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ORIGINAL CONTRIBUTION

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Inhibition of thymic stromal lymphopoietin production to improve pruritus and quality of life in infants and children with atopic dermatitis

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Abstract

Background: Atopic dermatitis (AD) is an inflammatory pruritic chronic dermatosis involving the alarmin thymic stromal lymphopoietin (TSLP), which is directly implicated in AD pruritus.

Aims: To evaluate the efficacy of *Tambourissa trichophylla* leaf extract (TTLE) titrated in polyphenols and 18β-glycyrrhetinic acid (GA) in vitro and in vivo for AD pruritus.

Patients/Methods: Initially, in vitro assessment of TSLP production in keratinocytes was undertaken. In normal human keratinocytes in vitro, TSLP was induced by polyinosinic:polycytidylic acid (Poly:IC), tumor necrosis factor (TNF)-α, and interleukin (IL)-4 and then quantified by ELISA in supernatants. Some cells were pretreated with TTLE and/or GA. Thereafter, an in vivo clinical study was performed including 48 infants and children with mild to severe AD flare-ups, some of which were treated with topical corticosteroids. A topical spray containing TTLE and GA was applied. After 21 days of topical spray application, pruritus, sleeplessness, the SCORing Atopic Dermatitis (SCORAD) index, the Infant's Dermatitis Quality of Life index (IDQOL), and the Dermatitis Family Impact Questionnaire (DFIQ) were assessed.

Results: Thymic stromal lymphopoietin secretion was inhibited significantly in an AD environment by TTLE and GA by up to 57.2% and 73.3%, respectively. The use of the topical spray induced a significant reduction in pruritus and sleeplessness scores, as well as the SCORAD, IDQOL, and DFIQ indexes in the total group. Similar results were observed in patient subgroups with or without topical corticosteroid treatment.

Conclusions: A topical spray containing TTLE and GA, which inhibit TSLP secretion, efficiently decreases AD pruritus and improves the quality of life of AD patients.

KEYWORDS

atopic dermatitis, emollient; pruritus, quality of life, thymic stromal lymphopoietin

Fitoussi and Virassamynaïk are co-first authors.

Trompezinski and Sayag are co-last authors.

1 | INTRODUCTION

Atopic dermatitis (AD) is a relapsing inflammatory cutaneous disease characterized by epidermal barrier dysfunction, eczematous lesions, and a chronic and intense pruritus.[1] Pruritus is the major diagnostic criterion for AD with 91% of patients affected[2] and is critical in the development of eczematous lesions in vivo.[3] Nocturnal scratching can lead to sleep disturbances and may impact the quality of life of the patient and their family.[4]

The physiopathological mechanism of AD pruritus is still not fully understood, although several factors have been identified,[1,5] such as neuromediators *via* PAR-2 (protease-activated receptor-2), the cytokine interleukin (IL)-31, and two alarmins: IL-33 and thymic stromal lymphopoietin (TSLP). TSLP is an IL-7-like cytokine expressed by keratinocytes as a result of environmental, endogenous factors and loss of barrier function.[6] Epidermal TSLP expression has been correlated in vivo with atopic march, AD severity, and AD itch score.[7,8] Furthermore, a sharp increase in TSLP expression has been observed in the atopic epidermis, while TSLP has not been detected in normal human skin.[7,9] Furthermore, TSLP secretion by keratinocytes is increased by several inflammatory inducers themselves involved in AD pathology[1] such as IL-4 and a T helper 2 (Th2) cytokine, in association with tumor necrosis factor-α (TNF-α)[10,11] and the polyinosinic:polycytidylic acid (Poly:IC; toll-like receptor 3 [TLR3] ligand).[11,12] Moreover, the TSLP receptor is expressed on sensory cutaneous neurons and induces itch.[8] Therefore, TSLP appears a potential target to explore the treatment of AD pruritus.

The aim of this study was to evaluate the effect of *Tambourissa trichophylla* leaf extract (TTLE) titrated in polyphenols and 18β-glycyrrhetinic acid (GA), first on TSLP secretion in an in vitro AD model and second in a clinical study with the application of a topical spray on atopic infants and children with flare-ups of pruritus. The evolution of the disease's severity and the quality of life of patients and their families were evaluated.

2 | MATERIALS AND METHODS

2.1 | Culture of NHEK

Normal human epidermal keratinocytes (NHEK; origin: foreskin) were amplified in keratinocyte basal medium (KBM; 00 192 151) supplemented with transferrin, epinephrine, gentamicin/amphotericin-B-1000, bovine pituitary extract, recombinant human epidermal growth factor, insulin, and hydrocortisone (00 192 152) at 37°C, 5% CO_2, and saturated humidity. At 60% confluence, NHEK were dissociated with trypsin-ethylenediaminetetraacetic acid (EDTA) 0.025% (P10-019100, PAN Biotech) and the enzymatic reaction was stopped by soybean 0.5 mg/mL (17075-029, Gibco, France).

2.2 | Induction of an AD-inflammatory environment in vitro

NHEK were seeded at 20 000 cells/well in a 96-well culture plate in supplemented KBM. After 24 hours, the hydrocortisone was depleted. After 24 hours, the cells were stimulated for 24 hours with a combination of inflammatory factors: 0.02 µg/mL TNF-α (300-01A, Peprotech), 0.1 µg/mL IL-4 (200-04, PeproTech), and 10-25 µg/mL Poly:IC (P9582, Sigma-Aldrich). Each procedure was performed in triplicate for one experiment. The culture supernatants were collected and frozen at −80°C.

2.3 | Chemicals

The efficacy of a TTLE titrated in polyphenols (>40% of polyphenols, SERDEX) and GA (purity >98%, EVD) on TSLP production was quantified. Dexamethasone at 1 µM (D8893-1MG, Sigma-Aldrich) was used as a positive control of inhibition. Cells were pretreated for 1 hour with active molecules before the addition of inflammatory factors. Tested doses were determined by preliminary cytotoxic tests. The highest concentrations tested were the maximal noncytotoxic doses. Each condition was performed in triplicate for one experiment.

2.4 | Cellular viability

The (3-4,5-dimethylthiazol-2-yl)-2,5-diphenyl tetrazolium bromide solution at 1 mg/mL (MTT; M2128-5G, Sigma-Aldrich, France) was added to each well after preliminary collection of culture supernatants. The plates were incubated for 3 hours at 37°C, 5% CO_2, and saturated humidity. The MTT solution was carefully removed from the wells, and 100 µL of dimethyl sulfoxide (DMSO; D4540, Sigma-Aldrich) was added to each well. The plates were gently swirled for 5 minutes. The optical density was read at 540 nm with a Victor3™ 1420 Multilabel Counter Plate Reader (PerkinElmer) and Wallac Workstation software. The cellular viability of each well was normalized relative to the corresponding control-supplemented KBM (without hydrocortisone) in an inflammatory condition (100% viability). Only data obtained with a cell viability threshold of above 80% were analyzed.

2.5 | Thymic stromal lymphopoietin quantification

Thymic stromal lymphopoietin secretion was quantified in the cell supernatant with the human TSLP DuoSet enzyme-linked immunosorbent assay (ELISA) development kit (DY1398, R&D Systems) according to the manufacturer's instructions. TSLP protein concentrations were calculated using a standard curve (15-1000 pg/mL)

established with human TSLP recombinant protein. TSLP quantification of each well was normalized by cellular viability evaluated by MTT test. The optical density was read at 450 nm with a Victor3™ 1420 Multilabel Counter Plate Reader and WorkOut 2.0 software.

2.6 | Clinical study design

The multicenter, prospective, observational, noncomparative study was conducted by two dermatologists and three pediatricians in Spain between December 2017 and March 2018. The study did not require approval from local ethics committees prior to inclusion of subjects according to the local legal requirements for this observational study. It complied with the Principles of the Declaration of Helsinki and Good Clinical Practices. Subjects and their caregivers consented prior to participation. Investigators recruited infants and children with AD flare-ups and prescribed topical corticosteroids (TC) from Classes 1 to 3 when necessary and in accordance with their current practices. The investigational product is a topical spray (Atoderm SOS Spray, NAOS, LABORATOIRE BIODERMA) consisting of an emulsion oil in water contained in particular TTLE (0.05%) and GA (0.45%). Subjects were instructed to use it for 21 days as often as necessary, holding it at a distance of about 20 cm from pruritic zones (body and face).

2.7 | Subjects and assessments

Suitable subjects were infants and children aged between 4 months and 5 years who presented flare-ups of mild to severe AD in the acute phase. All subjects had, at inclusion, a disease-related pruritus score ≥4 on a subject pruritus severity scale ranging from 0 = null to 10 = very severe. The total group was divided into two subgroups: treated or not with topical corticosteroids (TC), all treated with the topical spray. During the observation period, subjects were not allowed to apply any other cosmetic product to manage their pruritus.

Pruritus and sleep were evaluated by the investigator on a scale from 0 (null) to 10 (very severe); these scores were extracted from the SCORing Atopic Dermatitis (SCORAD) index. The evolution of AD at baseline and during the clinical study was assessed using the SCORAD index (0-103) evaluated by the investigators according to the recommendations of the European Task Force on Atopic Dermatitis.[13] The subjects' quality of life was assessed at baseline and after 21 days using the Infant's Dermatitis Quality of Life (IDQOL) index and the Dermatitis Family Impact Questionnaire (DFIQ) (scored from 0 to 30). At Day 21, the children's parents completed a questionnaire regarding their perception of the effectiveness of the treatment. During the study, tolerance follow-up was carried out by the investigators.

2.8 | Statistical analysis

For in vitro experiments, the *P*-value was calculated with the nonpaired equal variance Student's *t* test. For the clinical study, the statistical comparison of data between baseline and Day 21 was calculated with a paired equal variance Student's *t* test for the total group, with a Wilcoxon test in each subgroup. The statistical data between both subgroups were analyzed with a nonparametric Mann-Whitney test. A statistical significance threshold level of 5% was chosen and was asterisked in the figures: * $P < .05$, ** $P < .01$, and *** $P < .001$; NS = not significant.

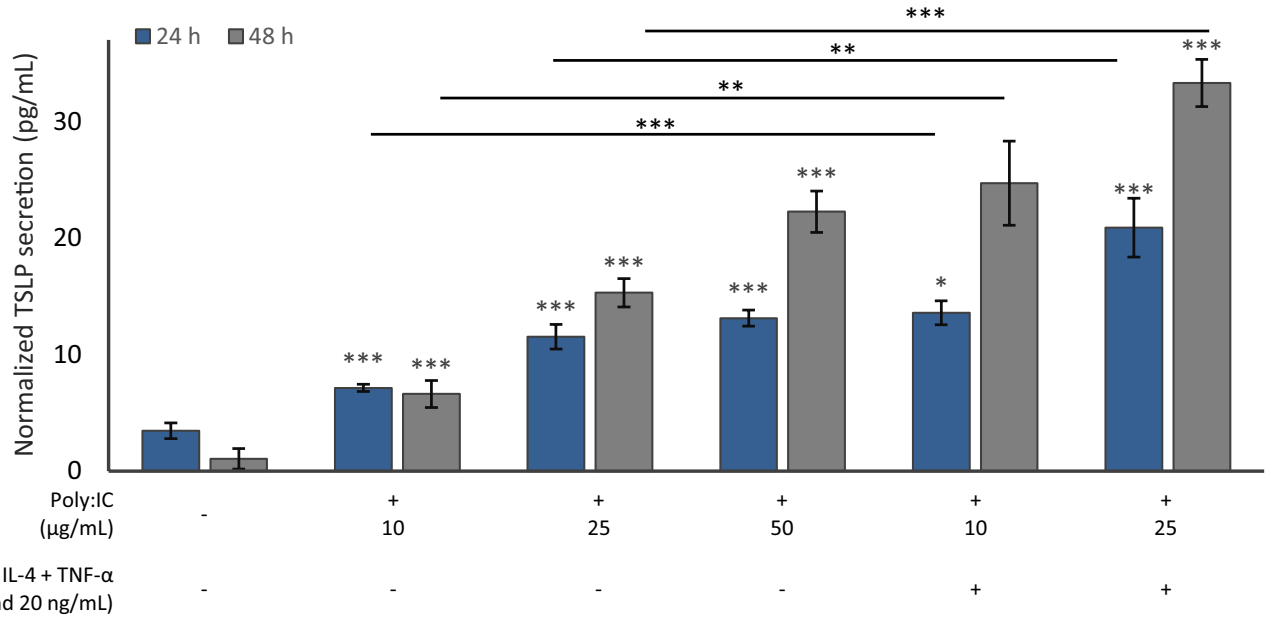

FIGURE 1 Induction of thymic stromal lymphopoietin (TSLP) secretion by polyinosinic:polycytidylic acid (Poly:IC) alone or in association with interleukine-4 (IL-4) and tumor necrosis factor (TNF)-α (representative of n = 3). * $P < .05$, ** $P < .01$, and *** $P < .001$, vs positive control

3 | RESULTS

3.1 | Thymic stromal lymphopoietin secretion by NHEK

The basal level of TSLP secretion by NHEK was quantified at 3.47 pg/mL after 24 hours and 1.06 pg/mL after 48 hours (Figure 1) but may differ according to NHEK donor. After both 24 and 48 hours, a dose-dependent increase was observed with Poly:IC alone. IL-4 and TNF-α potentiated significantly the Poly:IC effect tested at 10 and 25 μg/mL after 24 and 48 hours (Figure 1). Previously, IL-4 in association with TNF-α has been tested alone for 24 hours. No TSLP induction was observed. However, IL-4 and TNF-α potentiated significantly the Poly:IC effect (internal data) as described previously.

To evaluate TSLP secretion inhibition, the condition with 10 μg/mL for Poly:IC in association with TNF-α and IL-4 during 24 hours was selected. These conditions on the one hand promoted a sufficient cellular viability and on the other an optimal TSLP secretion induction (without saturating the system to be closer to the physiological condition).

3.2 | Efficacy of TTLE and GA on TSLP secretion

The positive induction control of TSLP secretion was defined at 100% corresponding to 40.9 and 44.8 pg/mL, respectively (Figure 2A and B). TTLE significantly decreased TSLP secretion in a dose-dependent manner, up to 57.2 ± 4.1% ($P < .001$) after 24 hours compared to the positive induction control (Figure 2A). Similarly, GA decreased TSLP secretion in a dose-dependent manner up to 73.3 ± 5.1% ($P < .001$) compared to the positive induction control. GA at 0.1 × $10\%^{-3}$% had no significant effect on the TSLP secretion (Figure 2B). The association of TTLE and GA, composed of 3 × $10\%^{-3}$% TTLE and 0.4 × $10\%^{-3}$% GA, decreased TSLP secretion up to 83.1 ± 0.7% ($P < .001$). No synergetic effect on TSLP production was observed (internal data).

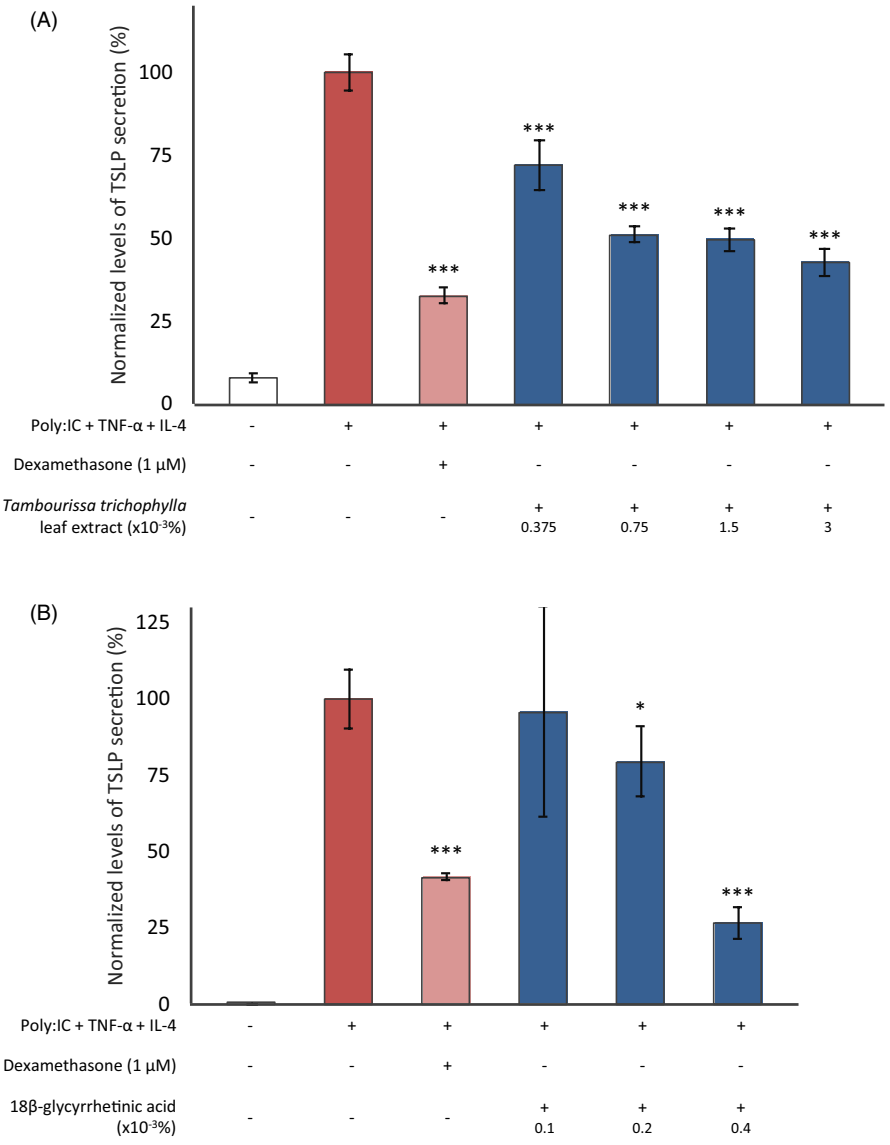

FIGURE 2 Inhibition of thymic stromal lymphopoietin (TSLP) secretion by *Tambourissa trichophylla* leaf extract (TTLE) (a) and 18β-glycyrrhetinic acid (GA) (b) (representative of n = 3). * $P < .05$, ** $P < .01$, and *** $P < .001$, versus positive control

TABLE 1 Demographic and AD characteristics of subjects enrolled

	All subjects	Subjects without topical corticosteroids	Subjects with topical corticosteroids
Number (girls/boys)	48 (24/24)	25 (11/14)	23 (13/10)
Mean age in year (min/max)	2.8 ± 1.3 (4 mo/5 y old)	2.7 ± 1.5 (4 mo/5 y old)	2.8 ± 1.1 (13 mo/5 y old)
SCORAD index (min/max)	33.5 ± 10.0 (17/69)	29.3 ± 6.3 (18/40)	38.0 ± 11.5 (17/69)
AD severity			
Mild	8	6	2
Moderate	38	19	19
Severe	2	0	2
Topical corticosteroids			
Class 1	6	/	6
Classes 2-3	17	/	17

Note: Data are presented as number or mean ± standard deviation. Classes 1, 2, and 3: weak, moderate, and strong corticosteroids, respectively.

Abbreviations: AD, Atopic dermatitis; SCORAD, SCORing Atopic Dermatitis.

3.3 | Subjects' characteristics

A total of 48 infants and children aged 4 months to 5 years (mean 2.8 ± 1.3 years) were enrolled with a mean SCORAD index of 33.5 ± 10.0, including a subgroup of 23 subjects applying topical corticosteroids Class I (hydrocortisone or flumethasone pivalate) or II/III (methylprednisolone or others) during the study (Table 1). The spray containing TTLE and GA was applied for a mean of 21.9 days with a mean of 1.6 applications/day.

3.4 | Pruritus and sleeplessness

After 21 days of product application, the pruritus score decreased significantly ($P < .01$) with reductions compared to Day 0 of 51%, 41%, and 59%, respectively, for all subjects, and the subgroups treated with TC (+ TC) or not (- TC) (Figure 3A). Similarly, for sleeplessness, the score significantly decreased ($P < .01$) for all subjects and the two subgroups with a respective reduction of 53%, 50%, and 57% compared to Day 0 (Figure 3B). The improvement in pruritus and sleeplessness scores in the two subgroups was similar at Day 21 (NS).

3.5 | SCORAD results

The average SCORAD index after 21 days of treatment significantly decreased ($P < .01$) for all subjects and also for subgroups treated or not treated with TC, corresponding to a reduction of 51%, 49%, and 53%, respectively, compared to Day 0 (Figure 3C). The SCORAD index improvement between the two subgroups was statistically different at Day 0 ($P < .001$) but similar at Day 21 (NS).

3.6 | Quality of life

At D21, IDQOL index presented a significant decrease of 33% for all subjects ($P < .01$), and 37% and 30%, respectively, for the subgroup treated with TC or not ($P < .05$) compared to Day 0 (Figure 4A). The DFIQ questionnaire showed a 37% decrease in score at Day 21 for all subjects ($P < .01$), 52% for subjects treated with TC ($P < .05$), and 19% for subjects not treated (NS) compared to Day 0 (Figure 4B). The improvement of the IDQOL and DFIQ between the two subgroups for both was similar at Day 21 (NS).

3.7 | Subjective efficacy

Parents' perception after 21 days' use of the topical spray was that it immediately relieved the child's itching, reduced the desire to scratch, and brought an immediate feeling of comfort (Figure 5). The difference at Day 21 between the two subgroups for the first two items was similar (NS) but statistically different to the last one ($P < .05$). The relief delay after application was also evaluated by the parents. Of all the subjects, 74% perceived that the topical spray relieved itching 30 seconds or less after application.

3.8 | Tolerance and safety

The investigators and the children's parents evaluated the tolerance to the topical spray at Day 21 as good to excellent (no discomfort or irritation) for 92% and 90%, respectively. During this study, the investigators estimated the tolerance as less favorable (1 bad and 3 medium) for four subjects, but did not result in premature withdrawal from the study.

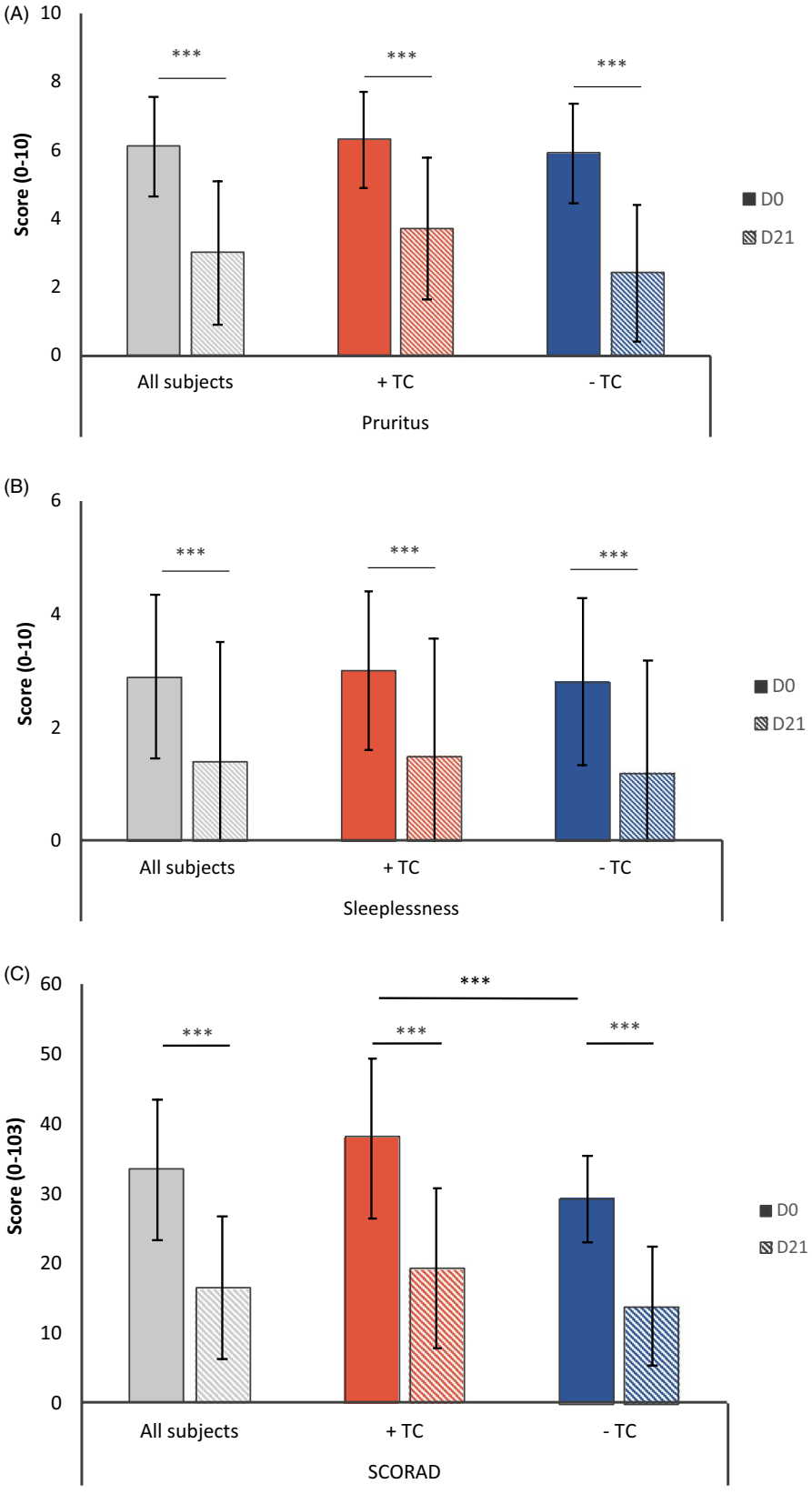

FIGURE 3 Pruritus score (A), sleeplessness score (B), and SCORing Atopic Dermatitis (SCORAD) (C) average comparison between Day 0 and Day 21 for all subjects and the subgroups treated (+TC) or not with topical corticosteroids (–TC). * $P < .05$, ** $P < .01$, and *** $P < .001$, compared to the baseline visit

4 | DISCUSSION

First, our in vitro AD model validated that IL-4, TNF-α, and Poly:IC induced TSLP production by NHEK, concurring with previous published studies.[10-12] Moreover, our data indicate for the first time that TTLE and GA are effective in inhibiting TSLP secretion by NHEK. Only one ex vivo study had demonstrated TSLP inhibition by GA in the nasal mucosa of rats with allergic rhinitis.[14] This

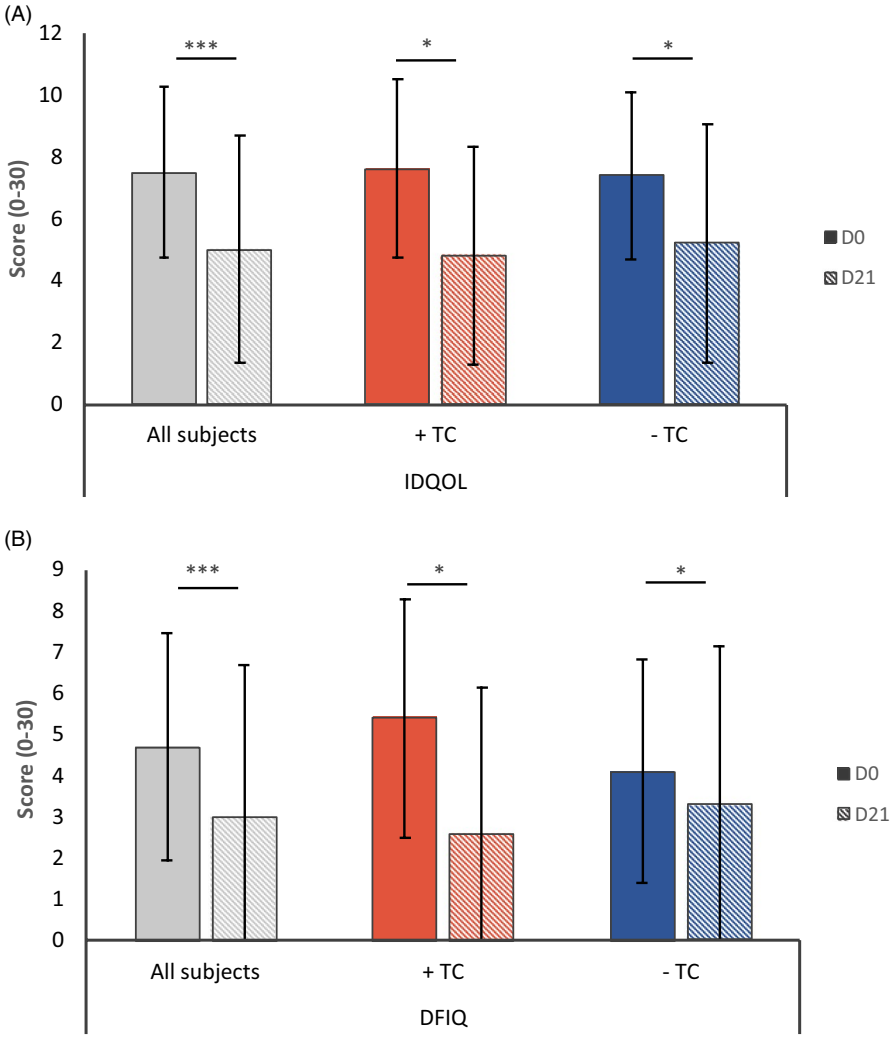

FIGURE 4 Infant's Dermatitis Quality of Life (IDQOL) index (a) and Dermatitis Family Impact Questionnaire (DFIQ) (b) average comparison between Day 0 and Day 21 for all subjects and the subgroups treated (+TC) or not with topical corticosteroids (–TC). * $P < .05$, ** $P < .01$, and *** $P < .001$, compared to the baseline visit

inhibition could be mediated by the IL-1α pathway since, in association with TNF-α, IL-1α induced TSLP expression in human skin explant,[10] and TTLE (SERDEX supplier data) and GA[15,16] reduced IL-1α production. Moreover IL-1α is increased in skin barrier disruption.[17] Internal data on TTLE suggest that troxerutin, a titrated polyphenol, is one of the active molecules in the plant extract. Furthermore, GA is known to have a cortisol-like action[18] and, as steroids are antipruritic, GA could reduce pruritus by this pathway. Since TSLP appears a potential target to explore treatment of AD pruritus,[7-9] TTLE and GA incorporated into a topical spray were evaluated in AD patients.

Second, the clinical study using the topical spray containing TTLE and GA resulted in significant relief of pruritus, both immediately

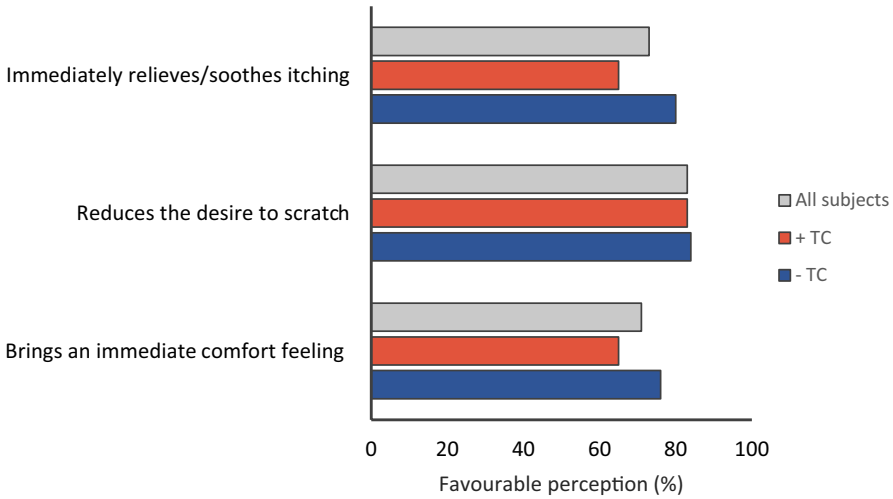

FIGURE 5 Subjective efficacy at Day 21 for all subjects and the subgroups treated (+TC) or not with topical corticosteroids (–TC). Favorable perception measured in percentage

(30 seconds) and in the medium term (after 21 days), in infants and children affected by AD. The results demonstrate that the dermocosmetic topical spray immediately relieved pruritus, with or without medical treatment such as TC. Since TC are applied only once a day, a dermocosmetic is complementary owing to its ease of application at any time of the day when required to relieve pruritus. Current treatment guidelines for AD management by the European Academy of Dermatology and Venerology and the American Academy of Dermatology recommend emollient use.[19,20] Most antipruritic dermocosmetics do not directly target mediators involved in pruritus, but only contain active ingredients restoring the skin barrier (ceramides, phospholipids, lipids from shea butter extract, glycerol, etc)[21-23] which indirectly, and therefore potentially less quickly, improve pruritus. Moreover, antipruritic dermocosmetic products are creams or hydrogel formulas, but their application with hand contact could induce friction, in particular on altered skin such as AD skin. Similarly to the scratching action, friction on the skin exacerbates pruritus and can initiate the "itch-scratch cycle".[24] Therefore, a topical spray spreading the formula without any hand contact can prevent skin friction and exacerbated itching.

Third, after 21 days of application, the topical spray showed a significant improvement in sleeplessness. Moreover, global parameters of AD evaluated by the SCORAD index were improved according to the clinical assessment. As expected, the subgroup with TC presented a SCORAD index at Day 0 statistically higher than the subgroup without TC. Interestingly, at Day 21 the SCORAD indexes presented no statistical difference between the two subgroups. As pruritus is the main clinical symptom impacting quality of life in AD,[2] two questionnaires evaluated both the qualities of life of infants and children (IDQOL) and their families (DFIQ). In both subgroups, the IDQOL statistically decreased at Day 21, but less than in a previous study that also evaluated the efficacy of a topical spray for 21 days.[25] The subjects were adults, and contrary to the subjects in this study, they presented pruritus without episodes of flare-up.[25] As expected, the efficacy of the topical spray is inferior for AD patients with flare-ups but is nonetheless significant and therefore improves the patients' quality of life. The DFIQ score was statistically reduced for all subjects, the subgroup with TC, but not the subgroup without TC. A possible explanation is that the initial DFIQ score at Day 0 in subjects without TC was lower than that of those with TC (NS). Thus, the assessment of quality of life confirmed that the topical spray allowed patients and their caregivers to improve not only AD but also their well-being and that of their families.

Finally, the topical spray showed good tolerance in all subjects whether treated with TC or not, confirming previous results.[25]

A limitation of this study is the absence of a control group treated with a placebo spray. Hence, we could not compare the efficacy of the topical spray with or without TTLE and GA. However, all ingredients are considered important for the skin-moisturizing effect and the indirect antipruritic effect through restoration of the barrier function. Beyond its limitation, this study demonstrates that the investigational product is effective and safe.

In conclusion, the topical spray containing TTLE and GA significantly improves pruritus, sleeplessness, and global AD, thus improving the quality of life of patients and their families. The topical spray is safe and can be used adjunctively or alternately to TC. The study results suggest that TTLE and GA could play a role in the decrease of AD-induced pruritus. Complementary studies assessing the benefit of the topical spray are necessary, which include further investigations and future objective measurements of pruritus and sleeplessness.

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