carried out on 20 healthy female/male participants aged between 18 and 65 years old, sensitive to the capsaicin stinging test. The stinging sensation was induced by a 10% capsaicin aqueous (hydroalcoholic) solution on both the right and the left side of the nose (alar groove) to induce skin irritation. The capsaicin assay is a standard experimental setting, used previously to investigate skin calming effects of cosmetic products [36]. The tested product was FC 16419, and the negative control was demineralized water, both applied to areas irritated with capsaicin. Timepoints of measurement were:

- (A) Application of 10% capsaicin aqueous solution
- (B) T_0 —Timepoint of maximum stinging/itch sensation (approximately 2/3 min after application of capsaicin solution)
- (C) Application of FC 16419/demineralized water on right/left nasolabial fold
- (D) T_i —Intensity of perceived discomfort (stinging/itch) immediately after the first products application
 - T_1' —Intensity of stinging/itch 1 min after products application
 - T_2' —Intensity of stinging/itch 2 min after products application
 - T_3' —Intensity of stinging/itch 3 min after products application
 - T_4' —Intensity of stinging/itch 4 min after products application
 - T_5' —Intensity stinging/itch 5 min after products application
 - T_{10}' —Intensity of stinging/itch 10 min after products application

If the stinging and itching feeling lasted more than 10 min, participants continued the evaluations every 2 min at T_{12}' – T_{14}' etc. until the discomforts disappeared.

For the measurement of stinging/itching sensation, we used a 4-point scale (Table 1).

Table 1. Measurement of clinical stinging/itching after capsaicin application in a 4-point scale.

Clinical Scoring of Stinging/Itching Sensation	Score
No reaction	1
Mild reaction	2
Moderate reaction	3
Severe reaction	4

2.2.2. Clinical Evaluation of the Soothing Effect of a Cosmetic Product on Skin Irradiated by a Solar Simulator (UVA+B)

The aim of the second randomized, controlled, experimental clinical study was to evaluate the effect of a cosmetic product in reducing skin redness caused by the exposure to UVA+B radiation. The source of UVA+B radiation was a Multiport 601–300 W Solar simulator (Solar[®] Light Co., Inc., Philadelphia, PA, USA) compliant with ISO 24444:2010 standard requirements. The UVB dose was adjusted with a model PMA 2100 radiometer (Solar[®] Light Co., Inc., Philadelphia, PA, USA) equipped with a PMA 2103 LLG SUV detector (Solar[®] Light Co., Inc., Philadelphia, PA, USA). Both the solar simulator and the radiometers were calibrated externally. With 20 healthy female/male participants aged at least 18 years old, the test was carried out on volunteers' backs in 2 areas. One area was treated with FC 16419 after UV Radiation, and one was left untreated as a control after UV radiation. The product's soothing effect was evaluated 30 min, 1, 2, and 24 h after its first application by means of non-invasive bioengineering techniques able to measure the skin erythema index (Mexameter[®] MX 18, Courage + Khazaka electronic GmbH, Cologne, Germany). Skin moisturization was measured by a Corneometer[®] CM 825 (Courage + Khazaka electronic GmbH, Cologne, Germany). The study scheme is summarized in Table 2.

Table 2. Evaluation of product soothing effect after UV radiation.

Experimental Times	Area 1 Control Area—Untreated Area	Area 2 Treated Area
T − 1	Evaluation of MED (minimal erythema dose) and Erythema index on volunteers' back before UV exposure (baseline values)	
T ₀	Exposure to a fixed dose of UVA+B radiation (calculated as 1.5 MED for each subject) Evaluation of Erythema index on volunteers' back 20 ± 4 h after the UV exposure	
	Product application by the experimenter (2 mg/cm²)	
T30 min *	Evaluation of Erythema index on volunteers' back 30 min after the first product application	
T1 h *	Evaluation of Erythema index on volunteers' back 1 h after the first product application	
T2 h *	Evaluation of Erythema index on volunteers' back 2 h after the first product application	
T24 h **	Evaluation of Erythema index on volunteers' back 24 h after the first product application	

* During the 2 h after the first product application, the participants remain in the laboratory in a room under controlled temperature and humidity conditions. ** In order to perform the T24 h measurement, participants were asked not to wash or expose to UV the tested skin areas until the end of the study.

2.2.3. Test of Use Aimed to Evaluate the Soothing Efficacy of the Cosmetic Product after Accidental Mosquito Bites and Sunburn

After 2 experimental controlled studies, our third study tested the effects of the cosmetic product under real conditions in a test of use study design. The participants were instructed in product application in case of mosquito-bites or sunburn. A total of 33 healthy female/male participants over 18 years were instructed to use the product during an observation period of 28 days under real-world conditions, such as after UV exposure on sunburn and after mosquito bites. The participants were asked to fill out a diary after each product application in the case of mosquito-bites (for 5 ± 1 bites) or sunburn (once/twice). The test product was FC 16419. In the case of at least two occurring insect bites, the evaluation was also taken in an untreated control area. Itching, redness, and irritation were scored by the participants on a Visual Analogue Scale (VAS 0–10 cm; 0 = no itching/redness/irritation and 10 = strong itching/redness/irritation). The evaluation of sunburn included a sub-group analysis of moderate vs. severe sunburn. Severe sunburn responders were all the subjects who scored the sunburn reaction ≥ 7 on the VAS. In addition, the participants were asked to describe the cooling effect after insect bites and sunburn.

2.3. Statistics

Statistical analysis was performed using NCSS 8 (version 8.0.4 for Windows; NCSS, Kaysville, UT, USA) running on a Windows Server 2008 R2 Standard SP1 64-bit edition (Microsoft, Redmond, WA, USA). A two-way t test of students was performed for normally distributed data (instrumental measurements), while a Wilcoxon test was performed for non-parametric data (clinical analysis). A $p < 0.05$ was considered statistically significant. Statistical analysis output was reported as follows: * $p < 0.05$, ** $p < 0.01$, and *** $p < 0.001$.

3. Results

3.1. Soothing Effect of a Cosmetic Product on Skin Discomforts Induced by a Chemical Irritant (Capsaicin)

This experimental setting, where the facial skin of volunteers was treated with capsaicin, was designed to assess the soothing effect of the test product on the capsaicin-induced itching and stinging sensation. The single application of the cosmetic product showed a statistically significant decrease in the discomfort sensations immediately after its application and at each checkpoint, for the stinging as well as for the itching sensation.

3.1.1. Clinical Scoring of the Stinging Sensation (20/20 Participants)

A single application of FC 16419 showed a statistically significant decrease in the stinging sensation compared to baseline, starting from T_i (immediately after product application) and at each following monitored timepoint (Figure 1). A decrease in the stinging sensation was recorded at T_i (immediately after product application), in the skin site treated with water, too. However, the decrease in the stinging sensation in the control was no longer recorded at $T1'$, $T2'$, and $T3'$. A physiological decrease of the stinging sensation was then recorded starting from $T4'$ up to the end of the study.

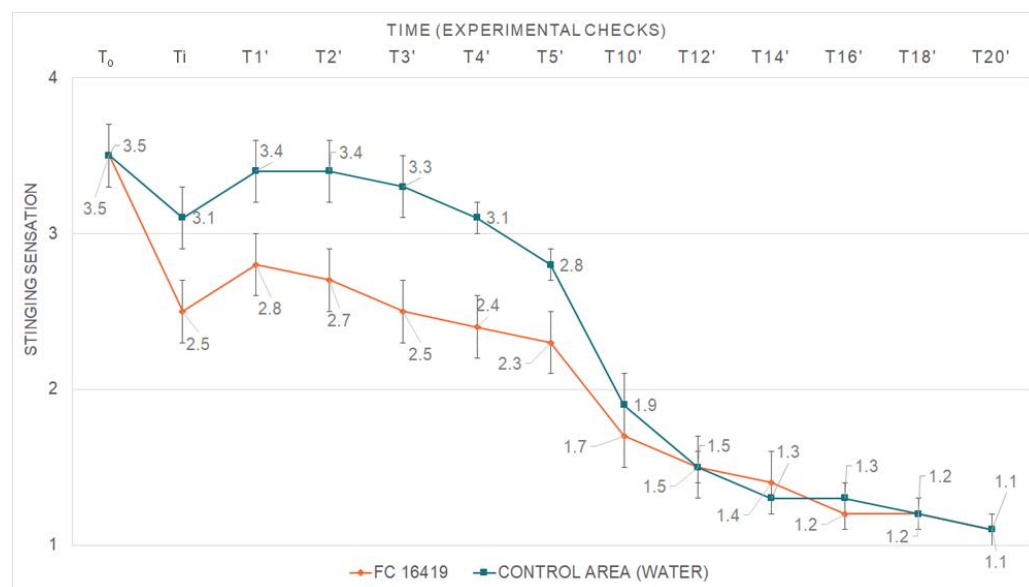


Figure 1. Clinical scoring of stinging sensation at different timepoints (Data are reported as mean $\pm$ SEM).

We could observe an onset of the product after 1 min. The inter-group statistical analysis highlights that the decrease in the discomfort sensations was faster due to the application of FC 16419. Statistically significant differences between FC 16419 and control (active vs. control $p < 0.05$) were observed at $T1'$, $T2'$, $T3'$, $T4'$, and $T5'$.

3.1.2. Clinical Scoring of the Itching Sensation (11/20 Participants)

In this experimental setting, only 11 participants experienced an itching sensation. For these participants, the single application of FC 16419 showed a statistically significant decrease in the itching sensation compared to baseline, starting from T_i (immediately after product application) and at each following monitored timepoint (Figure 2). A decrease in the itching sensation was recorded at T_i (immediately after product application), in the skin site treated with water. However, the decrease in the itching sensation in the control was no longer recorded at $T_{1'}$, $T_{2'}$, and $T_{3'}$. A physiological decrease in the itching sensation was then recorded starting from $T_{4'}$ up to the end of the study.

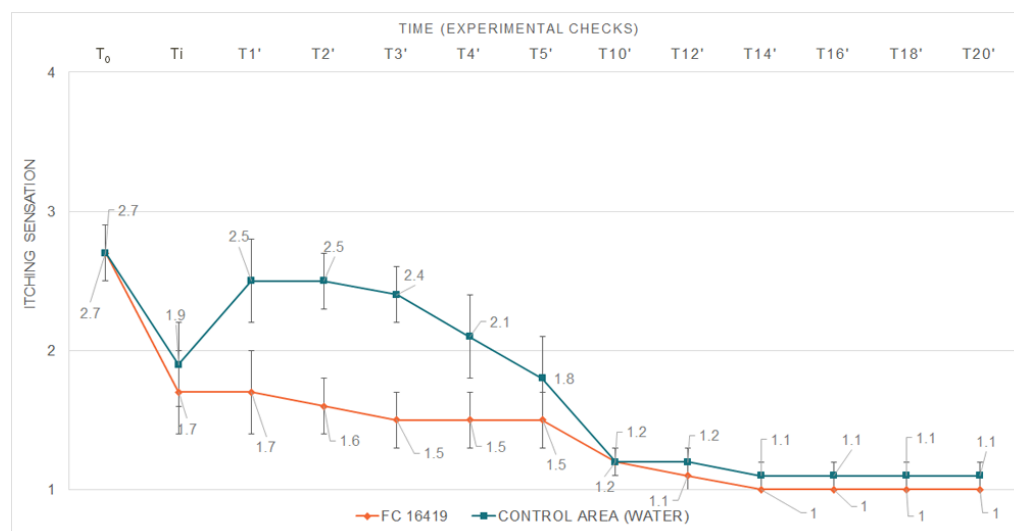


Figure 2. Clinical scoring of itching sensation at different timepoints (Data are reported as mean ± SEM).

Onset of itching relief started already at 1 min after application of the product. The inter-group statistical analysis highlights that the decrease in the discomfort sensations was faster due to the application of FC 16419. Statistically significant difference between FC 16419 and the control (active vs. control $p < 0.05$) were observed at $T_{1'}$, $T_{2'}$, and $T_{3'}$.

In this study, with capsaicin treatment of the skin, all the enrolled participants completed the study and none of them showed intolerance reactions to the product applied; no adverse events were recorded during the study.

3.2. Soothing Effect of the Cosmetic Product on Skin Irradiated by a Solar Simulator (UVA+B)

In the second clinical study setting, we tested the soothing effect of the cosmetic product FC 16419 on the backs of healthy volunteers after UV exposure. The application of FC 16419 showed a significant reduction in the UV-induced skin erythema up to T_2 h (intra-group statistical analysis vs. T_0). Moreover, the variations recorded in the treated area were statistically significant compared to the untreated area at each timepoint (inter-group statistical analysis vs. untreated). In the untreated area, the UV-induced erythema was almost maintained up to T_2 h, while in the skin site treated with FC 16419, the erythema index values decreased by 17.8%, 31.0%, and 28.7%, respectively, 30 min, 1 h, and 2 h after product application.

At T_{24} h in the untreated area, the UV-induced erythema further increased by 17.9% compared to T_0 , while it was almost maintained (vs. T_0) in the skin site treated with FC 16419 (−5.4% vs. T_0 , not significant) (Figure 3). The inter-group statistical analysis highlights that the erythema index was significantly lower compared to the untreated area. This indicates that our tested product counteracts a further increase of the UV induced skin erythema.

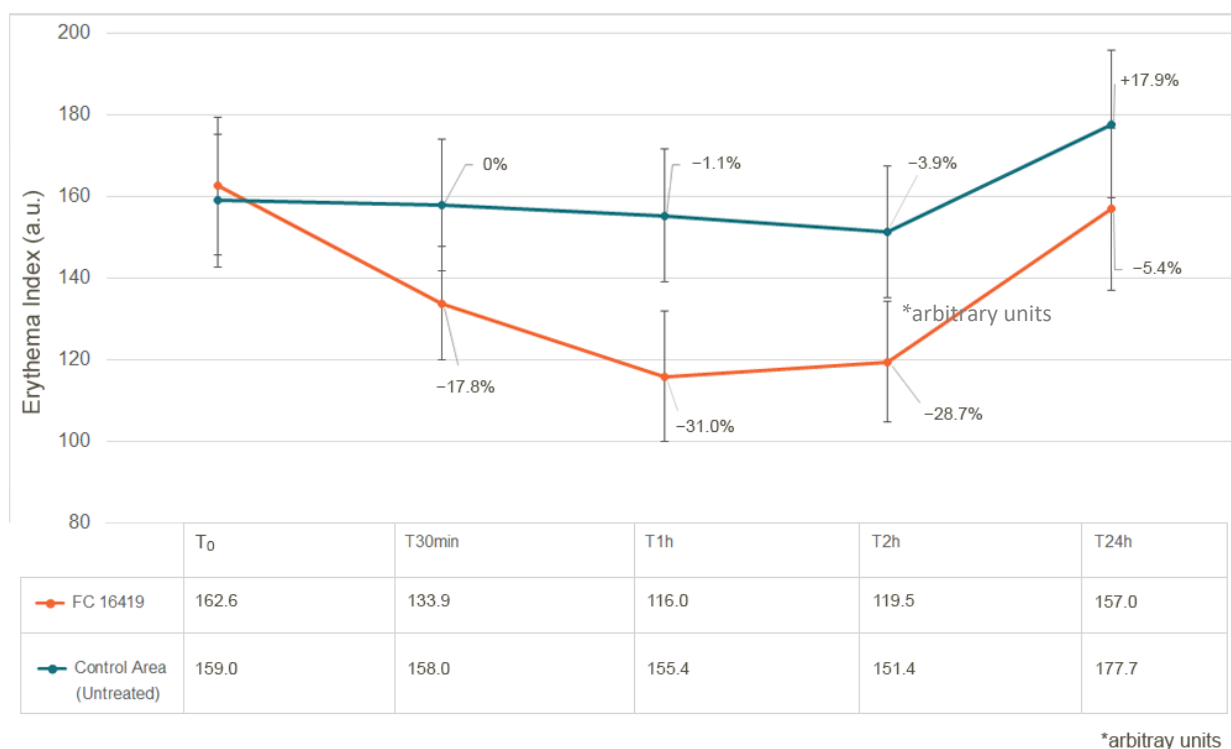


Figure 3. Mean variation of skin redness (expressed as Erythema index mean values) on data normalized versus basal values ($T - 1$). The graph shows the skin redness (expressed as Erythema index mean values $\pm$ SEM) caused by the UV-exposure and its % variation after application of FC 16419 or left untreated.

According to the above reported results, we can conclude that the tested product was effective in soothing the cutaneous erythematous reaction (skin redness increase) induced by a solar simulator (UVA+B exposure at 1.5 MED dose). All the enrolled participants completed the study and none of them showed intolerance reactions to the product applied; no adverse events were recorded during the study.

3.3. Test of Use of the Cosmetic Product after Mosquito Bites and Sunburn

After two controlled clinical studies, we confirmed the soothing effect of the cosmetic product on the sunburn/mosquito bites-induced itching, redness, and irritation in a real-world setting. In the test of use setting, participants used FC 16419 after mosquito-bites and sunburn and documented the effects they observed in a Visual Analogue Scale (VAS).

In the subjective evaluation of redness after sunburn, the application of FC 16419 showed a statistically significant mean decrease in skin redness related to sunburn, starting from 30 min ($T_{30'}$) and at each following monitored time. With a one-time application, only the reduction of VAS scores from 6.8 to 2.5 (mean difference of 4.3) within 24 h was observed. The p -values for the test vs. T_0 are included in the graph (Figure 4).

The data were also analysed with a focus on the documented sunburn events (data related to the first episode of sunburn and, if present, the second episode of sunburn, to the mean of the 1st and 2nd episode) for each volunteer divided into volunteers who experienced modest sunburn and volunteers who experienced severe sunburn. Data were reported as a score given by each subject on the VAS. The application of FC 16419 showed a statistically significant mean decrease in skin redness both related to modest sunburn and severe sunburn, starting from $T_{30'}$ and at each following monitored time. With a one-time application, only a reduction of the VAS Scores from 8.3 to 3.5 (mean difference of 4.8) within 24 h was observed in severe sunburn, and from 5.9 to 1.9 (mean difference of 4.0) in modest sunburn, respectively. The p -values for the intra-group vs. T_0 comparison are included in the graph (Figure 5).

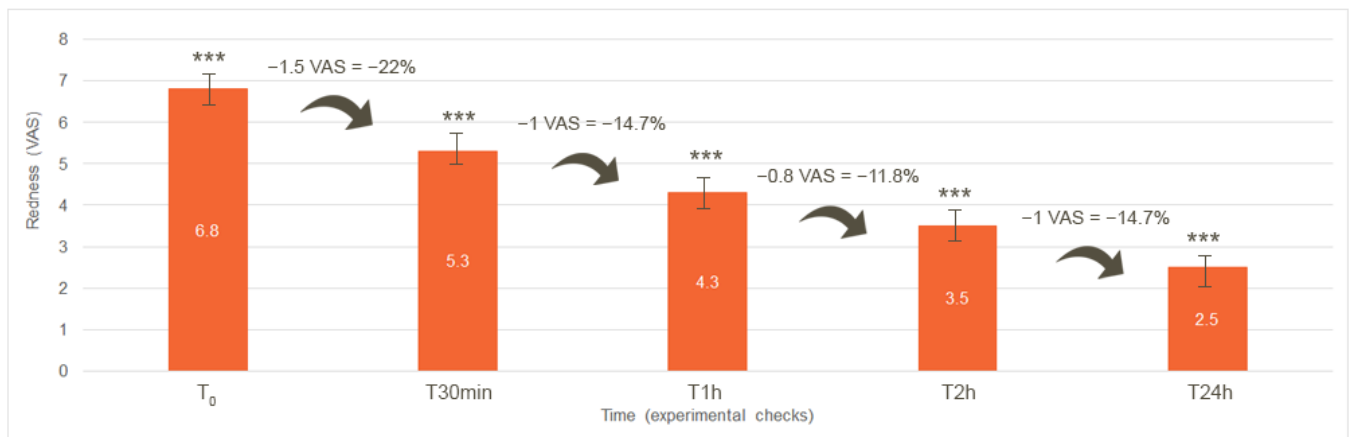


Figure 4. Evaluation of redness after sunburn (VAS score) after application of FC 16419 (Data are reported as mean $\pm$ SEM). Asterisks in the graph report the intra-group (vs. T₀) comparison; Legend (significance): *** $p < 0.001$.

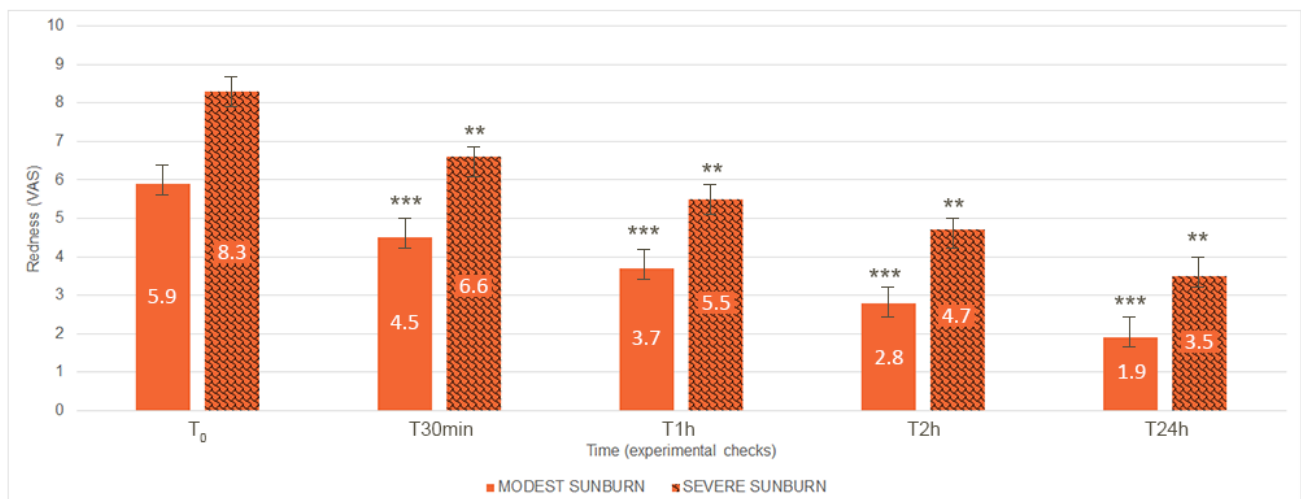


Figure 5. Evaluation of redness after modest and severe sunburn (VAS score) after application of FC 16419 (Data are reported as mean $\pm$ SEM). Asterisks in the graph report the intra-group (vs. T₀) statistical analysis. Legend (significance): *** $p < 0.001$; ** $p < 0.01$.

In their subjective evaluation, the participants described an improvement after the application of the cosmetic product after bites, focusing on the symptoms of “itching” and “irritation”. The mean of the data relates to bites 1, 2, 3, 4, 5, and, if present, 6. The application of FC 16419 showed a statistically significant mean decrease of the itching sensation (VAS score) related to mosquito bites, starting from T2' and at each following monitored time. After one application, only the soothing effect was still recognizable after 2 h (last monitored time). This decrease is statistically significant vs. the untreated area starting from T5' and at each following monitored time. A statistically significant physiological decrease of the itching sensation has also been observed in the untreated area starting from T5'. The p -values are included in the graph (Figure 6).

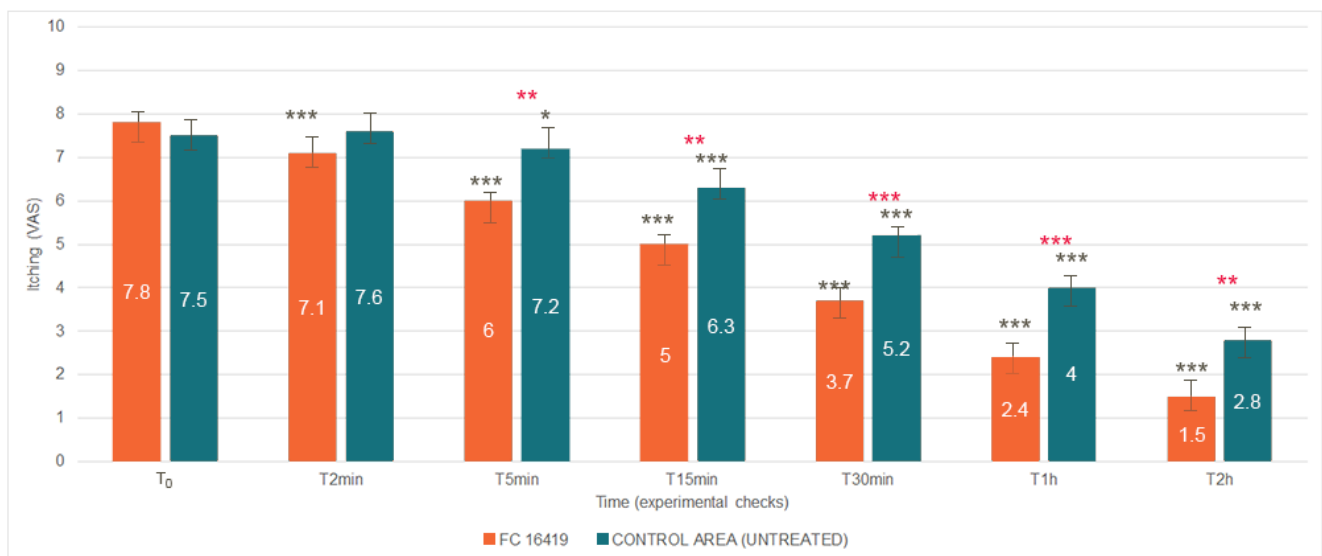


Figure 6. Evaluation of itching (VAS score) caused by bites after application of FC 16419 and on untreated bites (Data are reported as mean $\pm$ SEM). Black asterisks in the graph report the intra-group statistical analysis (vs. T₀) and red asterisks the inter-group statistical analysis (vs. untreated). Legend (significance): *** $p < 0.001$; ** $p < 0.01$; * $p < 0.05$.

The participants evaluated the degree of skin irritation after mosquito bites, too (Figure 7). The application of FC 16419 showed a statistically significant mean decrease in skin irritation (VAS score) related to mosquito bites, starting from T2' and at each following monitored time. This decrease is statistically significant vs. the untreated area starting from T15' and at each following monitored time. With one application, the soothing effect was still recognizable after 2 h (last monitored time). A statistically significant physiological decrease of skin irritation was also observed in the untreated area starting from T5'.

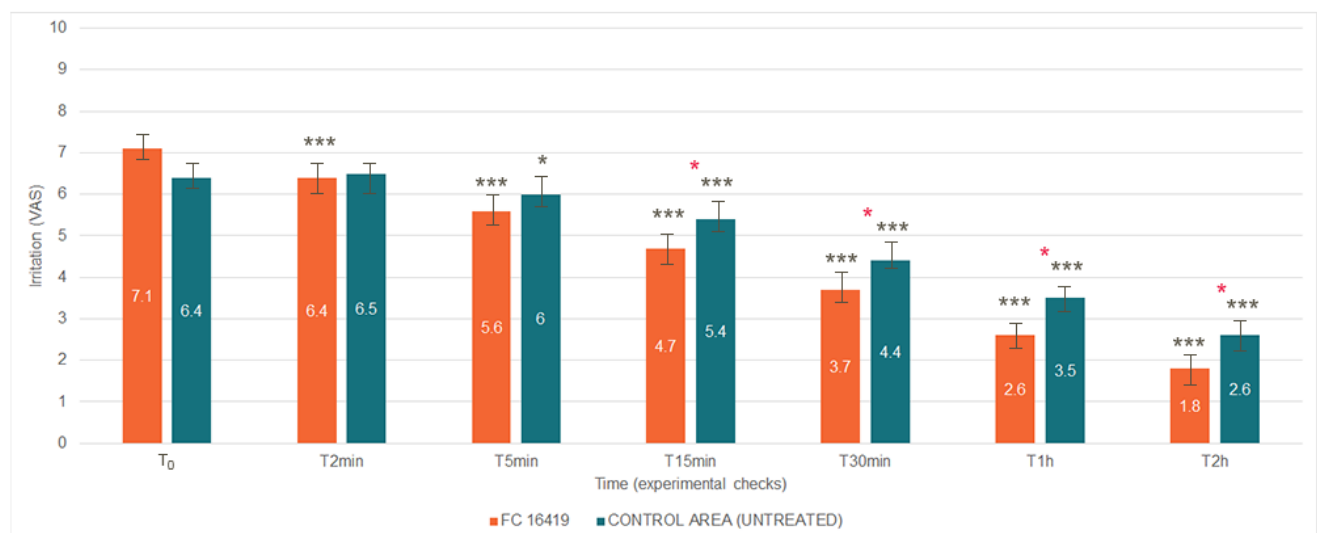


Figure 7. Evaluation of Irritation (VAS score) caused by bites after application of FC 16419 and on untreated bites (Data are reported as mean $\pm$ SEM). Black asterisks in the graph report the intra-group statistical analysis (vs. T₀) and the red asterisks the inter-group statistical analysis (vs. untreated). Legend (significance): *** $p < 0.001$; * $p < 0.05$.

In a scoring system, the 33 participants were asked to rate the cooling properties after they had applied the cosmetic product on skin irritated with a sunburn or insect bite. Immediately after application of FC 16419 on insect bites, a cooling effect was observed in

69.7% of participants (24.2% completely agreed, and 45.5% agreed to having a cold feeling). Here we emphasize the cooling properties in sunburn because the sensation of heat is a dominant feature. The 33 subjective evaluations of the first sunburn treated are summed up in Table 3. A cooling effect was confirmed by most of the participants; immediately after the application, more than 93.9% agreed with positive answers, as follows: 30.3% completely agreed, and 63.3% agreed.

Table 3. Subjective evaluation of the cooling effect of the product on sunburn 1 (first sunburn treated with FC 16419).

	Does the Product Give a Cold Feeling?							
	Completely Agree	Agree	Neither Agree or Disagree	Disagree	Completely Disagree	Positive Answers	Neutral Answers	Negative Answers
T immediately after	30.3%	63.6%	3.0%	3.0%	0.0%	93.9%	3.0%	3.0%
T 15 min	18.2%	66.7%	9.1%	6.1%	0.0%	84.8%	9.1%	6.1%

All the enrolled participants completed the study and none of them showed intolerance reactions to the product applied; no adverse events were recorded during the study.

3.4. Safety Evaluation

The tolerability of the treatment was closely followed by the study principal investigator during the course of the study. Participants had access to the investigators in case of intolerance reactions via a contact phone number provided with the informed consent form. All the enrolled participants completed the three studies, and none of them showed intolerance reactions to product use; no adverse events were recorded during any of the studies described here.

4. Discussion

European guidelines recommend moisturizers to stabilize the physiological skin barrier [3,4]. Here, natural plant oils can play an important role in the restoration of cutaneous homeostasis [5]. The above presented results of FC 16419 show that carefully selected cosmetic products can also provide certain relief for irritated and itchy skin. This is of special interest because consumers tend to opt for medication free, sustainable, and natural ways to treat uncomplicated skin irritations.

FC 16419 is a cosmetic product with 94% of its ingredients being of natural origin, each with beneficial properties. Nourishing shea butter, cooling menthol, and soothing bisabolol are the characteristic ingredients of this natural cosmetic and complement each other in the topical formulation.

4.1. Soothing Effect on the Capsaicin-Induced Itching and Stinging Sensation

In a clinically controlled study setting, we could show the soothing effect of FC 16419 after the application of capsaicin, a chemical irritant. A single product application led to a statistically significant decrease in the discomfort sensations immediately after its application. For the practical application, this would suggest that, from early on, after a trigger where discomfort is at its peak, the tested cosmetic product gives a natural relief by soothing the impaired skin barrier of the irritated skin. This is essential to combat the itch-scratch vicious circle with its risk of skin infections.

For a cosmetic product intended to be used in everyday life, suitable for children from 2 years on, the safety profile is very important: All participants completed the study, and none of them showed intolerance reactions to product use; no adverse events were recorded during this study.

4.2. Soothing Effect on UV-Induced Erythema

We could also show the soothing properties of the cosmetic product FC 16419 on the skin after UV radiation. In the controlled study, the application of the cosmetic product showed a decrease in the UV-induced skin redness (soothing effect) in the timepoints measured, up to 2 h after its application.

Erythema is the most visible trace of sunburn. After 24 h, UV-induced erythema increased further in the untreated area, while it was almost maintained in the skin site treated with FC 16419 (not significant). This gives us a hint about the importance of hydration in irritated skin, and we conclude that UV-erythema needs regular donation of moisture and nourishing cosmetics. Additionally, after sunburn, no safety events were observed, supporting the favourable safety profile.

As a sidenote, beside the study endpoints, we would like to emphasize the hydration of the skin with this cosmetic product: After application of FC 16419, we observed a statistically significant increase in the skin moisturization index at T30 min by means of Corneometer® measurements, both compared to baseline values and control area (intra-group statistical analysis vs. T₀ and inter-group statistical analysis vs. untreated), inducing a statistically significant increase of the skin moisturization index by +6.6% measured 30 min after a single application.

4.3. Real-World Data Replicating Effects on UV-Induced Redness and Itching after Insect Bites

Our last study proved the cooling and soothing effects observed in two experimental studies in a real-world setting after insect bites and sunburn.

Regarding the skin discomfort induced by sunburn, the results showed a statistically significant mean decrease in itching, redness, and irritation on both modest and severe sunburn. The product also showed a statistically significant mean decrease in the itching sensation after mosquito bites. In our real-world setting, the product tackled the two major situations where cooling properties are relieving acute symptoms, with a cooling sensation immediately after application in almost 70% of insect bites and almost 94% of sunburns. From a practical perspective, this seems very important as the warmth' sensation is the most prominent feature of skin discomfort after excessive sun exposure.

In this real-world setting, the favourable safety profile from the clinical experimental studies could be observed, too.

5. Conclusions

In two experimental, controlled clinical studies, we could describe a soothing effect of the tested cosmetic product on skin discomfort after a chemical irritant and after UV-exposure. We observed a soothing effect on the capsaicin-induced itching and stinging sensation immediately after its application. The tested product showed an ongoing significant reduction in the UV-induced skin erythema (UVA+B exposure) after one time application. In a third, real-world study, we confirmed the data obtained in the controlled clinical studies by a test of use. Volunteers applying the cosmetic product after insect bites or sunburn documented a significant decrease in itching, redness, and irritation after sunburn as well as in itching and irritation after insect bites.

With a favourable safety profile, the cosmetic product with 94% natural ingredients is a well-studied option for consumers seeking medication free, natural care for itchy and irritated skin in everyday life e.g., caused by sunburn and insect bites.

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Institutional Review Board Statement: The study was conducted in accordance with the Declaration of Helsinki. Ethical review and approval were waived for this study. According to the EU cosmetic Regulation no. 1223/2009, the cosmetic product must not cause damage to human health when applied under normal or reasonably foreseeable conditions of use and must be assessed for its safety of use before human subjects are exposed to it, and as such, further ethical approval is not required.

Informed Consent Statement: Informed consent was obtained from all participants involved in the study.

Data Availability Statement: The data presented in this study are available upon request from the corresponding author. The data are not publicly available since they are property of the sponsor of the study.

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