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Efficacy, Tolerability, and Acceptability of a Skin Repair Product Containing Active Extracts of *Centella asiatica*

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Synopsis

The reparatory capacity of *Centella asiatica* based on collagen synthesis stimulation and accelerating reconstruction and renewal of the epidermis has been the focus of research in cosmetology. Here we present the efficacy and safety results of a product that has been developed, combining the properties of asiaticoside and asiatic acid contained in *C asiatica*, in the form of a light-textured and rapidly absorbing cream (Blastoactiva™) particularly indicated for the treatment of damaged skin with altered barrier function. Experimental and human studies have shown the beneficial anti-irritant effect, skin barrier function repair, and epidermal cell renewal enhancing action of the product, as well as great acceptability referred to its cosmetic characteristics, with no allergenic or phototoxic potential. The incidence of sensitive skin due to minimal trauma and irritation is high in women due to erosions of the mammary areoles and nipples during lactation and in female genital lichen sclerosus. In the sensitive skin syndrome, characterized by the presence of subjective symptoms (burning, itching, stinging, pruritus, and tingling sensations) without any clinical signs on the skin, the use of cosmetics that restore the barrier function and decrease the reactivity of sensitive skin is recommended. Repair of the skin after performing nonsurgical aesthetic processes is an example where the use of Blastoactiva™ would be especially indicated.

INTRODUCTION

Integrity of the skin barrier is crucial for the maintenance of skin structure and functions. Disruption of the skin barrier can be caused by both endogenous factors such as age, systemic diseases, or genetic conditions, and exogenous factors such as solar exposure, pollution, trauma, or different cosmetic procedures. Disruption of the barrier results in increased permeability and thinning of the horny layer (1). These alterations in turn favor the penetration of irritants and allergens (2) and are associated with poorer protection of the nerve endings as well as transepidermal water loss (1).

The alteration of the skin barrier can be the cause of or aggravate some inflammatory diseases (i.e., atopic dermatitis, psoriasis, or genital lichen sclerosus), where in addition to the presence of skin atrophy, there may be erosions. Likewise, there are other physiological

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circumstances such as breastfeeding, where between 80 to 90% of women have pain or fissures due to friction and suction, which compromises the barrier and may be the cause of the interruption of said feeding (3). These alterations not only represent an important alteration in the quality of life of patients but also imply the modification of the absorption of drugs or cosmetics, which makes the preservation of the cutaneous barrier of vital importance not only in healthy skin but also on diseased skin (4).

Genital lichen sclerosus is a chronic, inflammatory disease that most frequently affects women of all ages (5), producing a great impact on quality of life and sexual health (6), and can progress to cancer. Erosions and itching may appear (7). It is recommended to avoid the use of irritating substances and perfumes (8). Persistent nipple pain is one of the most common causes of cessation of breastfeeding (9).

The sensitive skin syndrome is characterized by the presence of subjective symptoms (burning, itching, stinging, pruritus, and tingling sensations) without any clinical signs on the skin. Sensitive skin is a broad term applied to hypersensitive, reactive, intolerant, or hyperexcitable skin, and used to define some characteristics of the skin rather than a medical diagnosis. Sensitive skin is associated with different dermal conditions and precipitating factors, and the underlying pathophysiological mechanisms are not fully understood (10,11). The use of cosmetics that restore the barrier function and decrease the reactivity is recommended (1).

Centella asiatica extract is a rich source of natural bioactive substances, particularly triterpenoid saponins known as centelloids (12). The main compounds are the triterpenes asiatic acid and madecassic acid, and their derived triterpene (i.e., ester glycosides, asiaticoside, and madecassoside) (13,14). The triterpenic genin and asiaticoside contents of the purified extract have been shown to offer specific dermatological benefits related to skin healing and regeneration, increasing collagen synthesis and intracellular fibronectin, promoting fibroblast formation, stimulating hyaluronic acid synthesis, and improving cutaneous connective tissue regeneration (14–17). Asiaticoside is the fundamental active substance of *C asiatica* (18), and is responsible for most of its antioxidant, anti-inflammatory, immune modulating, and tissue repair properties (19,20). Asiatic acid in turn intervenes in molecular mechanisms related to enzymatic processes, growth factors, transcription factors, apoptotic proteins, and cell signaling pathways (21). Studies based on *in vitro* and *in vivo* models have found asiatic acid to prevent skin aging caused by ultraviolet radiation, suppress the accumulation of collagen produced by fibroblasts in the context of keloid scar formation, and favor wound epithelization (21). As a result of all this, formulations based on *C asiatica* extracts have been widely used over the years for different indicators, including improved healing of minor wounds and burns, hypertrophic scars, pregnancy stretch marks, and psoriatic or scleroderma lesions (22–24), and as antiaging products (25,26).

Cosmetological research has evidenced the great reparatory capacity of *C asiatica* extracts, thanks to the stimulation of collagen synthesis, accelerating reconstruction, and renewal of the epidermis (27). In this regard, a product has been developed, combining the properties of asiaticoside and asiatic acid contained in *C asiatica*, in the form of a light-textured and rapidly absorbing cream (Blastoactiva™, Almirall, S.A., Barcelona, Spain), with different indications.

Although this is a marketed and dermatologically tested product particularly indicated for the treatment of damaged skin with altered barrier function for adults, children, and babies 3 mo and older, no synthesis of the scientific evidence on its efficacy, tolerability, and acceptability under normal conditions of daily use has been published to date. The present

article describes the results of the clinical and laboratory tests made with Blastoactiva™, formulated with two main active constituents from *C asiatica*: asiaticoside and asiatic acid, which contribute to enhance skin repair and regeneration.

Thus, based on the properties of asiaticoside and asiatic acid, the cosmetic indications of Blastoactiva™ include the repair of skin damaged by dryness (xerosis), superficial acne scarring, and superficial aggression produced by physical agents (e.g., cold, wind, pollution, solar exposure), and cosmetic treatments (e.g., laser, peeling, depilation and epilation, tattoos, and phototherapy sessions).

METHODS AND RESULTS

IN VITRO AND *IN VIVO* EVALUATION OF TOLERABILITY

In vitro evaluation of eye irritant potential. The *in vitro* evaluation of the eye irritant potential of Blastoactiva™ was carried out based on a test involving application of the product in the chorioallantoic membrane (CAM) of 10-day incubated chick embryos. This technique constitutes an alternative to animal testing and is similar to that described by Luepke and Kemper (28). Use was made of four white Leghorn chicken eggs (40–70 g) incubated during 10 d under controlled temperature (37.8 ± 1°C) and relative humidity conditions (50–60%) on oscillating plates in the vertical position with the egg air chamber facing upwards. After breaking and sectioning the shell, 300 μL of the product was deposited onto the CAM with a micropipette. After 20 s of contact, the CAM was cleansed with 5 mL of isotonic saline solution. The following characteristics were analyzed over the subsequent 5 min: appearance of hyperemia (appearance of visible capillaries or dilatation and reddening of existing capillaries), hemorrhage (diffuse, in layers or punctate), and coagulation (opacity and/or thrombosis) after ≤30 s, between >30 s and ≤2 min, and >2 min and ≤5 min after contact with the CAM. The cases of hyperemia, hemorrhage, and coagulation were summed for each egg with a total score of 0 to 21 and classified as: <1 is practically nonirritating; ≥1 to <5 is slightly irritating; ≥5 and <9 is moderately irritating; and ≥9 is irritating. Negative and positive controls were included in the form of a 0.8% NaCl solution and different concentrations of sodium lauryl sulfate, respectively.

The results obtained *in vitro*, with a mean (± standard deviation) of 0 ± 0 for hyperemia, hemorrhage, and coagulation phenomena, showed the product to cause practically no eye irritation.

Allergenic potential. The allergenic potential of Blastoactiva™ was studied in 50 volunteers of either gender and between 18 and 70 yr of age with a Fitzpatrick I–V skin phototype and sensitive skin. For this purpose, use was made of the Human Repeat Insult Patch Test (HRIPT) described by Marzulli in 1973 (29). The study was approved by the evaluation committee of EVIC Romania (Bucharest, Romania) (registry CI-313/08). In accordance with standard practice of the HRIPT, the volunteers were exposed to the study product using adhesive patches (Finn Chamber standard®, Merck spol s.r.o., Bratislava, The Slovak Republic) with an aluminum cap containing 20 μL (~20 mg) of Blastoactiva™. The patches were affixed to a zone of the skin with hypoallergenic adhesive tape (Scanpor® [Norgesplaster, Granlivegen 21, NO-4707 Vennesla Norway]) with an internal diameter of 8 mm and surface area of 50 mm^2). Another 20 additional products were tested in parallel in the same way.

During the first 3 weeks (induction or sensitization phase), the patches were applied intermittently on days D1, D3, D5, D8, D10, D12, D15, D17, and D19, with removal after 48 h of contact of those patches that had been placed on days D3, D5, D10, D12, D17, and D19, and after 72 h of those placed on days D8, D15, and D22. This period was followed by a 15-day resting phase. Finally, the patch with Blastoactiva™ was again placed on day D37 (challenge phase), and was removed 48, 72, and 96 h after application (days D39, D40, and D41). The product was applied onto the skin of the dorsal region.

Test reading was performed by the dermatologist based on inspection of the study zone for 15 min (or longer if alterations were observed). The appearance of a positive test includes erythema, edema, vesicles, blisters, papules, dryness, skin coloring, and a soapy effect (reddened, glass-like appearance). The scale of the International Contact Dermatitis Research Group was used to evaluate the capacity of the product to cause allergic contact dermatitis, based on the following grades: ?+ (doubtful reaction), + (erythema, infiltration, minimum papule), ++ (erythema, papules, vesicles), and +++ (blisters). Likewise, the participants were questioned about possible reactions.

No skin reaction of any kind was observed in either the induction phase or in the challenge phase. Blastoactiva™, therefore, can be regarded as a product for topical use with low clinical potential to cause allergic contact dermatitis.

Phototoxic potential. The phototoxic potential of Blastoactiva™ was studied in 12 healthy volunteers (nine women and three men) between 18 and 65 yr of age (with a mean age of 48.3) with a Fitzpatrick I–III skin phototype and no skin alterations capable of influencing the test results. The participants gave written informed consent to participation, and the study protocol was approved by the evaluation committee of EVIC Hispania, Centro Experimental de Evaluación Cutánea (Barcelona, Spain) (registry CEN-41-09).

The test involved the application with occlusive patches of 0.2 mL of the product onto two 4 cm^2 zones on the dorsal region between the waist and scapula, while a third zone without product was used as control. The patches were removed after 24 h. Following visual inspection of the three zones and having discarded the presence of allergic contact dermatitis according to the International Contact Dermatitis Research Group scale, one of the treated areas and the control zone were irradiated with filtered light (with a wavelength of 320–400 nm) equivalent to 10.0 J/cm^2 of ultraviolet irradiation. Skin reaction in the irradiated zones was assessed after 24, 48, and 72 h. No phototoxic reactions were observed in the area treated with Blastoactiva™ and irradiated, in the treated and nonirradiated zone, or in the irradiated control zone. The tested product therefore can be considered to lack phototoxic capacity.

Blastoactiva™ is therefore a cosmetic product that has shown negligible risk of eye irritation *in vitro*, no allergic contact dermatitis, and no phototoxic effects, and can be regarded as safe.

CLINICAL EFFICACY AND ACCEPTABILITY

Study in healthy adult volunteers. Three clinical efficacy variables were evaluated in 36 healthy volunteers exposed to Blastoactiva™: anti-irritant action, skin barrier function repair, and epidermal cell renewal capacity. The volunteers served as their own control. The participants gave written informed consent to participation, and the study protocol (N°: 08-0319/1) was approved by the evaluation committee of EVIC Hispania, Centro

Experimental de Evaluación Cutánea (Barcelona, Spain) (registry CI-S22/08). The study involved subjects of either gender and between 18 and 70 yr of age with a Fitzpatrick I–V skin phototype and reactive skin. The study excluded individuals with skin alterations on the forearm or skin characteristics capable of interfering with evaluation of the product, such as scars, pigmentation disorders, abundant body hair, and allergy or intolerance of topically administered products of the same class as the tested product.

The three study variables were evaluated on both forearms (one treated arm and one control arm). An occlusive patch was applied with 45 μL of a 2% solution of sodium lauryl sulfate during 24 h (day 1, D1), followed by the application of Blastoactiva™ twice a day in the same zone. Evaluation of the three parameters (anti-irritant effect, skin barrier repair, and epidermal cell renewal) was made after 24 h, 48 h (D2 and D3, respectively) and over 14 d, as follows:

- Anti-irritant action was assessed by colorimetry (Mexameter® MX 18, Courage & Khazaka Electronic, Köln, Germany) based on the amount of light absorbed by the skin and the clinical inspection of erythema intensity (from 0 = absent to 4 = severe).
- Skin barrier function repair activity was quantified based on transepidermal water loss (Tewameter TM 300®, Courage & Khazaka Electronic) during 4 min, expressed as evaporated water in $g/m^2/h$.
- The effect upon epidermal cell renewal was assessed from the changes in skin color based on the individual typological angle (Cromameter CR, Minolta), where the faster the increase, the faster the cell renewal rate. In this test, 160 μL of the product was applied on a semiocclusive patch with 6% dihydroxyacetone, with analysis of the variations from D3 to D14.
- In addition, the cosmetic qualities of the product were evaluated using a 23-item questionnaire in which most of the questions were scored based on a 5-point Likert scale (Figure 1).

Testing showed Blastoactiva™ to exert a statistically significant anti-irritant effect ($p < 0.031$), reducing erythema intensity after four applications, as well as a statistically significant barrier function repair effect ($p < 0.001$), reducing transepidermal water loss by 24 and 29% after two and four applications, respectively. Likewise, a statistically significant effect ($p < 0.014$) was observed in terms of epidermal cell renewal with acceleration of this process in 61% of the participants. The cosmetic properties of the product were favorably rated by 83 to 100% of the participants (Tables I and II). The dermatologist interpreted product acceptability as being very satisfactory (30–32), since none of the subjects presented clinical signs or discomfort attributable to the tested product.

Study in a pediatric population. A group of 22 children (eight boys and fourteen girls) between 3 and 47 mo of age (with a mean age of 30 mo and range of 5–45) with Fitzpatrick I–V skin phototype and reactive skin were selected for the evaluation of skin and eye tolerability and of the cosmetic qualities and efficacy of Blastoactiva™. The children served as their own control. The parents signed the informed consent document, and the study was approved by the evaluation committee of Eurofins Product Testing, Cosmetics & Personal Care Spain, S.L.U. (Barcelona, Spain) (registry CI-S2/19).

1.5 g of the product was applied on a single side of the groin (zone of the fold) and on the entire waist (at diaper level) twice a day (morning and night) for 28 ± 2 consecutive d (4 weeks). The product could also be applied on any other localized zone presenting irritation during the study. One parent per child (the observing parent) assessed acceptability on a daily

QUESTIONS	POSSIBLE ANSWERS
1. I am concerned about scars of superficial wounds, irritations, and aggression of the skin. 2. I am concerned about post-peeling, post-depilation, and solar aggressions. 3. I have tried some type of treatment to help repair or strengthen my skin (soothing irritation, favoring skin regeneration, etc.).	- Too much - Much - Neither much nor little - Little - None
4. If affirmative, I applied the treatment...	- I bought the product but did not use it - 1 wk - 2 wk - 1 mo - More than 1 mo
5. The product has generally improved the appearance of my skin. 6. The product has a pleasant texture. 7. The product leaves my skin feeling soft and smooth. 8. The product hydrates my skin. 9. I consider that the product strengthens my skin. 10. The product has a pleasant smell. 11. The product is quickly absorbed. 12. The product leaves no residue on the skin. 13. The product is not oily. 14. The product does not stain clothing. 15. In general, I am satisfied with the product. 16. Would you recommend this product to your friends?	- Very much agree - Agree - Neither agree nor disagree - Disagree - Very much disagree
17. How much would you pay for the tested product?	- Less than 10€ - Between 10–15€ - Less than 20€ - Between 20–25€
18. Considering the previous answer, would you buy the product if it cost 15€?	- Yes, certainly - Probably - I don't know - No - Never
19. How often would you apply this product?	- 3 times a week - Once a day in the morning - Once a day at night - Twice a day - Three times a day
20. Do you consider it adequate to have two presentations (50 and 150 mL) of the product according to its point / extensive use? 21. Do you consider this to be a unisex product? 22. Would you use it again?	- Yes - No
23. Product format, 50 mand 150 mL; we would like to know which format you would use in each case.	- Post-healing - Irritation - Skin aggression - Sunburn - Post-peeling - Post-depilation - After shaving - Post-laser surgery - Tattoos

Figure 1. Questionnaire used in the efficacy and acceptability study of Blastoactiva™ in healthy volunteers.

basis and completed a questionnaire with eight items addressing the cosmetic qualities of the product, and five items referring to its cosmetic efficacy. Likewise, skin tolerability was analyzed by a dermatologist and a pediatrician through visual inspection of the study zone. An ophthalmologist evaluated ocular acceptability by examining the ocular mucosa and periocular zone before and after 4 weeks of use.

The results of the cosmetic and efficacy evaluations are detailed in Table III and Figures 2–4. Between 86.4 and 100% of the observing parents agreed with all the aspects referred to the cosmetic qualities of the product. On the other hand, the rating of efficacy was very satisfactory with agreement expressed by 88.9 to 100% of the observing parents.

Table I
Results Referring to the Anti-irritant, Skin Barrier Function Repair, and Epidermal Cell Renewal Effects of Blastoactiva™

Variable	Forearm control	Forearm treated	Difference	*p* value[a]
Intensity of erythema (anti-irritant)				
Colorimetry, % variation				
D2 versus D1	7 ± 28%	9 ± 32%	2 ± 24%	0.989
"Reactive"[b] subjects, $n = 31$ (11%)			–27%	
D3 versus D1	10 ± 28%	10 ± 33%	0 ± 21%	0.585
"Reactive" subjects, $n = 14$ (39%)			–22%	
Assessment by clinical inspection				
D2 versus D1	0.0 ± 1.1	–0.2 ± 1.3	–0.2 ± 0.9	0.181
"Reactive" subjects			11 (31%)	
D3 versus D1	–0.2 ± 1.2%	–0.6 ± 1.4%	–0.4 ± 0.9%	0.031
"Reactive" subjects			13 (36%)	
Repair of skin barrier function, % variation TEWL				
D2 versus D1	14.3 ± 40.7%	–9.5 ± 28.7	–23.8 ± 29.9	<0.001
"Reactive" subjects, $n = 26$ (72%)			34%	
D3 versus D1	5.5 ± 36.7%	–23.1 ± 29.8%	–28.6 ± 28.1%	<0.001
"Reactive"subjects, $n = 26$ (72%)			37.8%	
Epidermal cell renewal				
ITA angle, D3	14.9 ± 8.6	14.9 ± 8.6		0.01
ITA angle, D14	39.1 ± 11.8	45.3 ± 6.8		

D1, 1 h after removal of the patches and before application of the product; D2, after 24 h; D3, after 48 h; TEWL, transepidermal water loss; ITA, individual typological angle.
[a]Student t-test or Mann-Whitney *U*-test.
[b]"Reactive" subjects D2 versus D1 or D3 versus D1 in treated zone and control zone ≤10% or <0 in case of assessment by clinical inspection.

In 11 children that presented skin irritation during the study on the face, untreated diaper zone, or rest of the body, the irritation disappeared in all cases after application of the product within 24 h in four children, 2–3 d in five children, and in over 3 d in the two remaining children. Furthermore, 10 parents (91%) of these children considered that the product favored skin repair, alleviated reddening, and repaired rubbing or friction (chafing) zones. These results are detailed in Table IV and Figure 5. Lastly, according to the clinical

Table II
Assessment of the Cosmetic Qualities of the Product (Blastoactiva™)

Item of the questionnaire	Percentage of subjects who agree or very much agree
Has a pleasant texture	94
Leaves the skin feeling soft and smooth	89
Hydrates the skin	83
Has a pleasant smell	83
The product is rapidly absorbed	86
Leaves no residue on the skin	94
Not oily	92
Does not stain clothing	100
It has satisfied me	83
It is a unisex product	100

Table III
Results of the Cosmetic Qualities and Efficacy Evaluations

Aspect evaluated	Number (%) of observing parents			
	Strongly agree	Somewhat agree	Somewhat disagree	Strongly disagree
Cosmetic qualities				
General application of the product on the skin is easy	18 (81.2)	3 (13.6)	1 (4.6)	0
The product has a pleasant smell	13 (59.1)	6 (27.3)	3 (13.6)	0
The product has a pleasant texture	14 (63.4)	8 (36.4)	0	0
The product spreads easily on the skin	16 (72.3)	5 (22.7)	1 (4.6)	0
The product is rapidly absorbed	14 (63.6)	6 (27.3)	1 (4.6)	1 (4.6)
The product does not leave a sticky sensation on the skin	17 (77.3)	5 (22.7)	0	0
The product does not leave an oily sensation on the skin	15 (68.2)	6 (27.3)	1 (4.6)	0
The product does not stain clothing	14 (63.6)	6 (27.3)	1 (4.6)	1 (4.6)
Cosmetic efficacy				
Suitable for daily infant care	18 (81.8)	4 (18.2)	0	0
Suitable for application in diaper friction zones (waist, groin)	16 (72.7)	5 (22.7)	1 (4.6)	0
The skin of the infant is softer in the treated zone	14 (63.6)	8 (36.4)	0	0
I have noticed less irritation in the treated zones (groin, waist) with use of the product (evaluated in nine infants)	6 (66.7)	2 (22.2)	1 (11.1)	0
The product has avoided reddening and friction in the treated zones (groin, waist) (evaluated in nine infants)	7 (77.8)	1 (11.1)	1 (11.1)	0

evaluation by dermatologists, pediatricians, and ophthalmologists, Blastoactiva™ was well tolerated by the skin and eyes with no recorded adverse reactions attributable to the product. Thus, Blastoactiva™ has been found to be effective against irritation, exerting skin barrier function repair effects, and enhancing epidermal cell renewal capacity in the adult population. Likewise, in the pediatric population, the product has been found to be effective in treating damaged skin (e.g., diaper rash), well accepted from the parent point of view, and well tolerated as assessed by the dermatologist, pediatrician, and ophthalmologist.

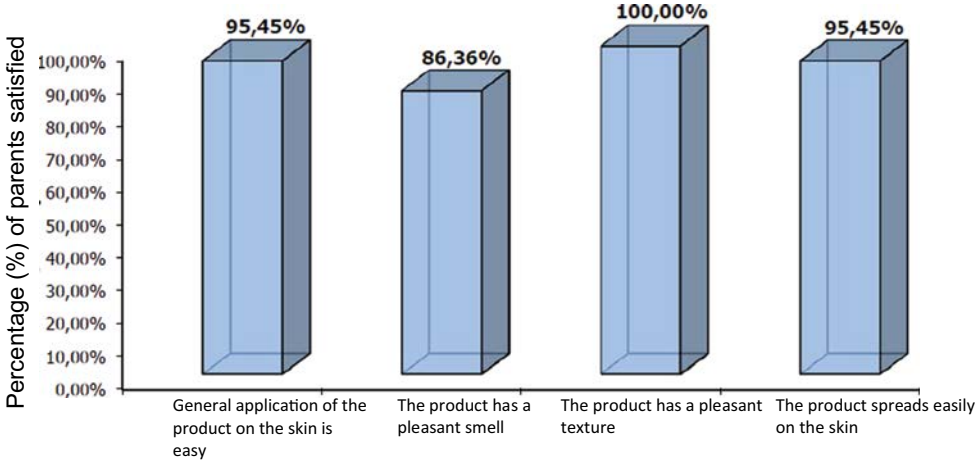

Figure 2. Results of the cosmetic qualities evaluation in the efficacy and acceptability study of Blastoactiva™ in pediatric population.

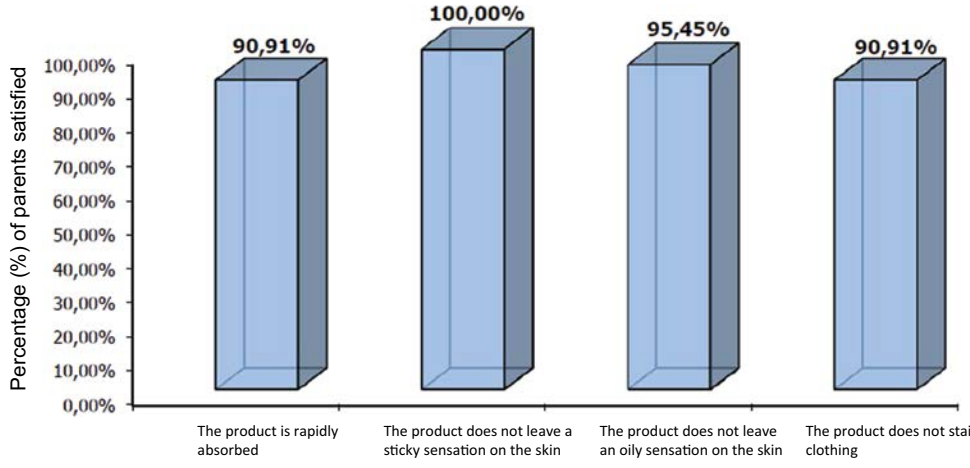

Figure 3. Results of the cosmetic qualities evaluation in the efficacy and acceptability study of Blastoactiva™ in pediatric population.

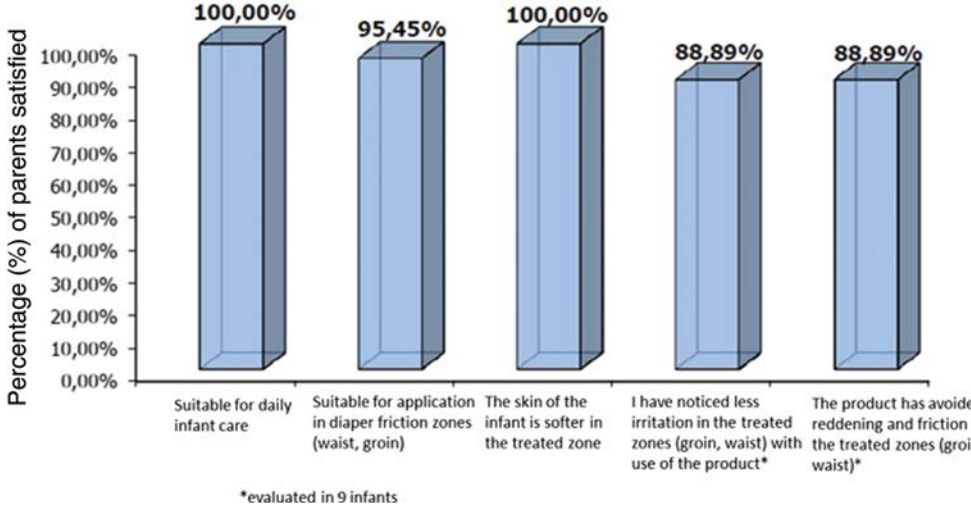

Figure 4. Results of the cosmetic efficacy evaluation in the efficacy and acceptability study of Blastoactiva™ in pediatric population.

Table IV
Results of the Cosmetic Qualities and Efficacy Evaluation

	Number (% of mothers or fathers)			
Aspect evaluated	Strongly agree	Somewhat agree	Somewhat disagree	Strongly disagree
Promoted skin repair	9 (81.8)	1 (9.1)	1 (9.1)	0 (0.0)
Alleviated reddening	9 (81.8)	1 (9.1)	1 (9.1)	0 (0.0)
Repaired rubbing or friction (chafing) zones	10 (90.9)	0 (0.0)	1 (9.1)	0 (0.0)

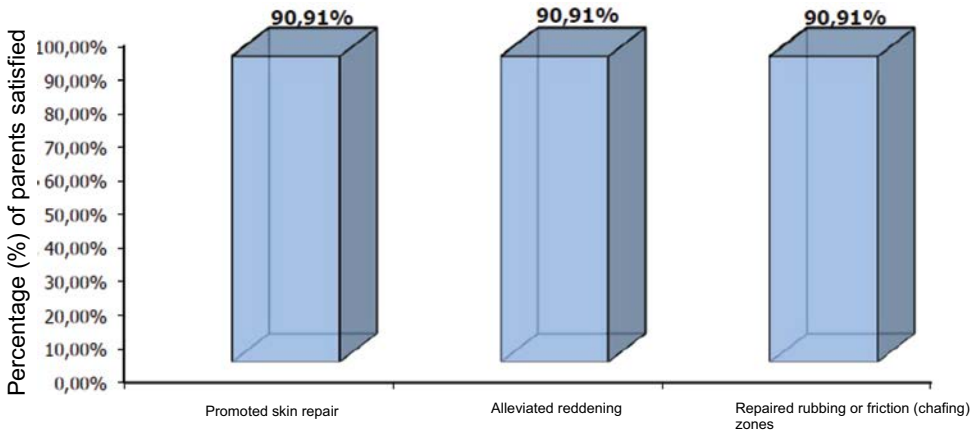

Figure 5. Results of the cosmetic efficacy evaluation in the efficacy and acceptability study of Blastoactiva™ in pediatric population.

CONCLUSION

Blastoactiva™ cream, based on the combination of the active extracts of *C asiatica*, asiaticoside and asiatic acid, has been the subject of different experimental and human studies. These studies confirm its beneficial anti-irritant effect, skin barrier function repair and epidermal cell renewal enhancing action, as well as great acceptability referred to its cosmetic characteristics with no allergenic or phototoxic potential. Repair of the skin damaged by dryness (xerosis), superficial acne scarring, or superficial aggression produced by physical agents such as cold, wind, pollution, solar exposure, and diaper rash, or after cosmetic/nonsurgical treatments (laser, peeling, depilation and epilation, tattoos, and phototherapy sessions) are some clinical scenarios where the use of Blastoactiva™ would be especially indicated.

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RESEARCH ETHICS

Any aspect of the work covered in this manuscript that has involved human patients has been conducted with the ethical approval of all relevant bodies.

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