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## ***“Complete aging repair needs five key dimensions to restructure skin face: biological & clinical evidence.”***

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### **Abstract**

The aging multifactorial process affects the cellular metabolism and stimulates inflammation in the skin, damaging its different layers. The epidermal barrier function is weakened, the dermo-epidermal junction (DEJ) is compromised, and the dermal extracellular matrix is impaired. These phenomena are amplified by the decline in fundamental proteins called collagens playing structural roles and contributing to mechanical properties of all skin layers. Results, the whole skin becomes thinner, leading to the appearance of aging signs such as altered texture, deep wrinkles, ptosis and sagging.

An effective strategy to combat skin aging is the development of a cosmetic NIGHT BANDAGE CREAM formulated with the highest concentration on the market of xylose-based molecule derived from Beech wood (hydroxypropyl-tetrahydro-pyrantriol).

- *Ex-vivo* study conducted on normal skin explants demonstrated the skin penetration of the xylose-based molecule.
- *Ex-vivo* studies conducted on normal and post-laser skin explants highlighted the global efficacy of the cosmetic NIGHT BANDAGE CREAM on “5 key dimensions of skin repair” (metabolism repair, inflammation relief, epidermal reconstruction, DEJ strengthening and dermal remodeling) and its capacity to “stimulate different types of collagens” in all skin layers.

- A clinical study set up on Asian women for 2 months proved that the cosmetic NIGHT BANDAGE CREAM containing the highest concentration of hydroxypropyl-tetrahydro-pyrantriol significantly decreased aging signs such as ptosis and deep wrinkles and improved skin radiance, texture, skin tone evenness, firmness, cheekbone replenishing and jaw line.

**Keywords:** Anti-aging, Regenerative beauty, Skin texture

## 1. Introduction

Aging of the skin is induced by both intrinsic (genetically determined and age-related), and extrinsic (sunlight, air pollution, stress...) factors, all contributing to the generation of free radicals that affect the cellular metabolism and stimulate the inflammatory process in the skin, damaging its structural integrity and physiological function. [1]

This multifactorial process affects the different layers of the skin: the epidermal barrier function is weakened; the DEJ is compromised and the dermal extracellular matrix is impaired. [2] These phenomena are amplified by the decline in fundamental proteins called collagens playing structural roles and contributing to mechanical properties of all skin layers. [3] Results, the whole skin becomes thinner, leading to the appearance of aging signs such as wrinkles, sagging and dryness.

An effective strategy to combat skin aging is the development a cosmetic NIGHT BANDAGE CREAM formulated with the highest concentration on the market of xylose-based molecule derived from Beech wood (hydroxypropyl-tetrahydro-pyrantriol), capable to protect growth factors and skin against free radical attacks, stimulate epidermal differentiation, glycosaminoglycans, proteoglycans and the major types of collagens at dermal-epidermal junction and dermal levels.

In the present work, we demonstrate thanks to *ex-vivo* studies the skin penetration of the xylose-based molecule and the underlying biological efficacy of the cosmetic NIGHT BANDAGE CREAM on “all the dimensions of skin repair” (metabolism repair, inflammation relief, epidermal reconstruction, DEJ strengthening and dermal remodeling) and “skin collagen” synthesis.

Then, we highlight the cosmetic NIGHT BANDAGE CREAM's results on the most visible signs of aging thanks to a clinical study conducted on Asian women for 2 months.

## 2. Materials and Methods

### 2.1. *Ex-vivo* study on “xylose-based molecule skin penetration”

To evaluate the skin penetration of the highest concentration on the market of hydroxypropyl-tetrahydro-pyrantriol formulated on a NIGHT BANDAGE CREAM, an *ex-vivo* study was conducted on skin explants either untreated or treated with the cosmetic NIGHT BANDAGE CREAM.

9 human skin explants of an average diameter of 11 mm ( $\pm 1$ mm) were prepared on an abdominoplasty coming from a 42-year-old Caucasian woman with a phototype II (according to Fitzpatrick skin type classification).

		D0	D1
T0	Tissue control	▼	
T	Untreated control		▼
P	NIGHT CREAM (evening)	▲	▼



 NIGHT CREAM application (evening)
  Explant sampling

Table I: Explants distribution & schedule of *ex-vivo* study on “xylose-based molecule skin penetration”

#### Product application

Batches P: NIGHT BANDAGE CREAM was topically applied in the evening, on the basis of 5  $\mu$ l per explant of 1 cm<sup>2</sup> ( $\approx$  5 mg/cm<sup>2</sup>).

Penetration of the xylose-based molecule was measured through Raman spectroscopy analysis.

Raman spectroscopy is a non-invasive analytical technique that uses laser light to detect molecular vibrations. When applied to skin, it can provide detailed chemical information by measuring the scattered light from different skin layers. By analyzing the Raman spectra at various depths, researchers can track the presence and concentration of a molecule, allowing them to visualize how deeply and how much of it has penetrated into the skin.

#### Statistical analysis

Statistical analysis was performed using a Student t-test. The tests were carried out in bilateral mode on two samples of supposedly different variances (heteroscedastic).

Student t-test gives the probability “*p*” for two batches to be significantly different. The difference between two batches is significant if  $p < 0.01$ (\*\*), so a probability of 99% for two batches to be significantly different or  $p < 0.05$ (\*), so a probability of 95% for two batches to be significantly different.

## 2.2. Ex-vivo studies on “dimensions of skin repair” and “skin collagens”

To demonstrate the underlying biological efficacy of the cosmetic NIGHT BANDAGE CREAM formulated with the highest concentration on the market of hydroxypropyl-tetrahydro-pyrantriol, ex-vivo studies on normal and post-laser skin explants were set up, and “all the dimensions of skin repair” and “skin collagens” were evaluated.

Ex-vivo studies were conducted on skin explants either untreated and non-exposed to stress or exposed to Laser or treated with the NIGHT BANDAGE CREAM and non-exposed to stress or exposed to Laser.

39 human skin explants of an average diameter of 11 mm ( $\pm 1$ mm) were prepared on an abdominoplasty coming from a 44-year-old Caucasian woman with a phototype II (according to Fitzpatrick skin type classification).

		D0	D1	D2	D3	D4	D5	D6	D7
T0	Tissue control	▼							
T	Untreated control		▼		▼				▼
P	NIGHT CREAM (evening)	▲	▼ ▲	▲	▼		▲	▲	▼
L	STRESS: Laser (D0)	■	▼		▼				▼
LP	STRESS: Laser (D0) + NIGHT CREAM (evening)	■ ▲	▼ ▲	▲	▼		▲	▲	▼

▲ NIGHT CREAM application (evening)      ■ STRESS: Laser      ▼ Explant sampling

Table II: Explants distribution & schedule of ex-vivo studies on “dimensions of skin repair” and “skin collagens”

### Product application

Batches P and LP: NIGHT BANDAGE CREAM was topically applied in the evening, on the basis of 2  $\mu$ l per explant of 1 cm<sup>2</sup> ( $\approx$  2 mg/cm<sup>2</sup>).

### Laser exposure

On day 0 (D0), in order to induce micro-lesions, the explants from the batches L and LP were exposed to laser Nordlys® 1550 nm equipped with XF handpiece able to generate 115 microbeams per cm<sup>2</sup>. Three exposure per explants every 90 seconds for 15 milliseconds with an energy level of 40 mJ have been performed. The laser lesions were made just before the application of the NIGHT BANDAGE CREAM to be tested.

### The evaluation was done by immunostaining and image analysis.

For the “5 dimensions of skin repair” evaluation, the immunostaining was performed with a polyclonal anti-ACO2 antibody (Sigma, ref. HPA001097), a monoclonal anti-IL-1 $\alpha$  antibody (Novus Biologicals, NBP2-45400, clone OTI2F8, Minneapolis, USA), a polyclonal anti-

syndecan antibody (Invitrogen, ref. 36-2900), a monoclonal anti-perlecan antibody (Invitrogen, ref. 13-4400, clone 7B5) and a polyclonal anti-fibronectin antibody (Sigma, ref. F3648).

For the “skin collagens” assessment, the immunostaining was performed with a polyclonal anti-collagen I antibody (Abcam, ref. ab138492-1001), a polyclonal anti-collagen III antibody (SBD, ref. 1330-01), a monoclonal anti-collagen IV antibody (Dako, ref. M0785, clone CIV 22), a polyclonal anti-collagen V antibody (Novotec, ref. 20511), a polyclonal anti-collagen VI antibody (Novotec, ref. 20611-1), a monoclonal anti-collagen VII antibody (Santa Cruz, ref. sc-53226, clone LH 7.2), a polyclonal anti-collagen XI antibody (Sigma, ref. SAB4500393), a polyclonal anti-collagen XII antibody (Santa Cruz, ref. sc-68862), a monoclonal anti-collagen XIII antibody (R&D system, ref. MAB6346, clone #584718), a polyclonal anti-collagen XIV antibody (Invitrogen, ref. PA5-49916), a polyclonal anti-collagen XV antibody (Novotec, ref. PA5-53668), a polyclonal anti-collagen XVI antibody (Sigma, ref. SAB4500398), a monoclonal anti-collagen XVII antibody (Abcam, ref. ab186415, clone EPR14758) and a polyclonal anti-collagen XVIII antibody (Saint John’s Laboratories, ref. STJ92381).

The immunostaining was assessed by microscopical observation and semi-quantified by image analysis using the software cellSens (Olympus, Rungis, France).

For each batch of explants, the percentage of the region of interest (ROI) covered by the staining was determined by image analysis. The stained surface percentage for the treatment was compared to the untreated condition T or to the stress-induced condition L.

### Statistical analysis

Statistical analysis was performed using classical Student t-test. The tests were carried out in bilateral mode on two samples of supposedly different variances (heteroscedastic).

Student t-test gives the probability “ $p$ ” for two batches to be significantly different. The difference between two batches is significant if  $p < 0.01$  (\*\*), so a probability of 99% for two batches to be significantly different or  $p < 0.05$  (\*), so a probability of 95% for two batches to be significantly different.

### 2.3. *In-vivo* study = clinical study

A 2-months clinical study was conducted on 47 Asian women from 47 to 65 years old (average age 59) to prove the effectiveness regarding skin aging signs of the cosmetic NIGHT BANDAGE CREAM formulated with the highest concentration on the market of hydroxypropyl-tetrahydro-pyrantriol.

Inclusion criteria were as follows:

Atlas:

- Ptosis of the lower part of the face - score  $\geq 2$  and  $\leq 4$  with 60% volunteers having a score  $\geq 3$  (inclusion only)
- Chin withering - score  $\geq 2$  and  $\leq 4$  if concerned
- Neck Sagging-Intermediate - score  $\geq 2$  and  $\leq 4$
- Nasolabial fold-Asian - score  $> 2$  and  $\leq 5$

Score scales from 0 to 9:

- Skin pores visibility (size and number) - score  $\geq 3$  and  $\leq 6$  if concerned
- Skin tonicity - score  $\geq 3$  and  $\leq 6$
- Skin ptosis (skin sagging) of the lower part of the face - score  $\geq 3$  and  $\leq 6$
- Skin firmness - score  $\geq 3$  and  $\leq 6$
- Skin tone evenness - score  $\geq 3$  and  $\leq 6$  if concerned
- Skin fine lines visibility - score  $\geq 3$  and  $\leq 6$
- Skin wrinkles visibility - score  $\geq 3$  and  $\leq 6$
- Skin texture-smoothness: tactile - score  $\geq 3$  and  $\leq 6$
- Skin radiance (clarity, luminosity, color complexion) - score  $\geq 3$  and  $\leq 6$

After a 15 days wash-out, the cosmetic NIGHT BANDAGE CREAM was applied every evening during 2 months. A neutral cream was applied every morning, combined with a suncare product (SPF 50+).

Assessments were carried out after 1 and 2 months of product application by clinical scorings (Atlas & score scales) and instrumental measurements with the AEVA-HE<sup>®</sup> system, based on the principle of patented fringe projection combined with stereometry.



Figure 1: Clinical study design

### Statistical analysis

Regarding statistical analysis, Tukey's test that compares the means of every treatment to the means of every other treatment; that is, it applies simultaneously to the set of all pairwise comparisons and identifies any difference between two means that is greater than the expected standard error ( $p < 0.05$ ), has been used.

### 3. Results

#### 3.1. Ex-vivo study on “xylose-based molecule skin penetration”

Regarding the penetration of the xylose-based molecule, a strong signal of the molecule is detected very quickly as soon as 4h after application. After 24h the signal is in the *stratum corneum* at about 10-20µm in depth, a clear signal is detected in the epidermis until 50µm in depth, a moderate signal is detected between 50 and 70µm in depth, thus reaching the dermal-epidermal junction. Molecule traces are even detected until around 80µm, at the papillary dermis level. So, the formulation allows the hydroxypropyl-tetrahydro-pyrantriol to penetrate faster, broader and deeper than ever seen before for such ingredient and compare to the hydroxypropyl-tetrahydro-pyrantriol pure indicating the high-level formulation technology used.

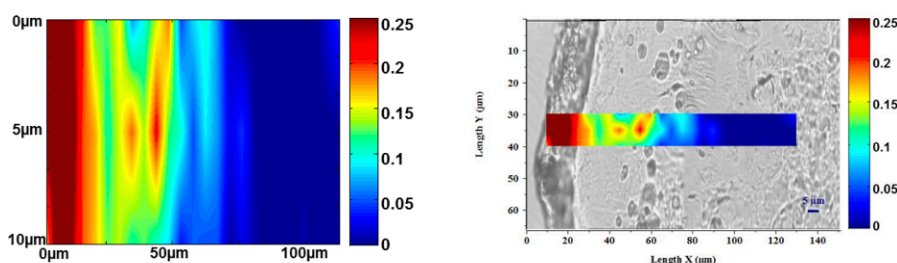


Figure 2: Ex-vivo study results on “xylose-based molecule skin penetration” - RAMAN analysis

#### 3.2. Ex-vivo studies on “dimensions of skin repair” and “skin collagens”

The cosmetic NIGHT BANDAGE CREAM formulated with the highest concentration on the market of hydroxypropyl-tetrahydro-pyrantriol, acted on “5 key dimensions of skin repair” and induced the following results:

- Under basal conditions, the cosmetic NIGHT BANDAGE CREAM application induces an increase of the cellular metabolism marker Aconitase (ACO2) of +84%, a decrease of the inflammatory marker IL1-alpha by -43%, an increase of the epidermal reconstruction marker SYNDECAN-1 of +86%, an increase of the DEJ strengthening marker PERLECAN of +141% and an increase of the dermal remodeling markers GAGs of +44% (P vs T).



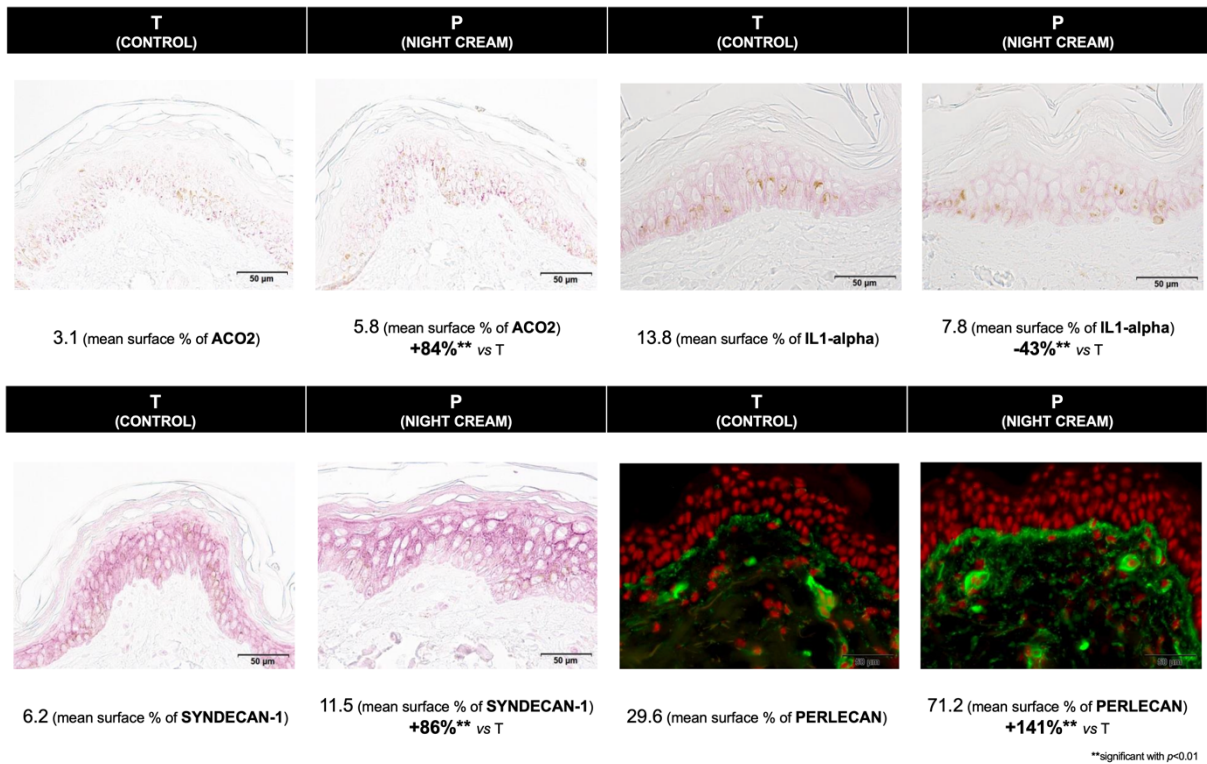


Figure 3: *Ex-vivo* study results on ACO2, IL1-alpha, SYNDECAN-1 & PERLECAN under basal conditions

- In post-laser conditions, all the previous markers evolve positively, and the cosmetic NIGHT BANDAGE CREAM application induces an increase of the dermal remodeling marker FIBRONECTIN of +26% (LP vs L).

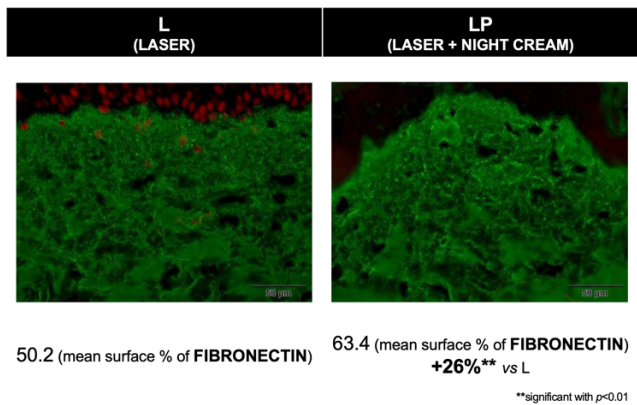


Figure 4: *Ex-vivo* study results on FIBRONECTIN in post-laser condition

Regarding “skin collagens”, the cosmetic NIGHT BANDAGE CREAM formulated with the highest concentration of hydroxypropyl-tetrahydro-pyrantriol induced the synthesis of 13 of the 14 collagens identified in the skin, i.e. 92% stimulation. It acted in all skin layers, increasing the synthesis of collagens present in the epidermis (collagen XIII), DEJ (collagens IV, VII, XV & XVIII) and dermis (collagens I, III, V, VI, XI, XII, XIV & XVI).



Interestingly, the high concentration of xylose derivative revealed new advantages of this molecule, such as the stimulation of acidic GAGs, including the known, hyaluronic acid, by +386% under basal conditions and +93% in post-laser never stimulated with lower concentration in cream.

### 3.2. *In-vivo* study = clinical study

*In-vivo*, application of the cosmetic NIGHT BANDAGE CREAM formulated with the highest concentration on the market of hydroxypropyl-tetrahydro-pyrantriol demonstrated efficacy on the main signs of aging (listed in Table II) from the first month of treatment (1 month vs D0), and a significant amplification of these results after 2 months of treatment (2 months vs 1 month).

Variation percentage	D0	1 MONTH	2 MONTHS	1 MONTH vs D0	2 MONTHS vs D0	2 MONTHS vs 1 MONTH
<b>AGING SIGNS</b>						
<b>Ptois of the lower face</b> (Atlas)	4.96	4.34	2.98	-12.4 %*	-39.9 %*	-31.4 %*
<b>Neck sagging</b> (Atlas)	2.49	2.36	2.12	NS	-15.0 %*	-10.3 %*
<b>Lack of firmness</b> (score scales 0/9)	5.13	4.70	3.85	-8.3 %*	-24.9 %*	-18.1 %*
<b>Nasolabial folds</b> (Atlas)	3.13	2.64	2.01	-15.6 %*	-35.6 %*	-20.0 %*
<b>Wrinkles</b> (score scales 0/9)	5.19	4.79	4.19	-7.8 %*	-19.3 %*	-12.4 %*
<b>Fine lines</b> (score scales 0/9)	2.77	2.30	1.57	-16.9 %*	-43.1 %*	-31.5 %*
<b>Lack of radiance</b> (score scales 0/9)	4.23	3.68	3.19	-13.1 %*	-24.6 %	-13.3 %*
<b>Heterogeneity</b> (score scales 0/9)	4.96	4.30	3.85	-13.3 %*	-22.3 %*	-10.4 %*
<b>Pore visibility</b> (score scales 0/9)	3.77	2.67	1.85	-29.3 %*	-51.0 %*	-30.8 %*

\*Significance p<0.05

Table III: *In-vivo* study results on skin aging signs after 1 & 2 months of cosmetic NIGHT BANDAGE CREAM application - clinical scorings.

After 2 months of application, the results of AEVA-HE® show statistically significant decrease of the parameters “Sagging - positive volume” (-8.8%) & “Face oval - negative volume” (-3.6%) mean value scores at 2 MONTHS compared to D0.

## 4. Discussion

This combination of *ex-vivo* and *in-vivo* studies highlighted the effectiveness of the cosmetic NIGHT BANDAGE CREAM formulated with the highest concentration on the market of hydroxypropyl-tetrahydro-pyrantriol, both in terms of the underlying biological repairing & restructuring mechanisms and the visible aging signs on the skin.

After 24h of application, the *ex-vivo* study using RAMAN analysis demonstrated a clear penetration of the xylose-based molecule in all the epidermis and even traces in the papillary dermis, sign of a quick, deep, broad impregnation of the various skin layers.

The *ex-vivo* studies demonstrated a biological efficacy of the cosmetic NIGHT BANDAGE CREAM apply topically on the “5 key dimensions of repair” which are cellular metabolism activation, inflammation relief, epidermal reconstruction, DEJ strengthening and dermal remodeling, but also on the “collagen synthesis” in all skin layers, essential parameters for deep skin reconstruction.

The clinical study conducted on Asian women proved that the product was effective on the most stubborn aging signs from the very first days (consumer test data not shown) to the first month of use, and that these results were significantly amplified after 2 months of application, demonstrating a progressive effect of the cosmetic NIGHT BANDAGE CREAM over time.

## 5. Conclusion

In conclusion, combined *ex-vivo* and clinical studies highlighted the repairing & restructuring efficacies of the cosmetic NIGHT BANDAGE CREAM, acting on “5 key dimensions of skin repair” and stimulating 92% of “skin collagens” to fight aging signs even the most stubborn.

These results are associated with the highest concentration on the market of hydroxypropyl-tetrahydro-pyrantriol in the cosmetic NIGHT BANDAGE CREAM, capable of intensely penetrate the skin, even its deepest layers, and demultiple the benefit of this molecule.

## Conflict of Interest Statement

*The research was funded by HELENA RUBINSTEIN. The authors report no other conflicts of interest in this work.*

## Publications

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