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Research Article

Effects of Novel All Natural Plant Based Ointment Formulation on Diaper Rash Severity in Infants: A Clinical Trial

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Abstract

An open-label, single-arm clinical study evaluated the efficacy and safety of a novel all natural/plant-based ointment formulation on diaper rash in healthy infants aged 0–36 months. Mothers/legal representatives of the subjects applied 1·5 g to 2·5 g diaper rash ointment on and around the affected areas along with each diaper change for 14 days. Overall severity of diaper rash, skin itching, skin redness, erythema, and skin dryness were evaluated at different time intervals. The overall severity score of diaper rash significantly reduced from baseline to 12 h ($p<0·0001$), 24 h ($p<0·0001$), Day 07 ($p<0·0001$), and Day 14 ($p<0·0001$). Overall severity started reducing from 6 hours with significant reduction at 12 h, thus the onset of action is less than 12 hours. Skin itching scores significantly reduced at all visits. Skin redness/erythema scores reduced significantly at 24 h ($p=0·001$), Day 07 ($p<0·0001$), and Day 14 ($p<0·0001$). Skin dryness scores significantly reduced at 24 h ($p<0·02$), Day 07 ($p<0·0001$), and Day 14 ($p<0·0001$). No cases of skin hypersensitivity reactions or any adverse events were reported during the study. Diaper rash ointment effectively reduces the overall severity of diaper rash, skin itching, redness, erythema, and dryness after application to the affected area. It is gentle and safe on baby's skin and promotes skin healing by providing effective moisturization.

Keywords: Diaper dermatitis; Diaper rash; Erythema; Infant; Natural product; Skincare; Skin itching; Skin redness; Zinc oxide

Introduction

Diaper rash or diaper dermatitis is described as an acute, inflammatory skin reaction occurring within the diaper area after prolonged exposure to diapers [1,2]. It is commonly observed on the genitals, buttocks, perianal area, inner thighs, and waistline. It is one of the most common skin disorders in infants [1] and varies according to setting, age group, and hygiene practices [3]. Children under the age of 24 months have the highest prevalence of diaper rash, with the most common occurrence between 9 and 12 months [2,3]. This is particularly because children in this age-group require frequent diapering than those in other age-groups [3].

Diaper rash is usually caused by a combination of factors such as type of diaper used, prolonged period of wetness and urine in the diaper area, presence of bile salts and other irritants from urine and faeces, friction, mechanic abrasion, increase in the skin pH levels due to urine and faeces, and occasionally due to the presence of microorganisms [1-3]. Water, friction (between fabric and skin causing physical damage to skin), urine (high pH and urine increases trans-epidermal permeability more effectively than water alone) and faeces all contribute to the diaper dermatitis. This might lead to further secondary infection [4].

Maceration (excessive wetting) of the stratum corneum is likely to be the most critical predisposing factor. Excessive wetness affects the stratum corneum, as it creates a fragile surface, thus more prone to physical damage to friction, affects the protective barrier function thus allowing the irritants to permeate through and facilitating secondary microbial infection. Thus, a lipid barrier from wetness would be the drug of choice. The use of herbal medicines on the skin of children has a long history in many parts of the world [5]. However, there are some products available claiming to provide barrier function, which are typically emulsions but there is a demand of an anhydrous preparation. The basic strategy for the treatment and prevention of diaper rash involves an ABCDE approach, viz., air, barrier, cleansing, diapering, and education [6,8]. Barrier emollients mostly as ointments/ lotions are the first-line agents for the prevention and treatment of diaper rash. These provide a protective lipid layer over the skin that prevents exposure to irritants and moisture, thereby allowing the repair of the stratum corneum underneath the emollient. Lotions and creams are emulsions containing additional aqueous phase [7] while anhydrous ointment creates a better lipid barrier and are more suitable if it is made of ingredients of natural origin.

There is a traditional practice of applying oils and butter to prevent Diaper Dermatitis. The present study evaluated the efficacy and safety of a natural ointment formulation on diaper rash in healthy infants.

Material & Methods

Study design

An open-label, single-arm clinical study was conducted to evaluate the efficacy and safety of diaper rash ointment on diaper rash in healthy infants aged 0–36 months. This study was conducted according to relevant SOP(s), study protocol, the Indian Council of Medical Research (ICMR) ethical guidelines, the International Council for Harmonization of Technical Requirements for Pharmaceuticals for Human Use (ICH) (Step 5) 'Guidance on Good Clinical Practice' (E6 R2), and Declaration of Helsinki. The study was approved by ACEAS – Independent Ethics Committee. Study protocol, English and Gujarati informed consent form, Screening and Study case report form (CRF), and English and Gujarati Study Diary were approved on 04 February 2021, prior to initiation of the investigation. (CTRI Registration No.: CTRI/2021/02/031265)

Test product composition

Diaper rash ointment is a 100% natural product consisting of ingredients from plants or natural sources. It consists of *Ricinus communis* Seed Oil, *Glycine soja* Bean Oil, *Garcinia indica* Seed Butter, *Yashada bhasma* (Zinc oxide), *Cocos nucifera* Fruit Oil, *Azadirachta indica* Seed Oil; combination of Cococin (Coconut Water) - *Cocos nucifera* (Coconut) Fruit Juice, Boswellin – *Boswellia serrata* Gum Extract, *Hamamelis virginiana* (Witch Hazel) Extract; combination of oils *Prunus amygdalus* dulcis Oil, *Borago officinalis* Seed Oil, *Linum usitatissimum* Seed Oil, and *Olea europaea* Fruit Oil, along with allowed excipients including Tocopherol & Ascorbyl palmitate (antioxidants).

Study population

Healthy subjects between the age of 0 to 36 months wearing diapers for at least 12 h per day and with an "overall severity score" [9] greater than or equal to 1·5 were included in the study after obtaining voluntary written informed consent. The overall severity score is based on overall severity scale for erythema and rashes on subject's skin and is calculated as the sum of scores of four domains: Severity of erythema and irritation, an area with any diaper dermatitis, papules or pustules, and skin integrity. Assessors used the scale to attribute severity scores using high-definition photographs of the subjects with diaper dermatitis.

Other inclusion criteria included: The mother/legal representative ensured that the subject continued wearing their usual brand of diapers and usual cleaning regimen using their regular products and methods. They were refrained from using ointments, lotions, creams, or powders or any other product that might affect subject's

skin condition (like laundry detergent, fabric softener, etc.). They agreed to come for regular follow up. Subjects who were not part of any other clinical study were included in the current study.

Subjects were not enrolled in the study if they met at least one of the following exclusion criteria: Subjects with medical history of significant dermatological diseases or conditions, such as atopy, psoriasis, eczema, vitiligo, or other conditions known to alter the skin's appearance or physiological response (e.g., porphyria, chronic urticaria, sunburn, rashes) or chronic illness influencing cutaneous state or with known history of an allergic response or any other concern that may require medical attention or deemed unsuitable as per the investigator's opinion or had participated in similar study in last 30 days or being toilet trained and if the mother/legal representative was reluctant to stop the use of other body milk/lotion/cream or any other face/body moisturizing product during the study period.

Study protocol

Subjects were initially screened at Visit 1 (screening visit, within 30 days from Day 1) for the eligibility criteria. On Visit 2, rash due to diaper was analysed to check on the eligibility criteria and this was considered as baseline (Prior to the application of the diaper rash ointment). After application of the ointment, the diaper rash was analysed at Visit 2 [6 (±15min) h and12 (±15min) h, Day 1], Visit 3 [24 (±2) h, Day 2], Visit 4 [Day 7 (±2 days)], and Visit 5 [Day 14 (±2 days)]. During enrolment, the mothers/legal representatives of the enrolled subjects were instructed to apply 1·5 g to 2·5 g of Diaper rash ointment for 14 days directly on the affected rash site, area around the buttocks and thighs, between the buttocks and thigh folds with each diaper change and to record the frequency of ointment application in the daily diary. Furthermore, they were instructed to change wet diapers immediately, and cleanse and dry the diaper area.

Quantification of Cyclooxygenase (COX2) inhibition: It was estimated by fluorescence assay according to the manufacturer's instructions. The inhibitory activity was expressed as IC50 (50% inhibitory concentration) and each experiment was performed at least twice.

Statistical analysis

All statistical analyses were done using SAS® statistical software with 5% level of significance (Version: 9·4; SAS Institute Inc., USA). The significance of continuous variables comparing baseline to post-treatment was determined using paired *t*-test. The within-treatment analysis comparing categorical variables from baseline to post-treatment was determined using Wilcoxon signed-rank test.

Safety testing

Human repeated insult patch test (HRIPT) for irritation and sensitization potential was assessed in healthy adult human subjects. Skin sensitization potential of diaper rash ointment and its active ingredients was analysed in HaCaT cell line in an ARE-Nrf2 luciferase assay.

Results

COX2 inhibition

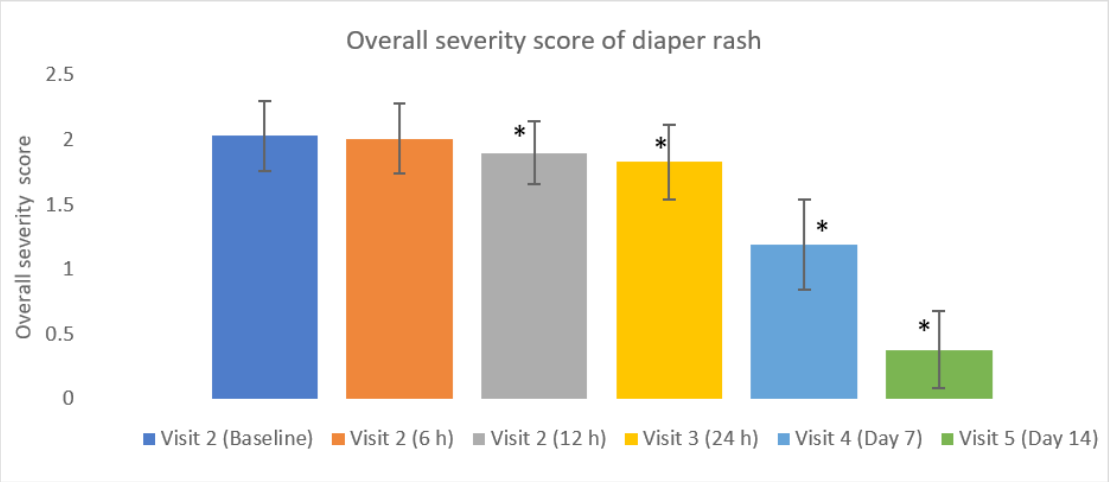
There was a concentration dependent inhibition of COX2 with IC50 being 24.79 mg/ml (data on file)

Clinical study

A total of 58 healthy subjects with equal no of male and female were enrolled and completed the study. Age of the subjects ranged from 1–32 months, with an average of 15·3 ± 8.91 months.

Primary outcomes

Overall severity score of diaper rash: The overall severity score of rash due to diaper reduced from baseline to Day 14 after application of diaper rash ointment [9]. The score significantly reduced from baseline at 12 h, 24 h, Day 07, and Day 14 ($p < 0·0001$) (Figure 1), using severity scoring analysis by the paediatrician. There was insignificant reduction at 6 hrs but at 12hrs there was significant reduction hence the onset time is less than 12 hrs with 80% mean reduction in diaper rash severity by 14 days.



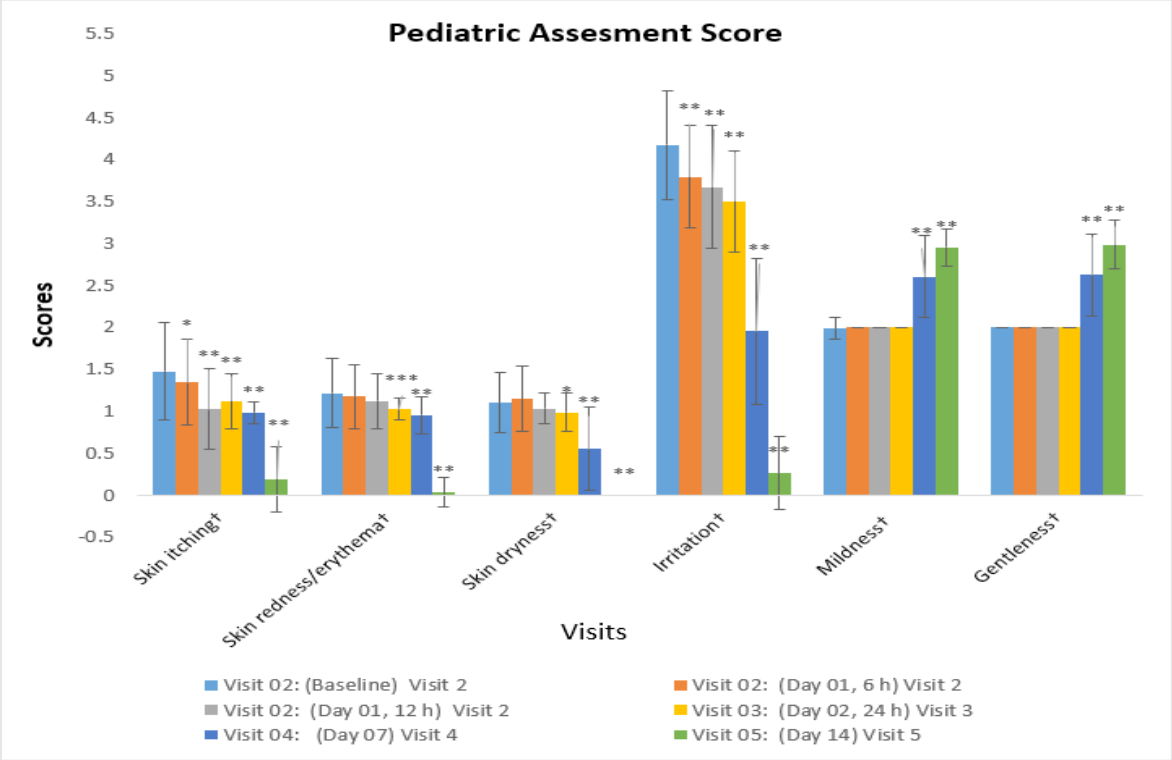
All values are presented as mean ± standard deviation.

*p <0·0001; significant for change in overall severity score from baseline to post-ointment application.

Grading Scale: 0 = None, 0·5 = Slight, 1 = Mild, 1·5 = Mild/Moderate, 2 = Moderate, 2·5 = Moderate/Severe, 3 = Severe.

Figure 1: Change in overall severity score from baseline to post-ointment application.

Paediatric assessment score [10,11]: Skin itching scores were significantly reduced at all visits. Skin redness/erythema and skin dryness scores reduced significantly at 24 h, Day 07, and Day 14 (P<0.05). Skin irritation scores reduced significantly at all visits, i.e., at 6 h, 12 h, 24 h, Day 07, and Day 14 (p <0·0001). Both mildness and gentleness scores statistically improved on Day 07 and Day 14 (p <0·0001) (Figure 2).



†All values are presented as mean ± standard deviation.

*Significant change in parameter from baseline to post-application of ointment $p<0.02$

**Significant change in parameter from baseline to post-application of ointment $p<0.0001$

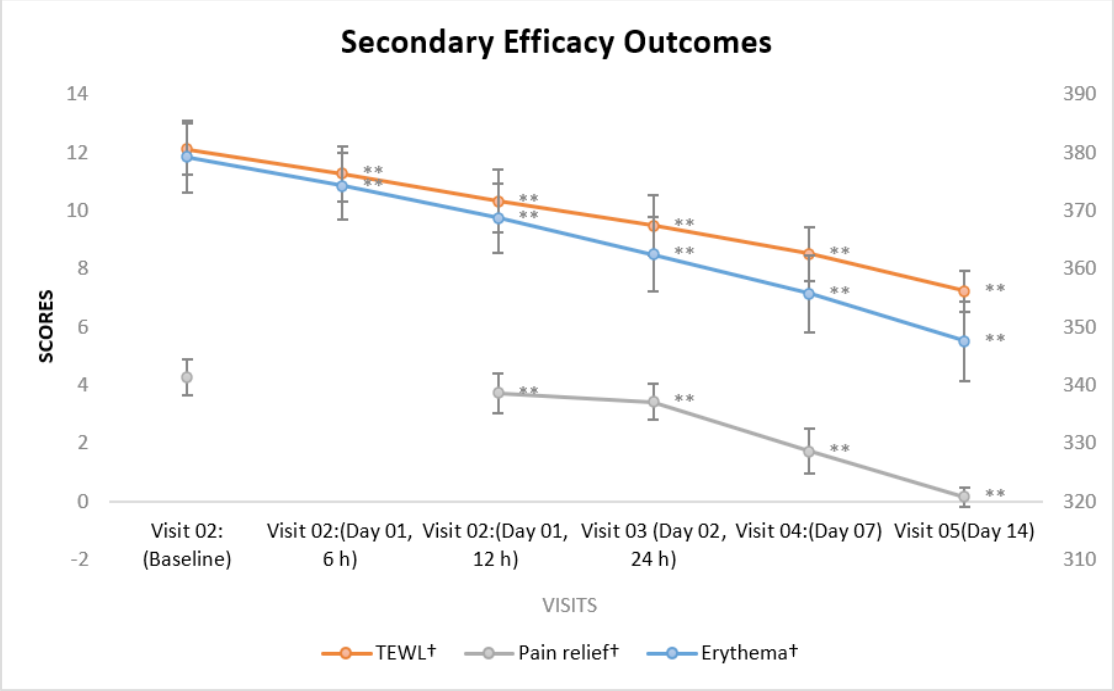
***Significant change in parameter from baseline to post-application of ointment $p<0.001$

Figure 2: Change in parameters of Peadiatric Assessment Score from baseline to post-ointment application.

Subjective Assessment Questionnaire analysis: The Subjective Assessment Questionnaire analysis showed that the mothers/legal representatives of all subjects observed a significant change in skin rash after the use of diaper rash ointment. Furthermore, in some questions, the subjects' mother/legal representative had strongly agreed to use the diaper rash ointment.

Secondary outcomes

Erythema and Transepidermal water loss (TEWL) measures reduced significantly from baseline at all visits post ointment application (p <0·0001 at all visits). The effect of the test product for the pain relief ability was assessed using visual analog scale (VAS) [12] scoring scale and the pain significantly reduced from baseline to post application of ointment at 12 h, 24 h, Day 07, and Day 14 (p <0·0001) (Figure 3). The pH of the skin changed significantly from baseline to post-ointment application on Day 14 (from 4·67 ± 0·07 to 4·76 ± 0·06; p <0·0001).



†All values are presented as mean ± standard deviation.

**Significant change in parameter from baseline to post-application of ointment $p<0.0001$

TEWL: Trans-epidermal Water Loss.

Figure 3: Change in secondary efficacy outcomes from baseline to post-ointment application.

Safety evaluation

The mothers/legal representatives of the subjects and their paediatricians reported no cases of skin hypersensitivity reactions like erythema/redness, oedema, pruritus, and urticaria when evaluated through the Subjective Assessment Questionnaire analysis. There were no adverse events reported during the course of the study.

Skin sensitization assay showed that the diaper rash ointment didn't show any skin sensitization up to 500 µg/mL. From HRIPT, diaper rash ointment emerged as hypoallergenic, it can be inferred that it will not show any allergenic reactions in majority of the population. The test product is also considered as mild and gentle on skin (data on file).

Discussion

Neonatal skin, especially the diaper area, when damaged may lead to diaper dermatitis. It compromises the skin barrier function, which may result in pain and infection. The severity of diaper dermatitis can be evaluated through standardized scoring systems and non-invasive measurements of TEWL, hydration of stratum corneum, skin surface pH, and sebum levels [13]. The present study evaluated the efficacy of the novel natural formulation of diaper rash ointment (anhydrous) through the overall severity score of diaper rash, Paediatric Assessment Score, subjective questionnaire analysis from the mothers/legal representatives, evaluation of barrier function through measurements of TEWL, and assessment of change in erythema, pain relief, and skin pH.

Barrier function of the skin is provided by the stratum corneum and damage to the stratum corneum will result in an increase in TEWL and inward penetration of potentially harmful molecules and microbes leading to diaper dermatitis.

Application of barrier preparations in the diaper area is the first-line therapy in the prevention and management of diaper rash. Barrier emollients reduce the severity of diaper rash by providing a lipid layer over the skin surface and/or by providing lipids that can penetrate the stratum corneum, thereby simulating the effects

of indigenous intercellular lipids. The aim of barrier preparations should be to maintain TEWL as near to normal as possible [14]. Traditionally, olive oil was one of the home remedies used for the treatment of diaper rash [15] and there is a tradition of using herbal treatments first along with oils [5].

Pastes that contain a high proportion (at least 10%) of finely powdered zinc oxide or titanium dioxide have been widely used across many countries as skin barrier formulations for the prevention and management of diaper rash. Lipophilic pastes are highly occlusive, while hydrophilic pastes can take up certain amounts of water; however, these are not effective as skin barrier. Studies have shown that water-in-oil/lipophilic formulations, with a lipid content ≥50%, provided a superior barrier from moisture as compared with lighter oil-in-water/hydrophilic formulations. Ointments are preferred over creams and lotions since the greater lipid content givesing a barrier layer, makinges it less likely that a preservative will be required [14]. Diaper rash ointment test product is an anhydrous lipophilic formulation with a blend of several natural ingredients. The properties of some ingredients are summarized in Table 1. Other ingredients include coconut water which provides moisturization and promotes cell growth, and Neem Seed Oil which has antimicrobial and antifungal effects [16].

Table 1: Effect of dDiaper rRash oOintment ingredients on diaper rash.

Ingredients	Effects on skin	Mechanism of action
Zinc oxide [15,16]	• Reduces skin contact with irritant factors such as urine and feces, and prevents exposure to wetness and infection	• Creates a lipid barrier • Repairs stratum corneum • Inhibits adhesion and penetration of microorganisms
Olive fruit oil [15,17-19]	• Skin protective and moisturizing effect • Antioxidant and anti-inflammatory functions	• Reduces prostaglandin synthesis at the site of application • Inhibits production of leukotriene B4 in a dose-dependent manner
Boswellin gum extract [20,21]	• Anti-inflammatory effect	• Inhibits synthesis of pro-inflammatory enzyme -lipoxygenase (5-LO), including 5-hydroxyeicosatetraenoic acid (5-HETE) and leukotriene B4 (LTB-4)

The present study has demonstrated that application of the novel diaper rash ointment reduced the mean overall severity score of diaper rash by 80% after 14 days post-ointment application with onset of action less than 12 hrs. A significant reduction in skin itchiness (by 86%), skin redness (by 97%), skin dryness (100%), skin irritation (by 94%), and pain (97%) was observed after 14 days of regular ointment application. In addition, there was significant reduction in redness as per the Mexameter value (Figure 3). Furthermore, on day 14, significant improvement in mildness score (by 50%) and gentleness score (by 49%) was also observed. Additionally, TEWL values started reducing from 6 h post-ointment application, with a 40% reduction by Day 14 of the treatment. This indicates that the diaper rash ointment provides effective moisturization from 6 h after ointment application by forming a protective layer over the skin and preventing trans-epidermal water loss. The diaper rash ointment was safe to use, as it did not cause any skin hypersensitivity reactions like erythema/redness, oedema, pruritus, or urticaria. Furthermore, there were no adverse events reported during the study.

Diaper rash is an acute inflammation of the skin in the diaper area and is the most common cutaneous disease among infants and children. COX-2 is produced in response to inflammatory and other physical stimuli leading to production of prostaglandins which play a key role in pain and inflammatory response. The beneficial anti-inflammatory and analgesic effects occur through the inhibition of COX-2. The IC50 values were assessed to evaluate the COX-2 inhibition efficacy of the product and the same was achieved at concentration of 24.79 mg/ml (Data on file). There was also reduction in the pro-inflammatory markers like IL6 and TNF-α (data on file).

Since ancient days, Boswellia and derived extracts had been used in traditional preparations, especially in ayurvedic practices it has been used in different inflammatory disorders with boswellic acids being the main constituent. Several preclinical and clinical studies have been reported for Boswellia [17]. Diaper rash ointment has a combination of oils with Boswellia extract. Thus, the clinical effectiveness of diaper rash ointment may be due to the occlusive lipid layer of the oils and the anti-inflammatory activity of Boswellia.

Conclusion

Diaper rash is a common condition in infants that can affect the lives of both infants and their caregivers. The present clinical study demonstrated that application of the novel all natural, anhydrous diaper rash ointment effectively reduced the overall severity, erythema, skin dryness and itching, and pain associated with diaper rash. Furthermore, the ointment was proved as mild and gentle on the baby' skin and provided a calming effect on the skin. It provided effective moisturization by forming a protective layer on top of the skin which prevented trans epidermal water loss and improved skin healing. Boswellia extract and the oils used could be the reason behind the efficacy and mediated through inflammatory cytokines. All the mothers/legal representatives and paediatricians were satisfied after using the ointment and strongly preferred the use, owing to the effectiveness, mildness, gentleness, and safety of this product. HRIPT also showed that the product was mild and gentle on the skin.

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Declarations of interest

None

Conflict of Interest

The authors declare that there is no conflict of interest regarding the publication of this article.

Role of Funding Source

This work was supported by Zydus Wellness. Authors from Zydus Wellness had no role in data collection, analysis, or interpretation; trial design; and patient recruitment. The study was carried out by Cliantha Research, an independent clinical research organization (CRO).

Ethics Committee approval

The study was approved by ACEAS – Independent Ethics Committee.

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