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https://doi.org/10.1051/ocl/2025029

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www.ocl-journal.org

RESEARCH ARTICLE OPEN ACCESS

Improving skin comfort and well-being with tea oil concentrate from *Camellia oleifera* obtained by molecular distillation☆

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Received 25 March 2025 – Accepted 5 September 2025

Abstract – Psychological stress causes release of neuropeptide and cortisol mediators, which negatively impact the skin, *e.g.*, *via* alteration of the skin barrier, inflammation, or itching. These reactions cause skin discomfort that amplifies psychological stress creating a vicious circle. We developed a tea oil concentrate (TOC), a new active ingredient from *Camellia oleifera* seeds, rich in unsaponifiable fraction. We present here the evaluation of its efficacy by *in vitro* models and clinical studies. *In vitro*, TOC significantly decreased cortisol and substance P release, respectively, in explant model stimulated by adrenocorticotropic hormone and temperature and in a reinnervated epidermis model. TOC improved the barrier integrity by increasing the *stratum corneum* thickness and decreasing the permeability of the barrier in a skin explant model mimicking the effect of cortisol on skin barrier. Results of clinical studies demonstrated that TOC improved self-perception, decreased skin sensitivity symptoms, reduced sensitive and dry skin clinical signs (redness, roughness, scaling, dryness) and reduced the impact of dry and sensitive skin on stress (decrease of vocal stress, increase of heart rate variability). TOC also reduced skin inflammation and stress assessed respectively by IL1-α and cortisol release. By counteracting the vicious circle of stress, TOC promotes skin comfort and improves the well-being of individuals with dry and sensitive skin.

Keywords: *Camellia oleifera* oil unsaponifiable / skin comfort / well-being / sensitive skin / cortisol

Résumé – Améliorer le confort et le bien-être de la peau avec un concentrat d'huile de graines de Camellia oleifera obtenu par distillation moléculaire. Le stress psychologique impacte négativement la peau *via* le relargage de médiateurs tels que les neuropeptides et le cortisol. Ces médiateurs vont altérer la barrière cutanée, induire de l'inflammation et des démangeaisons provoquant un inconfort cutané qui va amplifier le stress psychologique, créant ainsi un véritable cercle vicieux. Nous avons développé un ingrédient actif à partir des graines de *Camellia oleifera*, un concentrat d'huile de thé (TOC), riche en fraction insaponifiable. Nous présentons ici l'évaluation de son efficacité par des modèles *in vitro* et des études cliniques. *In vitro*, TOC a diminué la libération de cortisol et de substance P, respectivement dans un modèle d'explant cutané stimulé par l'ACTH et la température et dans un modèle d'épiderme réinnervé. TOC a amélioré l'intégrité de la barrière cutanée en augmentant l'épaisseur de la couche cornée et en diminuant la perméabilité dans un modèle d'explant cutané mimant les effets néfastes du cortisol. Lors des études cliniques, TOC a amélioré la perception de soi, diminué les symptômes de sensibilité cutanée, réduit les signes cliniques de la peau sensible et sèche (rougeur, rugosité, desquamation, sécheresse) et l'impact de la peau sèche et sensible sur le stress (diminution du stress vocal, augmentation de la variabilité de la fréquence cardiaque). TOC a également réduit l'inflammation cutanée et le stress évalués respectivement par l'IL1-α et la libération de cortisol. En contrecarrant le cercle vicieux du stress, TOC favorise le confort cutané et améliore le bien-être des peaux sèches et sensibles.

Mots clés : insaponifiable de *Camellia oleifera* / confort cutané / bien-être / peau sensible / cortisol

☆ Contribution to the Topical Issue: "Minor oils from atypical plant sources / Huiles mineures de sources végétales atypiques".

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Highlights

Countering the vicious circle linked to stress and the condition of dry and/or sensitive skin is a major challenge in cosmetics. The extract of *Camellia oleifera oil*, rich in unsaponifiable fractions including beta-amyrin demonstrated its efficacy *in vitro* and *in vivo* against the negative effects of psychological stress to provide comfort and well-being to the skin and the mind.

1 Introduction

An increasing number of individuals are exposed to psychological stress in current "modern" day-to-day life. Psychological stress is a normal physical, mental or emotional response to perceived challenges, threats, or demands in one's environment ("stressors"). However, when stress becomes chronic, it can have negative impacts on the body. Psychological stress is known to cause and exacerbate a number of skin diseases associated with skin barrier defects, such as pruritus, psoriasis or atopic dermatitis (Hall *et al.*, 2012; Graubard *et al.*, 2021; Marek-Jozefowicz *et al.*, 2022).

There are two main stress response axes in the body, namely the hypothalamic–pituitary–adrenal (HPA) axis and the sympathetic nervous system. In the HPA axis, psychological stress triggers the production of Corticotropin-Releasing Hormone (CRH) in the hypothalamus. This leads to the release of adrenocorticotropic hormone (ACTH) from the hypophyseal gland and to cortisol release in the adrenal gland. The skin also has its own equivalent of the HPA axis. Keratinocytes are able to synthesize cortisol (Pondeljak and Liborija, 2020; Cirillo and Prime, 2011). Local synthesis enables the skin to react to stress and is finely regulated to maintain cutaneous homeostasis. Numerous studies have described the negative effects of psychological stress on cutaneous homeostasis, mediated by an excessive level of cortisol. This can lead to immune and inflammatory response impairment; damage to the integrity of the *stratum corneum* and to epidermal barrier function (Choe *et al.*, 2018; Altemus *et al.*, 2001; Choi *et al.*, 2005); delayed healing (Ebrecht *et al.*, 2004); increase in reactive oxygen species production and DNA damage, factors which contribute to cutaneous aging (Krutmann *et al.*, 2017). Research conducted by Choe *et al.* in 2018 showed a higher level of cortisol in the *stratum corneum* of individuals experiencing psychological stress (students taking exams) *versus* individuals not experiencing stress (students not taking exams). They also observed an increase of trans-epidermal water loss in stressed students, indicating skin barrier impairment (Choe *et al.*, 2018). Other factors able to induce cortisol production include UV light (Skobowiat *et al.*, 2013; Boudon *et al.*, 2017; Slominski *et al.*, 2018), temperature, and surrounding humidity (Takei *et al.*, 2013; Zhu *et al.*, 2014). The sympathetic nervous system plays a role in high alert situations in which it is necessary to engage the "fight or flight response". It is responsible for the release of catecholamine neurotransmitters, in particular adrenalin and noradrenalin. These catecholamines are secreted in response to stress, leading for example to an increased heart rate (Chen and Lyga, 2014). The sympathetic nervous system is also responsible for releasing neuropeptides such as substance P. One of the most abundant neuropeptides of the central nervous system (CNS), substance P is involved in a wide range of physiological and pathophysiological processes, including regulation of stress and behaviors relating to emotions and anxiety (Ebner and Singewald, 2006). It is significantly involved in the transmission of pain signals, in inflammatory processes and sensitive skin.

Previous work has confirmed an association between sensitive skin and common psychological concerns (Farage, 2022). Symptoms of sensitive skin such as itching, stinging, burning, and pain can lead to sleep disorders, fatigue, stress, and anxiety. Conversely, lack of sleep and stress from external sources can make the individual with sensitive skin more susceptible to symptoms. This becomes a vicious circle that impacts on quality of life and well-being (Fig. 1). The purpose of this work was to develop a new cosmetic active ingredient which can countering this vicious circle between stress and the condition of dry and/or sensitive skin, which is a major challenge in cosmetic domain. We evaluated the biological efficacy of this ingredient by *in vitro* models targeting cortisol and substance P. We confirmed these effects by two *in vivo* studies.

2 Ecodesigned *Camellia Oleifera* seed oil concentrate: origin, production, and characteristics

2.1 *Camellia Oleifera*

The Camellia genus is native to East Asia and includes more than 200 evergreen woody species. Some species have high economic value such as *C. sinensis, C. japonica, and C. oleifera. C. oleifera*, also known as oil-tea camelia, can grow on sterile, unfertilized ground, begin to produce fruit 6 yr after initial plantation, and remain highly productive for 80 yr. This species is mainly grown in China for the production of food oils (camelia oil, tea seed oil) (Yang *et al.*, 2016). *Camellia oleifera* is a shrub 5 to 7 m tall with straight elliptical leaves. Its flowers are small, white and mildly fragranced. The fruits are capsules with 3 cavities containing 1 to 2 seeds 2 cm in size. The seeds are comprised of a husk and a kernel (Fig. 2), which represents around 60% of the seed's total weight. Oil can be extracted directly from the seed or kernel.

The quantity of oil contained in the seeds and fatty acid composition can vary depending on the variety, soil, and climate (Hu and Yang, 2018). Wen *et al.* (2018), consider light intensity during fruit growth and ripening (July-October) to influence fruit yield and quality. As for the varietal diversity, Yang *et al.* (2016) compared 10 different cultivars and seeds from several wild specimens and concluded that the oil content and fatty acid profile of their extracts were not influenced by artificial culture and cultivar selection. In many Asian countries (China, Taiwan, Japan, India, Indonesia) *Camellia oleifera* oil is used in cooking and used in traditional medicine. It is also recommended by the Food and Agriculture Organization of the United Nations as healthy alternative due to its specific composition (Guo *et al.*, 2023, Li *et al.*, 2022).

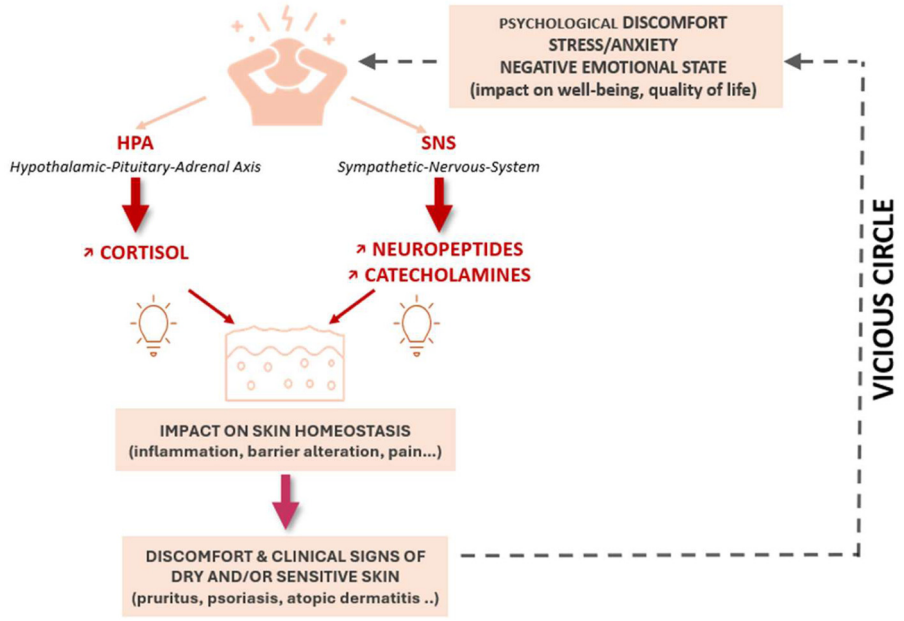

Fig. 1. Vicious circle of psychological stress and skin conditions.

Fig. 2. *Camellia oleifera* tree & seed.

2.2 Molecular distillation

Molecular distillation is a highly precise separation technique that operates under a vacuum environment and at high temperature, making it ideal for separating and purifying sensitive compounds in a gentle and eco-friendly manner. This solvent-free extraction method enables to concentrate the unsaponifiable fraction of oil by a factor of 5x or 10x, to obtain an enriched oil while preserving complex molecular integrity. The unsaponifiable fraction of vegetable oil is the most biologically active fraction, despite constituting a minor part (between 0.1% to 2.0% and up to 15% in rare cases). The main constituents of interest are phytosterols, tocopherols, and tocotrienols well known for their anti-inflammatory, anti-oxidative, and wound healing properties (Fontanel, 2013).

2.3 Phytochemical profile

The analytical profile of the Tea Oil Concentrate (TOC) obtained by gas chromatography technology is described below (Tab. 1).

We obtained a product with a specific unsaponifiable fraction containing a large amount of β-amyrin ((3β)-Olean-12-en-3-ol). β-amyrin is described as the major pentacyclic triterpenoid compound found in medicinal plants. Previous studies have demonstrated the biological role of β-amyrin including anti-inflammatory, antioxidant, antinociceptive, antimicrobial, immune-boosting, anxiolytic, and antidepressant properties (Abdel-Raouf *et al.*, 2015; Nogueira *et al.*, 2019; Viet *et al.*, 2021).

The safety of the extract had been demonstrated by several safety *in vitro* assays such as skin and ocular irritation, skin sensitization and mutagenicity.

3 Materials and methods

3.1 *In vitro* evaluation

3.1.1 Cortisol release in a skin explant model

Skin explants were obtained with the informed consent from abdominal surgery of a 55 yr old female Caucasian donor (Biopredic). Skin explants were cultivated into standard

Table 1. Typical analytical profile of tea oil concentrate.

Fatty acid profile (% /total)		Sterolic compounds profile (relative %/total sterolic fraction)	
Palmitic acid (C16:0)	10.5%	Campesterol	2.7%
Stearic acid (C18:0)	2.1%	Stigmasterol	2.5%
Oleic acid (C18:1)	76.0%	β-sitosterol	15.4%
Linoleic acid (C18:2)	10.0%	Ergosterol family	2.0%
Unsaponifiable fraction	***2.9%***	Lanosterol	5.8%
α-Tocopherol	*36 mg/100g*	β-amyrin + δ5-avenasterol	30.0%
Total sterolic fraction	***2.3%***	Lupeol + δ7-stigmasterol	27.0%

12-well plates in contact in DMEM (ThermoFisher) medium at 37°C in 5% CO_2 humidified air. They were treated in systemic with two products: TOC at 0.001% (v/v) or a positive reference metyrapone at 1 mM (Sigma-Aldrich). The explants were incubated for 24h then stressed with ACTH 0.6 μM (Sigma-Aldrich) and kept in survival conditions in an incubator at 42°C to imitate a dry environment. The explants were treated again with products. After 24h incubation, the culture media were collected, and an enzyme-linked immunosorbent assay (ELISA) of cortisol (EIAHCOR, Invitrogen) was performed. All experimental conditions were performed at least in triplicate. For each condition, means and standard deviations were calculated and compared with untreated control and stress control (ACTH + 42°C) without tested products. Statistical significance between conditions was assessed using a two-tailed, unpaired Student *t*-test, with $p < 0.05$ being considered significant.

3.1.2 Skin barrier protective effect in a skin explant cortisol topical stress model

Skin explants were obtained with the informed consent from abdominal surgery of a 41 yr old female Caucasian donor (Biopredic). Skin explants were kept alive by culturing on metal grids into standard 12-well plates in contact in OxiProteomics® medium at 37°C in 5% CO_2 humidified air. Six hours after the explant reception and equilibration in culturing optimal conditions (D0), skin explant surfaces were damaged by tape stripping followed by 6h topical stress with an aqueous solution of cortisol 0.001% (v/v) incubation. The explants were then treated with two products: a formulation (cream) containing 1% TOC or a placebo. One day after the first application (D1), the explants were treated with cortisol again for 6h before applying the products. These treatments (6h cortisol + product) were repeated a total of 5 times (D0 to D4). The day after the last treatment (D5), the explants were collected to perform hematoxylin (Merck) and eosin (Invitrogen) staining to analyze *stratum corneum* thickness and Lucifer Yellow (Merck) staining to analyze skin barrier integrity. Light microscope images were collected with an epifluorescent microscope (EVOS M5000 Imaging System) and analyzed with ImageJ software (Schneider *et al.*, 2012). All experimental conditions were performed at least in triplicate. For each condition, means and standard deviations were calculated and compared with untreated control and stress condition (cortisol) without tested products. Statistical significance between conditions was assessed using One Way ANOVA followed by Tukey's or Dunnett's test with $p < 0.05$ being considered significant.

3.1.3 Substance P quantification in a reinnervated epidermis model

This model was inspired by previously described models (Lebonvallet *et al.*, 2012; Lebonvallet *et al.*, 2013; Sakka *et al.*, 2018; Bocciarelli *et al.*, 2023). Human induced pluripotent stem cells (AXOL Bioscience) were differentiated into sensory neurons in culture inserts (Costar® Transwell® in a 24-well plate – Corning) according to manufacturer's instruction. A collagen gel (Corning) was then applied to the sensory neurons, to enable the axons to develop in three dimensions. After 3 weeks of culture, an explanted epidermis (from abdominal surgery of an adult female Caucasian donor with the informed consent), dissociated from the dermis with dispase treatment, was deposited on the collagen gel. The epidermis model was incubated for 5 days, for the epidermis to become reinnervated by the sensory neurons. The epidermises were then treated topically with TOC formulated at 0.5% and 1% in paraffin (Sigma-Aldrich). After 24h incubation, the epidermises were treated topically with lactic acid 10% (Sigma-Aldrich) for 15 min. The culture media were then collected (DMEM – Lonza) and an ELISA test was carried out on substance P (Cayman Chemical, Advion Interchim Scientific®). All experimental conditions were performed in at least four replicates. For each condition, means and standard deviations were calculated and compared with untreated control and stress condition (lactic acid) without tested products. Statistical significance between conditions was assessed using the Mann-Whitney U test with $p < 0.05$ being considered significant.

3.2 *In vivo* evaluation

The efficacy of *Camellia Oleifera* (TOC) was evaluated by 2 *in vivo* studies.

3.2.1 "Well-being" *in vivo* study

The objective of this randomized double-blind comparative study was to evaluate the efficacy of TOC *vs.* placebo in subjects whose well-being was impacted by dry or sensitive skin conditions.

Fig. 3. Examples of pictures used during the SIT test.

3.2.1.1 Subjects and products

Measurements were performed on 44 Caucasian women over 18 yr old with skin phototype I to IV, free from pathological findings on anatomical area studied, with even distribution of dry and/or sensitive skin on the face (with functional and/or clinical signs) and expressing psychological discomfort/stress/low mood due to their dry and/or sensitive skin. All volunteers gave their informed consent. The subjects were randomized (1:1) on inclusion and applied a cream containing the active ingredient (1% TOC) or a placebo for 28 days, twice a day (morning and evening) to their face and body. The evaluations were carried out on the face.

3.2.1.2 Physical self-perception profile (PSPP) questionnaire: self-esteem assessment.

Self-esteem was assessed using the physical self-perception questionnaire (Ninot *et al.*, 2000) corresponding to the approved French version of the Physical Self-Perception Profile (PSPP) developed by Fox and Corbin (1989). This questionnaire comprises 6 scales (general level, physical level, physical condition, athletic performance, appearance, strength). The questionnaire's hierarchical structure is used to differentiate levels of self-esteem, perceived physical value, and physical appearance.

3.2.1.3 Sensitive Scale questionnaire: sensitive skin assessment.

The Sensitive Scale (Misery, 2014) was used to evaluate the degree of overall cutaneous irritation and the severity of the skin condition. Based on 10 items corresponding to perceived signs (8 items) or obvious signs (2 items) in relation to cutaneous discomfort, the subject evaluated the intensity of each parameter from 0 to 10. A total score corresponding to the sum of the 10 items is calculated.

3.2.1.4 Scrapbooking Implicit Task (SIT) test: "Self-confidence / fulfilment" assessment.

The SIT test is based on a projective approach aiming to translate pre-verbal assumptions about the self into analog representations (*e.g.*, pictures, etc.). During the SIT, the volunteer selects as fast as possible an image among a sample of three (8 presentations), in line with what he is currently feeling. All images are calibrated in terms of semantic categories and selected according to the targeted dimension: "Self-confidence / fulfilment". A "SIT score" is calculated based on subject choices. The higher the score, the greater the match with the targeted dimension. Examples of 3 pictures used during the SIT test are illustrated Figure 3.

3.2.1.5 Clinical scoring

Clinical scoring of scaling, redness, roughness and overall dryness were performed on the face by a validated technician expert under controlled and reproducible illuminations conditions (numeric scales from 0 (best score) to 9 (worst score)).

3.2.1.6 Mirror Test^{TM}: vocal analysis (prosody), cardiac activity and semantic analysis (verbatim)

The Mirror Test^{TM} is a specific method developed by Spincontrol (Tours, France) (Vial *et al.*, 2018). Its objective is to confront a subject with their own reflection and to measure emotional reactions. The subject sits in front of a mirror and answers specific questions during self-observation, he answers specific questions which are recorded to detect voice and physiological response (*e.g.*, heart signal). Exposure to self-reflection is highly emotional and leads to an emotional burden related to self-esteem. Quantification of this emotional response is performed by 3 different analyses. A neutral question is first asked for baseline measurements of each parameter. Two questions about the skin condition of the subject and the impact on mood and feeling are then asked.

Heart Rate Variability (HRV) is calculated from the heart signal. Slight variations in HRV are commonly used in psychosociological studies of stress as it offers one of the most stable parameters of a subject's emotional stress. Stress and negative emotions are well known for disturbing cardiac coherence and lead to an irregular HRV signal. A more positive state of mind should therefore increase HRV values (Mather and Thayer, 2018).

Vocal stress is calculated from the voice signal. The emotional voice content (prosody) can be assessed by studying the vocal spectrum revealing variations in a number of parameters. Using a specific computerized solution which combined vocal parameters linked to stress as vocal intensity or fundamental frequency (Giddens *et al.*, 2013), the vocal stress load is quantified. Verbatim (semantic analysis) is analyzed from verbal responses given using a statistical approach (text mining method) (Talib *et al.*, 2016). This type of approach is the traditional social and human sciences approach. The frequency of the various verbal occurrences is calculated, and statistical significance is determined.

Results for HRV and vocal stress were given as a percentage of the baseline values measured using the neutral question.

3.2.1.7 *Self-assessment questionnaire*

After 28 days of treatment, the subjects completed a questionnaire to assess their overall opinion of the efficacy of the active product and placebo tested (answers on 4 points Likert scale).

3.2.2 "Cutaneous comfort" *in vivo* study

The objective of the second randomized double-blind comparative was to evaluate the efficacy of TOC *vs.* placebo on the skin of subjects with dry or sensitive skin conditions.

3.2.2.1 *Subjects and products*

Measurements were performed on 48 Caucasian women over 18 yr old with skin phototype I to IV, free from pathological findings on anatomical area studied, with dry and/or sensitive skin on the face with stinging and/or sensations of heat, burning and/or itching, and a self-perceived cutaneous discomfort ≥4 on a scale of 0 to 10 on inclusion. All volunteers gave their informed consent. The subjects were randomized (1:1) on inclusion and applied a cream containing the active ingredient (1% TOC) or a placebo for 28 days, twice a day (morning and evening) to their face. The evaluations were carried out on the face.

3.2.2.2 *Evaluation of skin hydration*

Epidermal hydration was assessed using the skin capacitance Corneometer CM 825 (Courage & Khazaka). The device determines the water content of the superficial epidermal layers to a depth of about 0.1mm and expresses the values in arbitrary units (a.u.). With this method, the skin can be classified as very dry skin (<30 a.u.), dry skin (30–40 a.u.), and normal skin (>40 a.u.) (Heinrich *et al.*, 2003).

3.2.2.3 *Evaluation of the skin barrier function by measuring Transepidermal Water Loss (TEWL)*

Transepidermal water loss was measured using a Tewameter TM 300®. A steam flow crosses a probe placed on the skin with two sensors. The partial pressure difference is measured between the two sensors. The value obtained corresponds to the rate of water evaporation.

3.2.2.4 *Clinical scoring*

Clinical scoring of desquamation, redness, roughness, and overall dryness was performed on the face by a dermatologist under controlled and reproducible illuminations (scales from 0 (best score) to 9 (worst score). In addition, skin discomfort expressed by the subject was recorded (scales from 0 (best score) to 9 (worst score)).

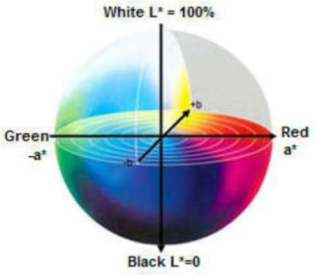

Fig. 4. L*a*b* space illustration.

3.2.2.5 *Evaluation of skin color by spectrophotometry*

Skin color was measured using a MINOLTA CM700-d spectrophotometer with an 8-millimeter diameter head. The spectrophotometer works in the color space CIELAB defined by the International Commission of Illumination (CIE) and converts colors perceived by humans into three parameters L*, a* and b*, where L* is skin lightness (from the darkest to fairest), a* and b* are color channels (a*from green to red and b* from blue to yellow) as illustrated Figure 4. Lightness L* and redness a* were assessed for this study.

3.2.2.6 *Evaluation of Quality of life by questionnaire*

Subjects completed a quality of life questionnaire on D0 and D28 specifically designed for the study. The questionnaire included 19 questions covering 5 general dimensions (emotion, pain, sleep, mental state, general). An analysis of each question and of the total score (summing of the 19 questions) was performed.

3.2.2.7 *Evaluation of cutaneous inflammation and stress by quantification of biomarkers*

Two skin samples (swab and D-Squame) were taken from each subject on D0 and D28. Swab sampling was performed for skin inflammation assessment by quantifying the Interleukin-1α (IL-1α), which is found in the epidermis and released in response to various stimuli (Akdis *et al.*, 2016). After defining an area on the cheek, the swabs were applied strongly on skin for 45 s. The samples were stored at −20 °C before analysis. IL-1α was extracted from swabs using a cocktail buffer. After a 30 min sonication, the cytokines were quantified using specific enzyme-linked immunosorbent assay (ELISA) kit (R&D Systems). A decrease of this biomarker points to reduced cutaneous inflammation.

D-squame sampling were performed for skin stress assessment by quantifying cortisol. D-squame are adhesive tapes allowing to collect superficial corneocytes. After defining an area on the cheek, 5 successive D-squames were applied on the same area with a pressure during 30 s. The last 3 D-squames were kept and stored at −20°c. Corneocytes were extracted from these 3 D-squames and cortisol was quantified by liquid chromatography and mass spectrometry detection. A decrease of this marker points to less severe stress. Cortisol was analyzed in 15 subjects in the 1% TOC active ingredient group and in 17 subjects in the placebo group (cortisol was undetected in 9 subjects in the 1% TOC group and 7 subjects in the placebo group).

3.2.2.8 *Self-assessment questionnaire*

After 28 days of treatment, the subjects completed a questionnaire to assess their overall opinion of the efficacy of the products tested.

3.2.3 Statistical analysis of clinical studies

For both *in vivo* studies, statistical analysis was performed using R software version 3.6.1 (R; 2024). For each statistical test performed between 2 timepoints or between active ingredient *vs.* placebo, the normality of the data was tested by a Shapiro-Wilk test with a threshold $\alpha = 0.01$. The following was performed depending on the result of this test (Millot 2018):

- For before/after comparisons of each product, the Student's *t*-test for paired data (following normal distribution) or the Wilcoxon signed-rank test (not following normal distribution).
- For comparisons between the active ingredient *vs.* placebo, the Student's *t*-test for unpaired data (following normal distribution) or the Mann-Whitney test (not following normal distribution).

A *p*-value $p < 0.05$ was considered statistically significant and $p < 0.1$ indicative of a borderline significant difference.

Results obtained by self-assessment questionnaire are interpreted by comparison of the percentage of positive answers to a percentage of 50% (considered as a random answer percentage) using a binomial statistical test. Active ingredient *vs.* placebo results were compared using a chi-square test.

4 Results

4.1 *In vitro* results

4.1.1 TOC decreases cortisol release in skin explant

ACTH and temperature (42°C) stress induced a significant increase in cortisol release (+28% *vs.* untreated explant, $p < 0.05$) (Fig. 5). The positive reference, metyrapone, decreased the amount of cortisol release (−16%) and protected skin explants from stress by 70%.

TOC 0.001% also allowed a significant decrease in cortisol (−21%, $p < 0.01$) and protected skin explants from stress by 93% (Fig. 5). These data show that TOC was able to reduce cortisol release and that it could protect and improve the skin barrier.

4.1.2 TOC shows protective effect in cortisol stress model impairing the skin barrier explant

Damaging the *stratum corneum* by tape stripping followed by repeated cortisol treatment over five days significantly decreased *stratum corneum* thickness (−38% *vs.* untreated explant, $p < 0.001$) and the integrity of the skin barrier (Fig. 6). Diffusion of Lucifer Yellow fluorescence increased strongly (+141% *vs.* untreated explant, $p < 0.001$) showing an alteration of skin barrier. The cream formulated with 1% TOC significantly protected skin explants from stress by increasing *stratum corneum* thickness (+55%, $p < 0.001$, corresponding to 88% protection *vs.* untreated explant) and by reducing the penetration of Lucifer Yellow stain (−49%, $p < 0.001$, corresponding to 83% protection *vs.* untreated explant).

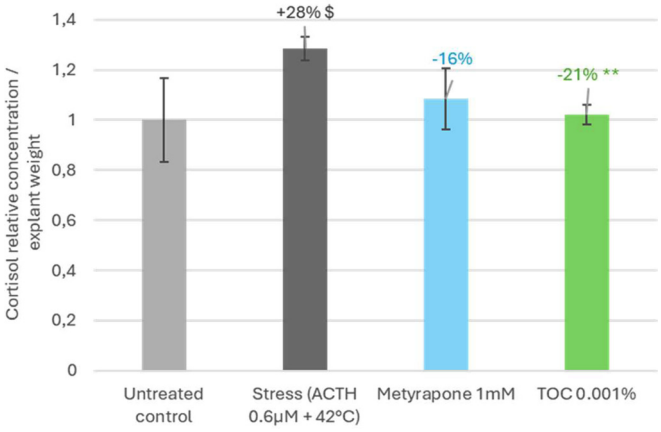

Fig. 5. Assay of cortisol produced by skin explants stimulated by ACTH + 42°C. $ $p < 0.05$ vs untreated control; ** $p < 0.01$ vs stress; two-tailed, unpaired Student *t*-test

Placebo treatment showed an efficacy 35% and 36% protection, respectively, but the active ingredient was superior and the difference between active ingredient and placebo was significant ($p < 0.001$) (Fig. 6). Overall, TOC improved the integrity of the skin barrier, promoted skin barrier repair and protected it from psychological stress.

4.1.3 TOC inhibits substance P release in a reinnervated epidermis model

Lactic acid 10% induced an increase of substance P release (+48% *vs.* untreated epidermis). TOC 1% and 0.5% significantly decreased substance P release (−56% and −48% *vs.* lactic acid respectively, $p < 0.05$) (Fig. 7).

These data show that TOC inhibited substance P release and has the potential to improve the comfort of sensitive skin.

4.2 *In vivo* results

4.2.1 "Well-being" *in vivo* study results

The group receiving active ingredient included 22 subjects aged 51.3±14.7 yr (range: 19–70 yr), including 18 subjects with dry/dryness-prone skin and 19 subjects with sensitive skin. The group receiving placebo included 22 subjects aged 45.3±13.8 yr (range: 23–68 yr), including 19 subjects with dry/dryness-prone skin and 20 with sensitive skin.

Results for the PSPP, SIT score, Sensitive Scale, clinical scoring, and Mirror Test™ (HRV and vocal stress parameters) are in Table 2.

PSPP results showed an improvement in the overall self-esteem with the active ingredient (+5.0%, $p = 0.218$) whereas the placebo diminishes the overall self-esteem (−3.6%, borderline significant change, $p = 0.060$). The difference between the active ingredient and the placebo was significant in favor of the active ingredient (−163.8%, $p = 0.040$). The same observation was made in the PSPP strength scale, with a borderline significant difference between the active ingredient

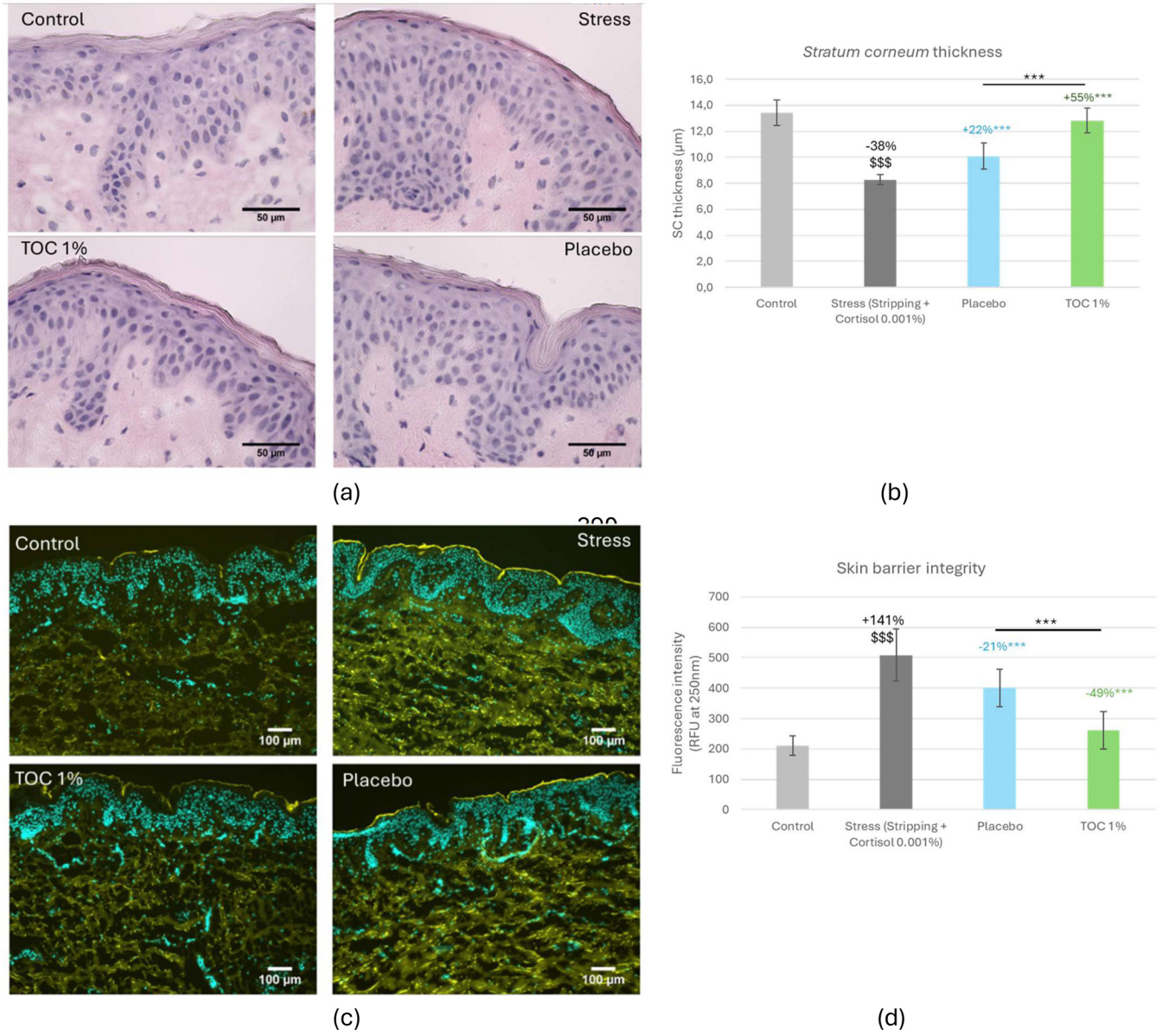

Fig. 6. Histological analysis of explant model (hematoxylin, eosin stain); (b) Quantification of *stratum corneum* thickness; (c) Analysis of Lucifer Yellow fluorescent dye diffusion through the explants (yellow: Lucifer Yellow dye, blue: DAPI; (d) Quantification of Lucifer Yellow dye penetration. $$$ $p < 0.001$ vs control; *** $p < 0.001$ vs stress or placebo; one Way ANOVA followed by Tukey's or Dunnett's test

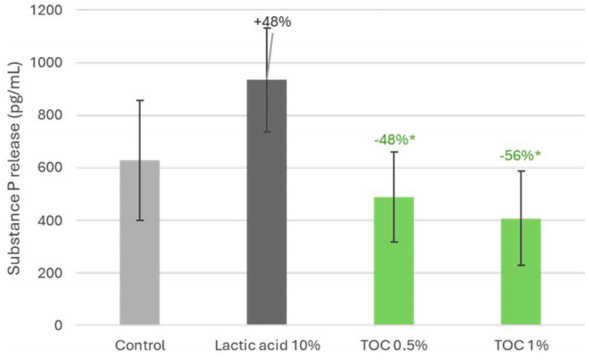

Fig. 7. Assay of substance P released by reinnervated epidermis model. * $p < 0.05$ vs lactic acid; Mann-Whitney U test.

and the placebo in favor of the active ingredient (−171.2%, $p = 0.093$).

The SIT score showed a significant improvement for the active ingredient between D0 and D28 (+42%, $p = 0.030$) without significant difference with the placebo (−30.6%, $p = 0.833$).

In the Sensitive scale evaluation, results showed that for all 10 signs evaluated and for the total score, the improvement was significant between D0 and D28 with the active ingredient (Tingling: −92.2%, Burning: −89.7%, Warm Felling: −84.7%, Tautness: −77.2%, Itching: −87.8%, Pains: −68.8%, General discomfort: −83.3%, Hot flushes: −72.2%, Redness: −79%, Desquamation: −75.7%, Total Score: −77.2%, $p < 0.05$) compared with only 5 signs and the total score with placebo (Warm Felling: −56.4%, Tautness:

Table 2. " Well-being" *in vivo* study results.

Part	*Evaluation*	TOC				Placebo				TOC vs Placebo p value
		D0 (m±σ)	D28 (m±σ)	%D28/D0	p value / D28 vs D0	D0 (m±σ)	D28 (m±σ)	%D28/D0	p value / D28 vs D0	
PSPP	Global self-esteem	20.91±4.87	21.95±3.51	5%	0.218	18.62±4.99	17.95±5.55	-3.6%	0.06	0.040
	Perceived Physical Value	19.73±4.96	18.64±4.16	-5.5%	0.112	16.38±4.62	15.86±4.41	-3.2%	0.312	0.498
	Condition	16.59±4.15	16.59±3.8	0%	1.000	15.1±2.83	15.24±3.28	0.9%	0.759	0.844
	Skill at sports	15.05±4.36	14.86±4.86	-1.2%	0.587	13.52±3.3	12.67±3.35	-6.3%	0.211	0.64
	Appearance	20.73±4.38	21.23±4.7	2.4%	0.48	18.86±4.05	18.52±4.63	-1.8%	0.816	0.554
	Strength	17.32±4.64	18.45±4.57	6.6%	0.16	16.33±4.1	15.52±3.64	-5%	0.334	0.093
SIT	SIT Score	9.32±16.24	13.23±12.63	42%	0.03	5.57±12.92	8.29±13.65	48.7%	0.359	0.833
Sensitive Scale	Tingling	5.8±2.82	0.45±1.19	-92.2%	0.000	4.05±2.91	2.67±2.73	-34.1%	0.079	0.000
	Burning	3.55±2.7	0.36±1.5	-89.7%	0.000	2.19±2.54	1.19±2.23	-45.7%	0.157	0.027
	Warm Felling	4.05±3.23	0.62±1.77	-84.7%	0.000	2.75±2.81	1.2±1.96	-56.4%	0.032	0.076
	Tautness	5.86±3.17	1.33±1.85	-77.2%	0.000	6±2.45	3.29±3.29	-45.2%	0.002	0.096
	Itching	4.09±2.93	0.5±1.34	-87.8%	0.000	3.19±3.19	1.76±2.53	-44.8%	0.07	0.027
	Pains	1.52±2.04	0.48±2.18	-68.8%	0.029	0.95±1.56	0.43±1.21	-55%	0.219	0.177
	General discomfort	5.14±3.21	0.86±1.85	-83.3%	0.000	4.76±3.1	2.33±3.28	-51%	0.004	0.081
	Hot fluches	3.27±3.35	0.91±2.35	-72.2%	0.013	2.48±3.27	0.71±1.65	-71.2%	0.008	0.226
	Redness	4.77±3.1	1±2.02	-79%	0,000	4.86±3.02	2±2.55	-58.8%	0.001	0.421
	Desquamation	3.33±2.73	0.81±2.06	-75.7%	0.004	2.29±2.9	0.71±1.9	-68.8%	0.056	0.386
	Total Score	42.07±22.09	9.6±18.87	-77.2%	0.001	34.6±17.61	17.05±17.39	-50.7%	0.003	0.109
Clinical Scoring	Desquamation / Scaling	0±0	0±0	NA	NA	0±0	0.1±0.3	NA	NA	NA
	Redness	3.45±2.09	3.18±2.08	-7.9%	0.459	3.71±1.85	3.1±2	-16.7%	0.05	0.463
	Roughness	0.73±1.28	0.55±0.8	-25%	0.73	0.24±0.44	0.43±0.51	80%	0.388	0.414
	Overall dryness	3.18±2.06	4.82±1.89	51.4%	0.000	2.57±1.75	4±1.55	55.6%	0,000	0.679
Mirror Test™	HRV	111.58±13.14	124.57±9.56	11.6%	0.000	106.53±10.97	112.98±12.33	6.1%	0.002	0.005
	Vocal Stress	123.47±13.14	109.87±9.16	-11%	0.000	128.75±10.97	127.15±11.26	-1.2%	0.393	0.000

Abbreviation: PSPP (Physical self-perception profile questionnaire.), SIT (Scrapbooking Implicit Task test) Score, clinical scoring and Mirror Test™ parameters. D: Day, NA: Not Applicable. m±σ: mean ± standard deviation.

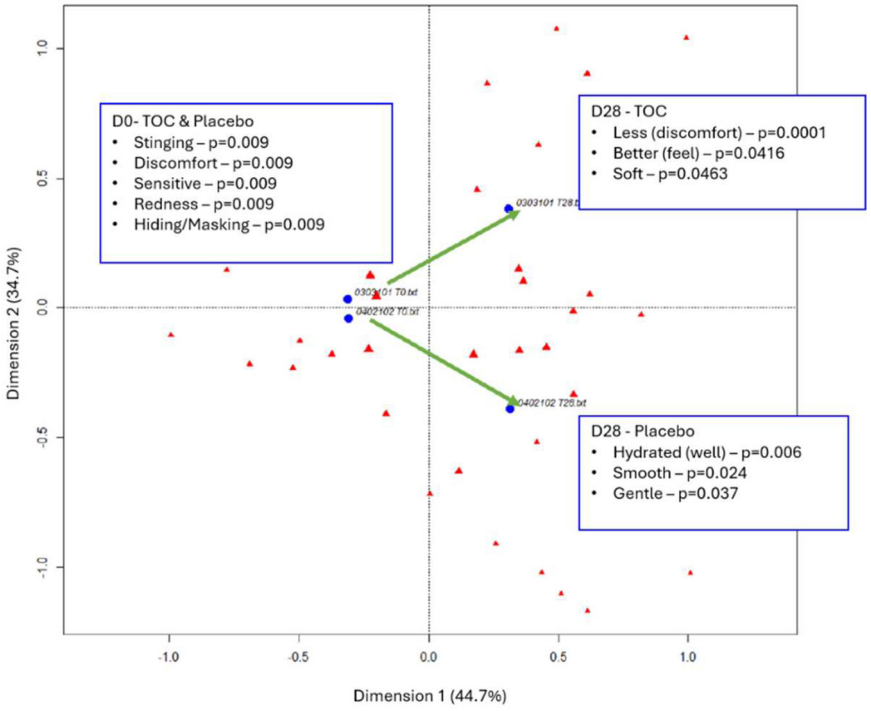

Fig. 8. "Well-being" *in vivo* study results: verbatims from the Mirror Test™. Blue dots represent the verbal corpus for the active ingredient and placebo groups. Red triangles represent the main specific expressed terms by the subjects following the questions during the Mirror Test™. The inserts list the specific terms significantly associated with a specific corpus ($p < 0.05$). Green arrows illustrate the change in the semantic spaces for each group.

−45.2%, General discomfort: −51%, Hot flushes: −71.2%, Redness: −58.8%, Total Score: −50.7%, $p < 0.05$). There was a significant difference between the active ingredient and the placebo in favor of the active ingredient for signs of tingling (−74.2%, $p < 0.001$), burning (−68.6%, $p = 0.027$), and itching (−60.2%, $p = 0.027$). Borderline significant difference was also observed between the active ingredient and placebo in favor of the active ingredient for signs of warm feeling (−54.8%, $p = 0.076$), tautness (−40.0%, $p = 0.096$), general discomfort (−43.3%, $p = 0.081$).

The clinical scoring of scaling, redness, roughness and overall dryness assessed by an expert did not show any improvement of the cutaneous condition for the active ingredient.

Results from the Mirror Test™ showed a significant increase of the HRV with the active ingredient (+11.6%, $p < 0.001$) and a significant difference with placebo in favor of the active ingredient (−50.3%, $p = 0.005$). There was also a significant decrease of vocal stress with the active ingredient (−11%, $p < 0.001$), with a significant difference *vs.* placebo in favor of the active ingredient (−88.2%, $p < 0.001$). Outcomes on HRV and vocal stress showed an improvement in the emotional state of the subjects.

The verbatims or words used on D0 and D28 to answer the questions during the Mirror Test™ are illustrated in Figure 8. Using a Factorial Analysis of Correspondences, the two main statistical dimensions represented 79.4% of the total variance, indicating an accurate account of the semantic space evoked by both groups. Dimension 1 clearly discriminated the points in time (D0 *vs.* D28). The semantics expressed at D0 by the two groups were very similar and were clearly discriminated in Dimension 2 at D28. Both treatment groups expressed generally positive assessments at D28. However, the specific verbatim produced by the group testing the active ingredient was related to the reduction in cutaneous discomfort compared to the D0 skin condition, whereas the placebo group spoke in less specific terms (*i.e.*, hydration, softness).

In the self-assessment questionnaire at D28 (Tab. 3), the active ingredient was perceived as significantly effective on 10 items ($p < 0.05$). The difference between the active ingredient and the placebo was significant in favor of the active ingredient for 6 items out of 20 ($p < 0.05$).

4.2.2 "Cutaneous comfort" *in vivo* study results

The group receiving active ingredient included 24 subjects aged 50.0±16.7 yr (range: 24–71 yr). Nineteen subjects had dry/dryness-prone skin and 23 had sensitive skin in this group. The group receiving placebo included 24 subjects aged 54.2 ±16.8 yr (range: 24–74 yr). Of these, 22 subjects had dry/dryness-prone skin and 22 had sensitive skin.

The results for instrumental measurement (hydration and TEWL), clinical scoring, color (L* and a* parameters) and biomarkers (IL1-α and cortisol) are in Table 4.

Hydration significantly improved from D0 to D28 with the active ingredient (+25.1%, $p < 0.001$) but there was no significant difference *vs.* placebo (−10.4%, $p = 0.787$). For the skin barrier, a significant improvement was observed from D0 to D28 with the active ingredient (−12.5%, $p < 0.001$) along

Table 3. Results of the "Well-being" *in vivo* study on self-assessment questionnaire.

Question	TOC		Placebo		TOC vs Placebo
	% Positive response	Significance	% Positive response	Significance	
The product has reduced the dryness of my skin	68.2%	NS	47.6%	NS	NS
The product reduced skin redness	61.1%	NS	31.6%	NS	NS
The product improves the roughness of my skin	61.9%	NS	47.6%	NS	NS
The product strengthens the skin barrier	66.7%	NS	33.3%	NS	NS
The product immediately soothes my skin	81.8%	S	65.0%	NS	NS
The product durably soothes my skin	77.3%	S	38.1%	NS	S
The product immediately reduces feelings of tightness, tingling, itching	71.4%	S	57.1%	NS	NS
The product durably reduces feelings of tightness, tingling, itching	80.0%	S	38.1%	NS	S
The product protects my skin against external aggressions	85.7%	S	47.6%	NS	S
The product strengthens my skin against external aggressions	77.3%	S	42.9%	NS	S
The product does not irritate the skin	90.9%	S	80.0%	S	NS
The product improves the condition of my sensitive/dry skin immediately	76.2%	S	66.7%	NS	NS
The product improves the condition of my sensitive/dry skin durably	71.4%	S	33.3%	NS	S
The product improved my emotional state	38.1%	NS	20.0%	NS	NS
The product improved my sleep	15.8%	NS	15.0%	NS	NS
The product improved my mental state	36.8%	NS	20.0%	NS	NS
The product improved my self-confidence	40.0%	NS	5.3%	NS	S
The product improved my well-being	50.0%	NS	45.0%	NS	NS
The product improved my overall quality of life	36.8%	NS	15.8%	NS	NS
I will consider continuing to use this product	72.7%	S	42.9%	NS	NS

S: p value <0.05, NS: p>0.05.

with a significant difference *vs.* placebo in favor of the active ingredient (−34.8%, $p = 0.046$).

The clinical scoring of desquamation (−57.1%, $p = 0.016$), redness (−32.9%, $p < 0.001$), roughness (−42.0%, $p < 0.001$) and overall dryness (−48.4%, $p < 0.001$) performed by a dermatologist showed a significant improvement with the active ingredient from D0 to D28 but no significant differences *vs.* placebo ($p > 0.05$).

Color measurements showed a significant improvement of lightness L* and redness a* with the active ingredient from D0 to D28 (+5.1%, $p < 0.001$) but no significant differences *vs.* Placebo (+15.4%, $p > 0.05$).

Results from biomarker quantification after 28 days of application showed that the active ingredient significantly decreased the quantity of IL1-α in skin (−42.2%, $p < 0.05$). The placebo also decreased levels of IL1-α with a borderline significant change (−4.1%, $p = 0.087$). The difference between the active ingredient and placebo was significant in favor of the active ingredient (−88.9%, $p < 0.001$). The active ingredient also significantly decreased cortisol (−25.2%, $p = 0.002$) but the difference between the active ingredient and placebo was not significant (−32.0%, $p = 0.737$).

The results for the quality of life questionnaire (Tab. 5) show a significant improvement with the active ingredient except for pain, sleep, and walking at night (improvement was borderline significant for these last two parameters). A significant improvement in favor of the active ingredient *vs.* placebo was observed on emotional (anger and irritability) and leisure activity aspects. A borderline significant improvement in favor of the active ingredient *vs.* placebo was observed on emotional (sadness), on sex life, and overall quality of life aspects.

Self-assessment questionnaire results showed that the active ingredient was perceived as significantly effective on 11 out of 14 items. No significant differences between the active ingredient and placebo were observed (Tab. 6).

5 Discussion and conclusion

Psychological stress is known to have an impact on skin and generates skin disorders of varying severity that affect well-being and quality of life (Hall *et al.*, 2012; Graubard *et al.*, 2021; Marek-Jozefowicz *et al.*, 2022). Stress and skin conditions exacerbate each other in a vicious circle (Farage, 2022). The body has two major stress response systems, namely the HPA axis and the sympathetic nervous system, which allow the release of hormones and neurotransmitters such as cortisol and substance P. These responses are necessary, but when stress becomes chronic, they can have harmful consequences on the skin. Stress hormones, such as cortisol, can weaken the skin's immune defenses, trigger allergic responses, delay healing, and disrupt the skin's natural protective barrier (Zhang *et al.*, 2024). Stress can increase overall inflammation in the body, which may have dermatological manifestations. Moreover, stress activates the nervous system, which can lead to increased sensitivity and reactivity in the skin (Chen and Lyga, 2014). These stress-induced changes can provoke various dermatological symptoms, such as eczema or psoriasis, that may in turn increase psychological

Table 4. "Cutaneous comfort" *in vivo* study results on instrumental measurement, clinical scoring color and biomarkers parameters.

Part	Evaluation	TOC				Placebo				TOC vs Placebo p value
		D0 (m±σ)	D28 (m±σ)	%D28/D0	p value / D28 vs D0	D0 (m±σ)	D28 (m±σ)	%D28/D0	p value / D28 vs D0	
Instrumental Measurement	Hydration (a.u.)	48.73±16.97	60.97±13.27	25.1%	0.000	45.34±15.74	56.31±13.93	24.2%	0.000	0.787
	TEWL ($g/m^2/h$)	13.6±2.38	11.9±2.34	-12.5%	0.000	12.78±2.83	11.68±2.5	-8.7%	0.000	0.046
Clinical Scoring	Desquamation / Scaling	0.88±1.45	0.38±0.92	-57.1%	0.016	1.5±1.87	0.63±0.92	-58.3%	0.002	0.402
	Redness	3.54±1.56	2.38±1.56	-32.9%	0.000	3.88±1.62	3±1.59	-22.6%	0.000	0.309
	Roughness	2.08±2.34	1.21±1.64	-42%	0.001	2.58±1.95	1.71±1.71	-33.9%	0.002	0.689
	Overall dryness	3.96±2.33	2.04±2.24	-48.4%	0.000	4.79±2.06	2.92±2	-39.1%	0.000	0.932
	Cutaneous discomfort	6.08±1.86	2.38±2.75	-61%	0.000	6.38±1.56	2.67±2.6	-58.2%	0.000	1.000
Color	L*	61.24±2.29	64.35±2.14	5.1%	0.000	60.94±3.11	64.52±1.96	5.9%	0.000	0.258
	a*	13.04±2.69	10.14±1.91	-22.2%	0.000	13.21±2.66	10.07±2.33	-23.8%	0.000	0.710
Biomarkers	IL1-α	858.45±523.56	496.4±316.72	-42.2%	0.000	965.5±567.2	925.45±534.54	-4.1%	0.087	0.000
	Cortisol	423.89±257.23	317.2±172.78	-25.2%	0.002	465.81±300.69	393.29±288.19	-15.6%	0.004	0.737

Abbreviation: TEWL: Transepidermal Water Loss. L: lightness. A*: redness. D: day. m±σ: mean ± standard deviation.*

distress (Hall *et al.*, 2012). Visible symptoms of skin disorders cause embarrassment and affect social interaction, in addition to other symptoms such as physical discomfort due to itching or pain and sleep disruption caused by itching (Zhang *et al.*, 2024).

During psychological stress, alteration of the epidermis and its barrier function are recognized targets (Choe *et al.*, 2018). By reducing epidermal thickness and organization, psychological stress leads to reduced hydration and impaired protection against external agents. Studies have established the negative effects of psychological stress on the skin, which has been shown to impair the permeability barrier homeostasis (Garg *et al.*, 2001) and *stratum corneum* integrity (Choi *et al.*, 2005). As described in the literature (Zhang *et al.*, 2024), we have observed that stress induces numerous negative impacts, including degradation of epidermal structure and barrier.

The active ingredient decreased cortisol and substance P release in skin explants and in reinnervated epidermis models, respectively. TOC also preserved the structure and improved the repair of skin barrier in a skin explant model stressed by cortisol. The *in vitro* studies presented here demonstrate that TOC has the potential to protect skin from the damaging effects of psychological stress.

The efficacy of the active ingredient demonstrated by *in vitro* studies was confirmed by two *in vivo* studies. The first demonstrated the positive impact of the active ingredient in subjects whose sensitive/dry skin had an impact on their well-being/emotions and their self-esteem by combining subjective questionnaires such as the PSPP and Sensitive Scale questionnaires, the subjective projection of skin conditions on image (SIT test) and objective approaches *via* physiological measurements carried out during the Mirror Test™ and verbatim analyses used to describe the perceived impact of the participant's skin condition on mental state. The second *in vivo* study focused on the impact of the subjects' sensitive skin/dry skin conditions on the skin physiological state itself. This analysis also demonstrated the efficacy of the active ingredient through instrumental measurement of hydration, skin barrier, color, but also through quantification of skin biomarkers of inflammation (Il1-α) and stress (cortisol) and through a quality of life questionnaire. These two *in vivo* studies have, therefore, highlighted the efficacy of the active ingredient that is both subjectively perceived *via* emotions, well-being, and quality of life and objectively measured by instrumental methods. The active ingredient has the potential to counter the vicious circle linked to the condition of dry and/or sensitive skin, thus providing effectiveness for the comfort and well-being of the skin and mind.

Acknowledgments

The authors thank the Expanscience laboratory team for their contributions: Clément Le Bras, Beatriz Soengas, Dorothée Piton, Marine Alluyn, Marion Kerdrain and Séverine Marchand. The authors thank Genel for testing the extract on the model of explant stressed by ACTH and temperature. The authors thank Oxiproteomics for testing the extract on the cortisol stress model impairing the skin barrier explant. The authors thank Université de Bretagne Occidentale, Laboratoire LIEN, for testing the extract on the reinnervated epidermis model. The authors thank Spincontrol and Dermscan for the clinical studies.

Table 5. Results of the "Cutaneous comfort" *in vivo* study on quality of life questionnaire.

	TOC				Placebo				TOC vs Placebo
In the last week, has your skin discomfort/dry or sensitive skin condition ...	D0 (m±σ)	D28 (m±σ)	%D28/D0	p value / D28 vs D0	D0 (m±σ)	D28 (m±σ)	%D28/D0	p value / D28 vs D0	p value
... negatively impacted your emotional state?	5.79±2.48	7.79±1.84	34.5%	0.003	5.63±2.58	7.5±2.17	33.3%	0.001	0.874
... provoked an angry emotion?	6.54±2.57	8.38±1.31	28%	0.005	7.54±2.17	7.88±2.17	4.4%	0.500	0.027
... provoked an emotion of sadness?	6.21±2.52	8.63±0.97	38.9%	0.000	6.88±2.27	7.67±2.18	11.5%	0.044	0.078
... increased your irritability?	5.25±2.71	8.13±1.54	54.8%	0.000	6.58±2.15	7.67±2.16	16.5%	0.002	0.011
... caused a state of anxiety?	6.75±2.31	8.29±1.71	22.8%	0.004	7.17±2.26	8.08±1.79	12.8%	0.012	0.656
... generated pain?	7.13±2.54	8±2.17	12.3%	0.127	7.83±1.66	8.54±1.06	9%	0.049	0.996
... overall disturbed your sleep?	7.5±2.04	8.58±1.35	14.4%	0.052	7.63±2.18	8.5±1.47	11.5%	0.057	0.672
... caused nocturnal awakenings?	7.67±2.08	8.58±1.35	12%	0.080	7.58±2.38	8.54±1.22	12.6%	0.036	0.986
... negatively impacted your concentration?	6.63±2.58	8.33±1.31	25.8%	0.005	6.96±2.24	8.17±1.76	17.4%	0.007	0.469
... negatively impacted your mental state?	6.96±2.22	8.54±0.93	22.8%	0.004	7.13±2.36	8.29±1.52	16.4%	0.012	0.612
... negatively impacted your sex life?	7.33±2.3	8.79±0.51	19.9%	0.002	8.13±2.21	8.54±1.32	5.1%	0.375	0.056
... negatively impacted your state of psychological stress?	6.96±2.27	8.5±1.02	22.2%	0.006	7.46±2.28	7.92±1.93	6.1%	0.227	0.102
... negatively impacted your self-confidence?	6±2.57	8.42±0.97	40.3%	0.000	5.88±2.88	7.58±2.32	29.1%	0.005	0.334
... negatively impacted your energy/dynamism?	6.75±2.33	8.63±0.77	27.8%	0.000	7.21±2.23	8±1.84	11%	0.089	0.152
... negatively impacted your daily activities?	7.08±2.21	8.79±0.51	24.1%	0.000	7±2.47	8.13±1.62	16.1%	0.012	0.473
... negatively impacted your social or family relationships?	7.42±1.74	8.79±0.51	18.5%	0.000	7.29±2.4	8.25±1.57	13.1%	0.013	0.394
... negatively impacted your well-being?	6.08±2.47	8.25±1.07	35.6%	0.000	6.33±2.58	7.79±2.02	23%	0.008	0.296
... negatively impacted your leisure activities?	7.25±1.78	8.79±0.51	21.3%	0.000	7.67±2.22	8.08±1.59	5.4%	0.285	0.033
... negatively impacted your overall quality of life?	7.13±1.6	8.67±0.64	21.6%	0.000	7.46±2.45	8.25±1.62	10.6%	0.010	0.081

Abbreviation: D: day. m±σ: mean ± standard deviation.

Table 6. Results of the "Cutaneous comfort" *in vivo* study self-assessment questionnaire.

Question	TOC		Placebo		TOC vs Placebo
	% Positive response	Significance	% Positive response	Significance	
The product has reduced the dryness of my skin	62,5%	NS	45,8%	NS	NS
The product reduced skin redness	70,8%	S	75,0%	S	NS
The product improves the roughness of my skin	83.3%	S	58.3%	NS	NS
The product strengthens the skin barrier	79.2%	S	62.5%	NS	NS
The product immediately soothes my skin	79.2%	S	62.5%	NS	NS
The product durably soothes my skin	62.5%	NS	58.3%	NS	NS
The product immediately reduces feelings of tightness, tingling, itching	75.0%	S	54.2%	NS	NS
The product durably reduces feelings of tightness, tingling, itching	66.7%	NS	41.7%	NS	NS
The product protects my skin against external aggressions	87.5%	S	70.8%	S	NS
The product strengthens my skin against external aggressions	87.5%	S	66.7%	NS	NS
The product does not irritate the skin	91.7%	S	87.5%	S	NS
The product improves the condition of my sensitive/dry skin immediately	79.2%	S	62.5%	NS	NS
The product improves the condition of my sensitive/dry skin durably	70.8%	S	50.0%	NS	NS
I will consider continuing to use this product	70.8%	S	45.8%	NS	NS

S: p value <0.05, NS: p>0.05.

Funding

This research was funded by Laboratoires Expanscience.

Conflicts of interest

The authors are employees of Expanscience. The funders had no role in the design of the study; in the collection, analyses, or interpretation of data; in the writing of the manuscript; or in the decision to publish the results.

Author contribution statement

Conceptualization: S.L., M.L.R., and G.B.; formal analysis: M.L.R., G.B.; funding acquisition: C.B.; investigation: S.L., M.L.R., and G.B.; methodology: S.L., M.L.R., and G.B.; project administration: S.L., and C.B.; supervision: C.B; validation: S.L., M.L.R., and G.B.; visualization: S.L., M.L.R., and G.B.; writing—original draft preparation: S.L., M.L.R., and G.B.; writing—review and editing: S.L., M.L.R., G.B., and C.B. All authors have read and agreed to the published version of the manuscript.

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Cite this article as: Leclère S, Le Roux M, Boyer G, Baudouin C. 2025. Improving skin comfort and well-being with tea oil concentrate from *Camellia oleifera* obtained by molecular distillation. *OCL* 32: 33. https://doi.org/10.1051/ocl/2025029