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A PROPRIETARY ROSEMARY BASED TERPENIC COMPOSITION FOR TOPICAL SCAR MANAGEMENT POST ACNE TREATMENT

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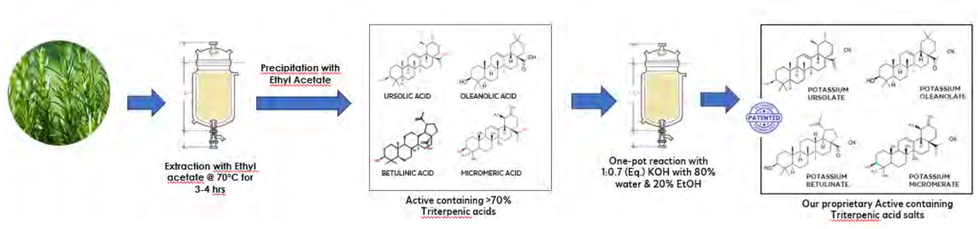
1 INTRODUCTION

Acne scars are a result of acne lesions and appear most often in people struggling with severe forms of acne. Scar formation is part of the wound healing process, which is divided into three phases: inflammatory phase, healing or proliferative phase, and remodeling phase. The inflammatory phase is marked by the activation of resident immune cells and infiltration of circulating immune cells. The second phase is the proliferative phase wherein the proliferation and migration of fibroblasts, keratinocytes, and stem cells occur, in addition to the secretion of extracellular matrix (ECM) and angiogenesis. Finally, the wound-healing program culminates in the remodeling phase which comprises the removal of excess ECM and restructuring of cell-cell and cell-matrix interactions. Impairment of any of these phases can lead to delays in the kinetics of the wound-healing process. Treatment of acne scarring creates a challenge for both patients and dermatologists. Many options are available: laser surgery, radiofrequency intervention, chemical peels, dermabrasion, needling, punch techniques, fat transplantation, and other tissue augmenting agents. These options are, however, quite intrusive and there remains a strong need for more natural solutions to address the wound healing aspect of acne scarring more holistically.
The present work highlights our proprietary active ingredient from the leaves of *Rosmarinus officinalis*. It is composed of a combination of ursolic acid, oleanolic acid, betulinic acid, and micromeric acid, modified with potassium hydroxide.
This active shows promising results in terms of wound healing in an in vitro reconstructed skin model, with a positive effect on the healing and epidermal differentiation phases.

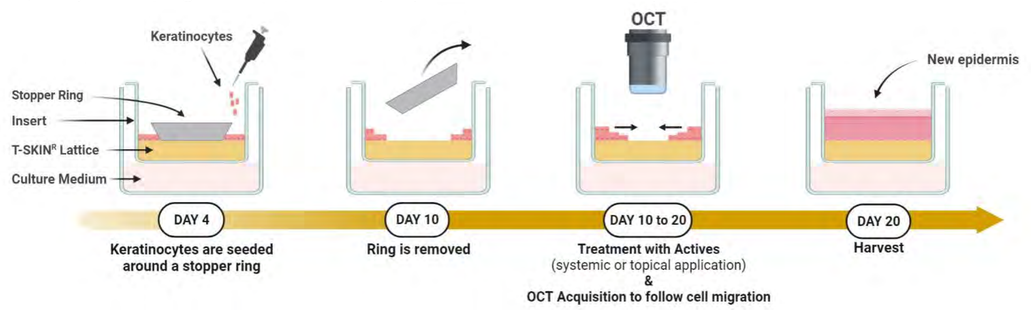
2 MATERIALS & METHODS

Novel Active ingredient – Terpenoids from Rosmarinus officinalis
The ground powdered leaves of the *Rosmarinus officinalis* plant were extracted using 100% Ethyl Acetate at 70 °C at 300 rpm and reduced under pressure to afford a syrupy mass.
To this syrupy mass, cold Ethyl acetate was added which yielded a white precipitate. The process afforded white colored solid precipitate containing Ursolic acid, Oleanolic acid, Betulinic acid and Micromeric acid.
This Rosemary extract was further treated with KOH to obtain a salified extract of triterpenic acids.



Wound Healing Evaluation

The wound healing efficacy of the Rosemary extract was evaluated on the re-epithelialization migration TSkin™ model mimicking the phase III and IV of wound healing process (at Episkin, Lyon, France).
The T-Skin™ lattice was ballasted by a metal ring (Ø1cm) to create a modified version called Migration T-Skin™ model. Keratinocytes were seeded on the living dermal equivalent around the ring while the center of the ring remaining empty. After 6 days of immersion in culture medium, the tissue samples were lifted to the air-liquid interface inducing epidermal differentiation and stratification. Finally, the ring was removed after D10 and stored at 37°C until the end of the study at D20.
The test samples or controls were added to the culture medium at Day 10 with the treatments being renewed at regular intervals. At the end of treatment (D20), Migration T-Skin™ model were fixed in 4% neutral buffered formol, dehydrated in graded alcohol / isopropanol and embedded in paraffin blocks.

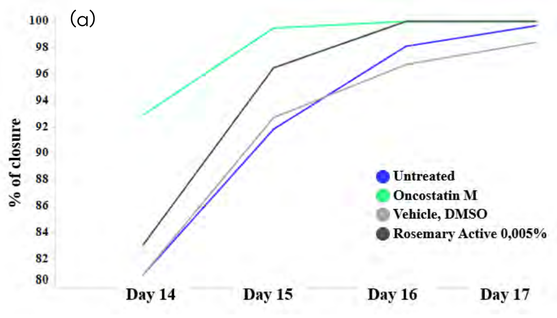


A faster and robust method, developed by EPISKIN, was used to assess tissue features and to make quantitative measurements objectively for following 3D closure kinetics based on a non-invasive Optical Coherence Tomography (OCT) approach combined with a final quantification of the histological quality. OCT is a technique based on the analysis of infrared light reflected by tissues and on the creation of an interference signal and is capable to image thin sections within thick, living biological tissues nondestructively and without exogenous dyes by measuring their optical reflections.
Through optical acquisition and processing with specifics algorithms combined with a final quantification, epidermal and dermal thicknesses, and epidermis profile of the tissue after reconstruction are also determined.
Then, global morphology of the treated tissues is scored at the end of treatment by histology.

3 RESULTS

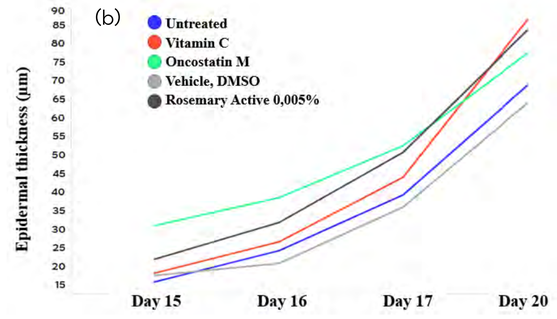
Two positive references are used in the present evaluation as pro-epithelialization controls.
Oncostatin M (OSM) for its capacity to induce keratinocyte migration and increase reconstituted epidermal thickness.
Vitamin C (VITC) improve the quality of reconstruction, organization and differentiation (equivalent to quality of re-epithelialized skin).
The patented active from Rosemary was tested at the highest non-cytotoxic doses (at 0.005%) and showed increase in the kinetics of wound closure at Day 15 & Day 16 which was similar to the control, Oncostatin M (Graph 1 (a)).
The active at 0.005% also demonstrated through the epidermal thickness, proliferative effect at the earliest maturity stage (between both positive references) and differentiation effect at day 20 which was similar to the effect demonstrated by Vit C (Graph 1 (b)).

PROLIFERATION PROFILE



% CL0SURE

Kinetics of closure were determined by image analysis using the newly developed software (untreated vs Oncostatin OSM as positive controls).



EPIDERMAL THICKNESS (µm)

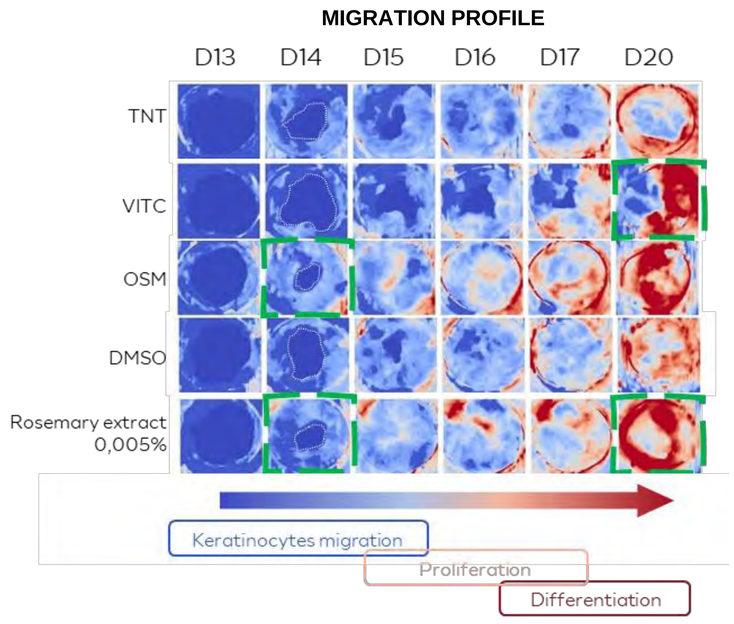
Mean of tissues (n=6) determined by image analysis using the newly developed software (untreated vs vitamin C VITC and Oncostatin OSM as positive controls).

The figure on the right side shows the OCT visualization images of the wound closure along with the epidermal thickening gradient on day 13 to day 17 and day 20 for all the samples.
The diminishing wound size can be seen in all the treatments from Day 13 to Day 20.
OSM shows a much higher rate of wound contraction at Day 14 (91%) and Day 16 (100%) versus the untreated control (78% and 96%).

Our proprietary active from Rosemary leaves shows an interesting 85% closure on day 14 and 100% closure on Day 16, comparable to OSM positive reference as shown in the images in D14.

The rosemary based active also shows a stronger red coloration, close to that obtained with the VITC reference, demonstrating the ability of the *Rosemary extract* to promote the differentiation of the newly reconstructed epidermis.

MIGRATION PROFILE



MEAN VALUE 24MIG07: 9 samples	CLOSURE SPEED (%) D14	D15	D16
UNTREATED CONTROL	78,0 ± 7,0	89,9 ± 4,8	96,9 ± 2,8
VITAMIN C	76,1 ± 4,6	87,5 ± 3,9	91,3 ± 2,8 ***
ONCOSTATIN M	91,3 ± 3,9 ***	99,1 ± 1,0 ***	100 ± 3,0 **
ROSEMARINUS OFFICINALIS-0,005%	85,4 ± 9,9 **	97,5 ± 3,5 ***	100 ± 3,0 **

4 CONCLUSION

Our research demonstrates that this novel active ingredient from *Rosmarinus officinalis* leaves exhibits promising wound healing activity, comparable to established growth factors like Oncostatin M and our cosmetic reference Vitamin C. This finding demonstrates its significant potential for effective application in the treatment of post-acne scars and marks along with a new avenue for cosmetic formulations targeting skin recovery and scar management.

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