Technical Report

Product

UPLEVITY™

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Sagginess inducers

It is a fact that skin changes when growing older, as a result of a lifetime of exposure to environmental agents, personal habits such as smoking and diet, and modifications that happen in the normal process of cellular aging. The skin starts appearing less smooth and tight than before, which can lead to visible sagginess, lines and wrinkles, among other evidences.

Several external factors are known to exacerbate the natural aging process like UV exposure or extreme temperatures, but gravity plays a particularly relevant role. As it is a constant force pulling downwards, the skin needs to be firm and elastic to counteract its pressure and stay in place.

Although this attraction force cannot be avoided, the elements that provide skin firmness and elasticity can be certainly enhanced. This is the case of elastin and collagen, both key proteins of the dermal Extracellular Matrix (ECM) that provide the foundation for skin, working in tandem. Collagen cushions and supports the epidermis while elastin allows skin to stretch and flex smoothly. Thus, they confer cohesion and elasticity to the skin, as well as the capacity to recoil after common facial movements like smiling, laughing, drinking or crying. Additionally, several intracellular elements help to reinforce these skin properties and oppose flaccidity.

It is agreed that the functionally active form of such both proteins is reduced with increasing age as well as their correct assembly, diminishing the skin capacity to deal with deforming agents and avoid their visible consequences in facial look [1].

Stimulating the adequate mechanisms that strengthen skin cohesion and tightness would reduce sagginess induced by gravity for instance.

uplevity™ Aimtec®

Skin firmness when aging

Like in other organs of the body, the physiological functions and structures within the skin continuously decline with advancing age. Skin aging results from the deterioration of its structures and the slowing of its functions, caused by many factors and origins, which may be included into different categories: intrinsic, mechanical and extrinsic aging.

Biological or intrinsic aging is the result of often genetically-determined changes that occur naturally within the body from the mid-20s onwards, despite their later evident effects. The biological clock or chronological age determined by genetics also applies to the skin, which gradually loses its ability to function as it once did. This deterioration occurs due to a gradual shift in the balance of certain messenger molecules excreted within the body that lead to natural changes manifesting in outward signs of aging.

Understood as the consequence of continually repeated muscle movements like smiling or frowning, mechanical aging also contributes to skin deterioration day by day, exacerbating expression lines.

Environmental or extrinsic aging takes place due to the daily exposure to external sources in the environment: ultraviolet rays, pollution, smoke, harsh weather, gravity and external stress. These agents limit the ability of cells to function properly and alter the integrity of overall cell composition. Years of accumulated environmental stress on skin cellular structures translates into premature aging.

UV damage from sun exposure accounts for 90% of premature skin aging. The damage to skin components caused by both prolonged and incidental sun exposure is called photoaging, which is a process that occurs over a period of years (the effects are cumulative) and can lead the skin to lose its repairing ability.

All aging types cause alterations in the skin which include a slower cellular turnover, reduced collagen production, elastin disturbances and skin thinning [1-2]. Additionally, UV radiation disturbs melanocytes and moisture barrier, and accelerates collagen and elastin loss as well as their fibres breakdown in the skin [1-2]. The alteration of collagen and elastin is controlled by the activity of Matrix Metalloproteinase (MMP) enzymes known as collagenase and elastase, respectively, both of them being activated by UV radiation. Long-term elevation of the MMPs results in disorganised and clumped collagen and elastin, that is characteristic of photodamaged skin.

Thus, there are differences between intrinsic and extrinsic aging effects on the skin, and obviously versus young skin. If we look at intrinsic or chronological aged skin, without environmental influences, it is smooth, generally unblemished and with some exaggerated expression lines, but the skin is well preserved in general, despite an inner flattening of the epidermal-dermal interface and some disruption of the dermal tissue [2].

In direct contrast, extrinsically-aged skin (mainly the face, hands and chest) presents wrinkles, hyper/hypopigmentation, sallow areas, increased fragility, roughness and a loss of tonicity and elasticity, due to a more fragmented and thick collagen and elastin [2-3].

Elastin fibres are present in adult skin in various stages of maturity, forming a distinctive arrangement within the papillary (outer) and reticular (inner) dermis [2, 4]. The least mature fibres course perpendicularly from the dermal-epidermal junction to the top of the reticular dermis (oxytalan fibres), whereas more mature fibres containing added deposited elastin are horizontally arranged (elaunin fibres) [2, 4-5]. Both elastin fibres are connected as oxytalan merge from elaunin fibres [2, 4-5]. The most mature fibres are found deeper in the reticular dermis [4].

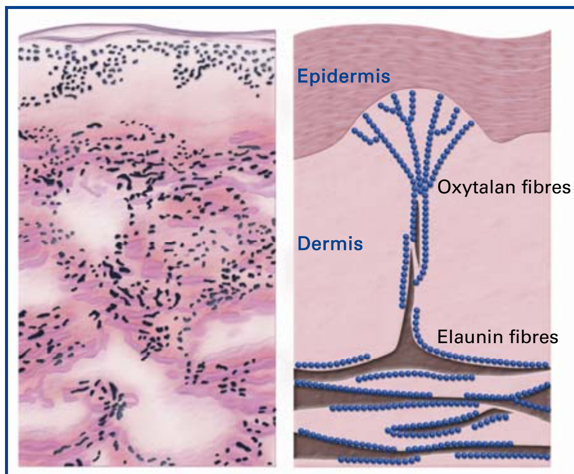


Fig. 1. Elastin presence in young skin.

All aging types alter elastin fibres, but in different ways. Biologically, our body naturally diminishes elastin production within fibroblasts as we age, so fewer fibres are created and the skin loses resilience. Environmentally, UV rays can penetrate skin layers to damage elastin-producing fibroblasts. Also, as skin cell renewal decreases, the skin thins becoming more susceptible to environmental damage [1]. Finally, mechanical stress can permanently stretch out elastin fibres.

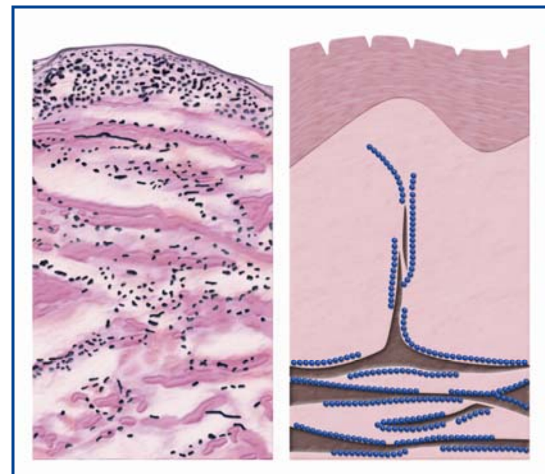


Fig. 2. Elastin in photoprotected aged skin (fewer elastin fibres).

Changes in elastin fibres are so distinctive in photoaged skin that the condition known as elastosis is considered one of its hallmarks [1, 4]. This is characterised by an accumulation of amorphous elastin protein and a breakdown in the typical structural layout, which results in decreased skin elasticity and tensile strength. This phenomenon accounts for why more photoexposed skin takes longer to assume its original position when extended or pulled.

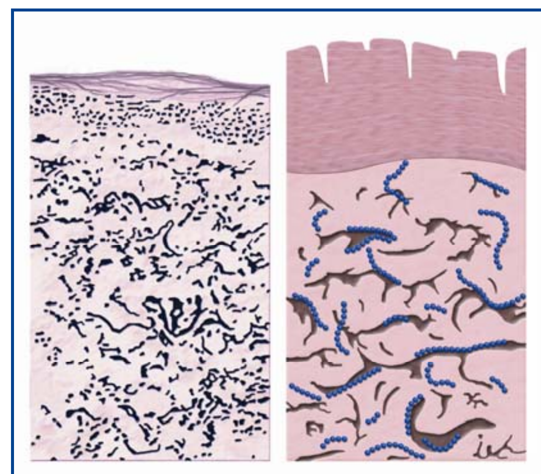


Fig. 3. Elastin in photoexposed aged skin (thicker and disorganised elastin fibres).

Aging alters skin structure and inner components like elastin and collagen, which need to be enhanced to reduce skin flaccidity.

Key elements combating skin flaccidity

In order to protect skin from external and internal agents that reduce its capacity to stay firm, it is first important to know the current mechanisms and elements that manage to do so, preserving skin elasticity and firmness until passing years reduce this intrinsic capacity. Although elastin and collagen are the most well-known proteins that provide firmness, other elements located in the ECM and inside skin cells contribute to such important task. All together, they capacitate the skin to be firm and elastic at the same time, avoiding sagginess.

Elastin fibres

With an estimated molecular mass of 64-66 kDa, elastin is a protein found in any elastic connective tissue and, in the skin, it is mainly located in the dermis, being responsible for cutaneous critical properties [2, 5-7]. The unique gene responsible for elastin production is mainly expressed before birth and in the first years of life, but it is substantially turned down with the passing years, so most of elastin found in adults comes from this initial production [6, 8]. Although elastin has proved to be the longest lasting protein in the body with a half-life of 70-74 years approximately, its slower adult production may lead to a non-complete repair when the passing years damage it, fact that implies a reduction of skin elasticity [2, 6-7].

Elastin and microfibrils are the two components of the elastic fibres, which represent the largest structure of the ECM [2, 5, 8-9]. The major and core component is elastin, which is formed in the process of elastogenesis through the assembly and cross-linking of its precursor protein known as tropoelastin [2, 6-8]. In fibroblasts, the expression of the elastin gene results in the intracellular formation of soluble tropoelastin monomers of 60-70 kDa, that may be different in length due to undergoing alternative splicing, and their secretion to the cell surface [2, 6-9].

Mature tropoelastin monomers are able to self-assembly and aggregate by coacervation, which implies tropoelastin being more concentrated and aligned for subsequent cross-linking [2, 6-9]. Coacervated tropoelastin (microassembly) is then deposited onto long linear microfibrils (10-15 nm) of the ECM (macroassembly), which serve as a scaffold to guide cross-linking [2, 6-9]. In tissues, microfibrils form packed parallel bundles close to cell surface and their main structural elements are fibrillins, which are large glycoproteins (by 350 kDa) that form their backbone [2, 5-7]. Being a product of fibroblasts and keratinocytes, fibrillin-1 appears as the principal component of these microfibrils in adults [2, 6-8].

It is agreed that specific elements are needed for this last step of the elastin fibre formation to occur properly, Fibulin 5 (FBLN5/DANCE) and Lysyl Oxidase-Like 1 (LOXL1) being key players for a proper assembly.

FBLN5 and LOXL1 role

Fibulins are a family of ECM glycoproteins between 50-200 kDa that are associated with the stabilisation of structures like elastic fibres, binding to tropoelastin with different affinities [8, 10-12]. FBLN5 (66 kDa) is one of the five members of this family and it is thought to be essential in

elastin fibre organisation as it is colocalised with such fibres, its overexpression increases their assembly and its decrease and absence causes their defective development and disorganisation, as it happens when aging [8, 10-17]. This glycoprotein is recognised as a bridge molecule because it binds not only to tropoelastin but also to LOXL1, fibrillin-1 and integrins, all of them necessary components for the adequate assembly of elastin fibres [5, 8, 10, 12-13].

LOXL1 is one of the members of the lysyl oxidase family (LOX), which comprises LOX and LOX-like proteins from 1-4 [5, 8, 10, 12-13]. Secreted to the ECM, this enzyme catalyses the formation of covalent cross-links between two adjacent tropoelastin molecules, ensuring spatially defined deposition of elastin and originating the insoluble elastin polymer [5, 8, 10, 12-13, 16, 18-19]. Thus, it is found in sites of elastogenesis, where FBLN5 could be responsible for its binding and activation as well [8, 16, 19]. As it occurs with FBLN5, LOXL1 levels decrease with advanced age [18].

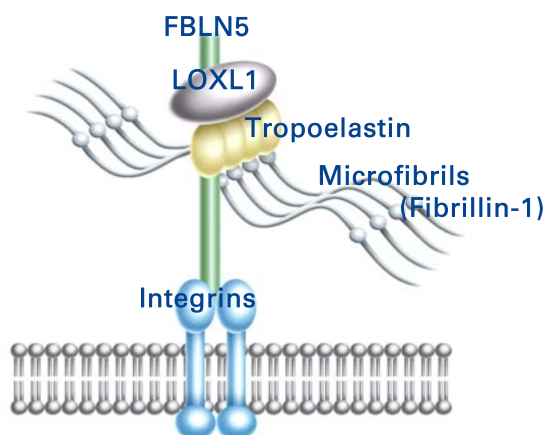


Fig. 4. Mature elastin fibre formation.

Apart from binding to FBLN5, fibrillin-1 from the microfibrils also binds to integrins, which are transmembrane receptors that externally bind to the ECM and internally to the contractile cytoskeleton [8]. Therefore, the complex forming the mature elastin fibres gets linked to cells due FBLN5 and to fibrillin-1 as both elements connect with this family of receptors, which in turn join other important elements for skin firmness like type I, IV and VI collagen [20-22].

Collagen cohesive function

When the term collagen appears, it is usually applied to type I collagen, which is the most abundant protein in the ECM and in the human body. Actually, this type is the principal collagen in the skin, first found as procollagen before it is cleaved and assembled into collagen fibril polymers first and then aggregated into larger bundles as collagen fibres. It offers the major platform for cell attachment and anchorage to macromolecules, providing cutaneous structural support.

Conversely, type IV collagen is a specific non-fibrillar type found in the basement membrane, which serve as structural barrier and substrate for cellular interactions [23]. Additionally, type IV collagen is able to join type I and VI collagen, among other compounds, and form supramolecular networks that bind to collagen fibrils and elastic fibres as well, providing cohesion to the fibrillar components of the dermis and influencing cellular adhesion and migration, all of them fundamental for the integrity and function of membrane basements under mechanical demands [20, 22, 24-26].

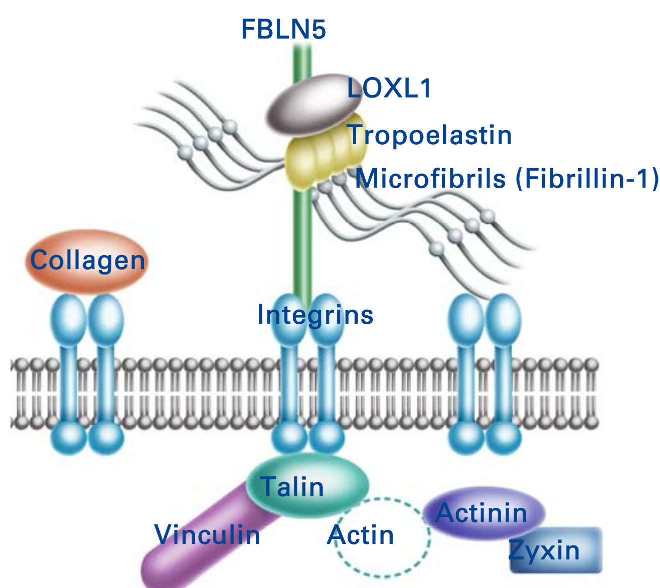
Furthermore, it is seems that type VI collagen is assembled into microfibrils distributed in elastic and non-elastic tissues, where the microfibrils function as essential structural elements [20, 23].

Type XIV collagen is localised near the surface of collagen fibrils, regulating the fibrillogenesis process in sites with high mechanical demand, like the skin, its alteration leading to skin laxity and flaccidity [20, 22-24, 27-30]. Moreover, it is thought that this collagen type is associated with type I collagen fibrils and also with cellular adhesion mechanisms [3].

Focal adhesions

Cellular adhesion to the ECM can occur due to cell surface integrins that get to link intra and extracellular components via multiprotein complexes, called Focal Adhesions (FAs). This bond needs the coordinated binding of integrins receptors to adhesive domains in ECM ligands but also FAs assembly and their interactions with the cytoskeleton of actin (a key protein in cellular movement, contraction and shape maintenance) [31]. Thus, FAs act as an interface between the actin cytoskeleton and the ECM compounds [32].

Upon cellular adhesion, one of the numerous structural elements of the FAs, known as talin, rapidly accumulates in focal contacts and is able to directly bind to integrins [33]. Talin is a high-molecular-weight protein with binding sites for actin but also for vinculin, another protein that stabilises cell-cell and cell-matrix junctions [33]. Tensile and mechanical forces acting on talin activate its union to vinculin, enhance FA assembly and increase the strength of the linkage between integrins and the actin cytoskeleton [30-31, 33]. Mechanical forces also induce the recruitment of zyxin, a protein that facilitates actin filament assembly and may be involved in adhesion-stimulated changes in gene expression and the cytoskeletal organisation of actin bundles, which translates into reinforcement of the final binding function of the FAs [31]. Actinin is a necessary protein as it links the actin filaments to zyxin, associating these filaments to the membrane.



FBLN5 and LOXL1 are key components to maintain elastin fibres properly assembled and functioning. Together with collagen molecules and elements of the FAs like talin and zyxin, they are responsible for the firmness and resistance of the skin.

UPLEVITY™, counteracting the force of gravity

UPLEVITY™ is a novel peptide designed to fight the undesired effects of a lack of skin firmness and cohesion by enhancing the natural elements that help to maintain collagen levels and elastin fibres correctly assembled, and facilitating the union between cells and the ECM.

This ingredient not only proved to activate the FBLN5 and LOXL1 promoters but also increased both protein levels *in vitro,* that as we previously mentioned are necessary elements for a correct assembly of elastin fibres. Moreover, it highly induced the synthesis of elastin.

It also showed to upregulate genes related with FAs and collagen synthesis, highly inducing the synthesis of type I collagen as well.

In vivo, the peptide showed to clearly reduce specific parameters linked to skin flaccidity and dermal disorganisation, which translates into a better inner restructure of the dermis and skin cohesion.

UPLEVITY™ is a new peptide that helps the skin to remain firm and fight the effects of external and internal agents that damage its cohesion and key firming elements, like elastin and collagen.

In vitro efficacy

Activation of FBLN5 and LOXL1 promoters

This study wanted to confirm the activation of the human FBLN5 and LOXL1 promoters on a double-transfected stable human epithelial FBLN5/LOXL1-reporter cell line expressing Firefly and Renilla Luciferase genes upon the activation of FBLN5 and LOXL1 promoters respectively, induced by UPLEVITY™.

Transfected cells were seeded for luciferase activity detection and, after 24 h, they were washed and incubated with medium for 6 h. Then, they were treated with IL-1β (10 ng/mL, positive control) or UPLEVITY™ (0.1 or 1.0 mg/mL), and incubated for 16-24 h. Cells cultured with just medium were used as the negative control (basal). At the end of the treatment, Firefly and Renilla luciferase substrates were added to quantify the reactions with their respective luciferases using a multiplate luminometer (relative light units per second).

In parallel, a different set of plates with transfected cells were washed and stained with crystal violet to quantify number of cells per well and normalise luciferase units.

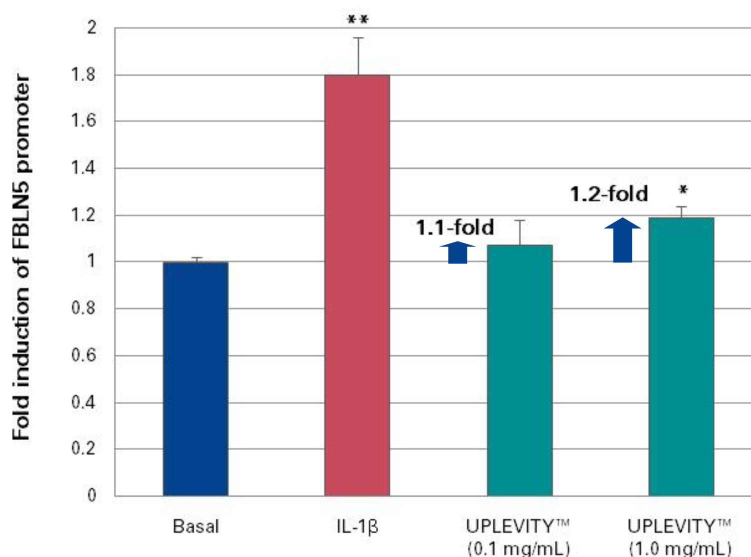


Fig. 5. Fold induction of FBLN5 promoter in transfected cells after the active treatment (*p<0.05, **p<0.01).

Results showed that the tetrapeptide increased the activity of the FBLN5 promoter up to 1.2 times compared to cells only cultured with medium.

UPLEVITY™ was able to activate the FBLN5 promoter.

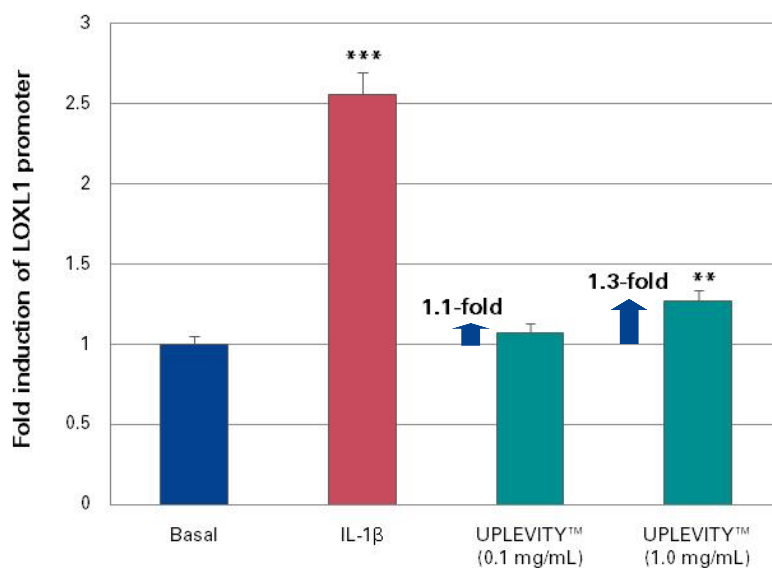


Fig. 6. Fold induction of LOXL1 promoter in transfected cells after the active treatment (**p<0.01, ***p<0.001).

As the obtained values confirmed, the active ingredient raised the activity of the LOXL1 promoter up to 1.3 times versus the cells only cultured with medium.

UPLEVITY™ activated the LOXL1 promoter.

INCREASE OF FBLN5 AND LOXL1 PROTEIN LEVELS

The aim of this assay was to evaluate the efficacy of UPLEVITY™ as an elastic fibre inducer due to its action on FBLN5 and LOXL1 proteins through and immunocytochemistry assay (with fluorescent antibodies) in Human Dermal Fibroblasts (HDFa).

After HDFa were seeded into well plates with supplemented medium for 72 h, cells were incubated for 48 h with medium alone (basal control), with TGF-β1 (5 ng/mL, positive control), with IL-1β (20 ng/mL, positive control) or with UPLEVITY™ (0.5 mg/mL).

After this period, an immunofluorescence staining protocol was followed to detect FBLN5 and LOXL1 proteins, consisting in washing, fixing and finally staining cells. From each taken image of these proteins, values of Integrated Optical Density (IOD) were quantified and normalised.

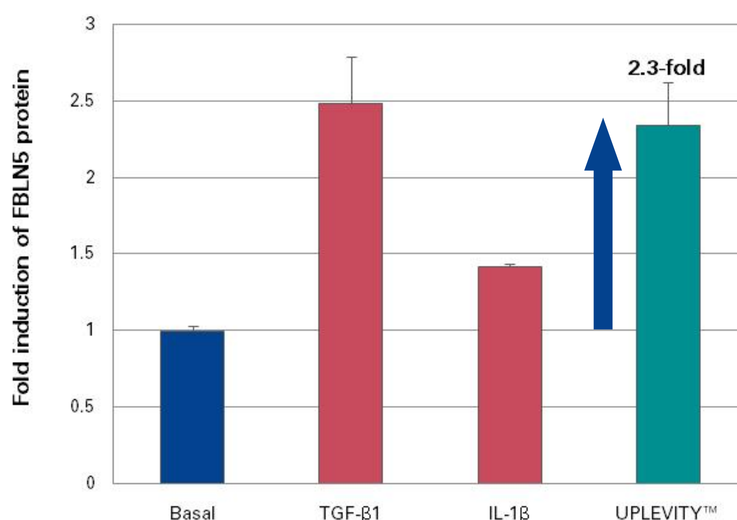


Fig. 7. Fold induction of FBLN5 protein levels after the different treatments.

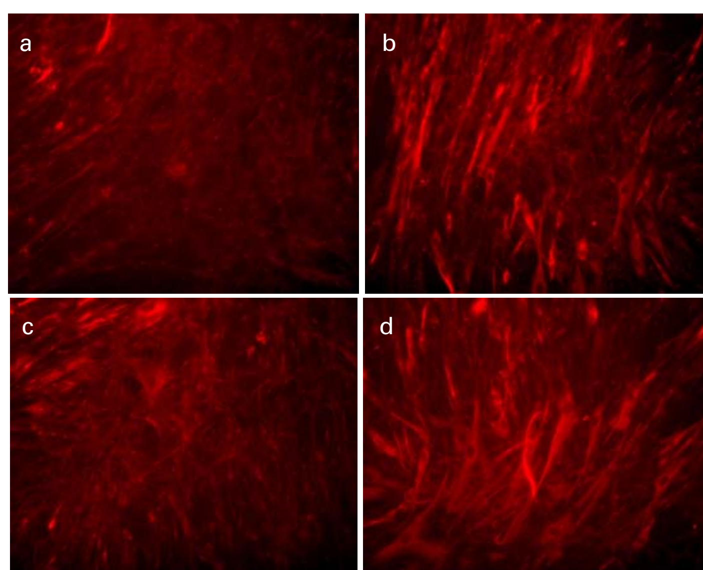


Fig. 8. Expression of FBLN5 protein in HDFa after the different treatments: a) Basal, b) TGF-β1, c) IL-1β, d) UPLEVITY™.

Results showed that the active peptide **multiplied FBLN5 protein levels** by **2.3-fold** compared to cells only cultured with medium.

UPLEVITY™ was able to raise FBLN5 protein levels.

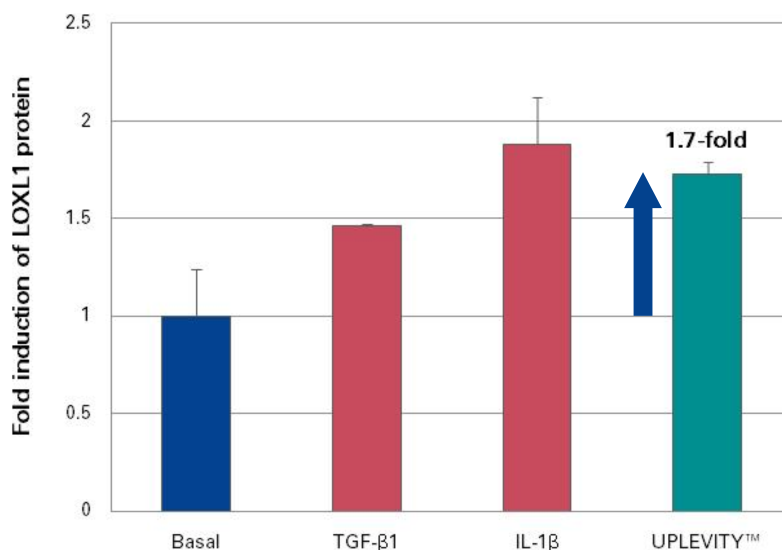


Fig. 9. Fold induction of LOXL1protein levels after the different treatments.

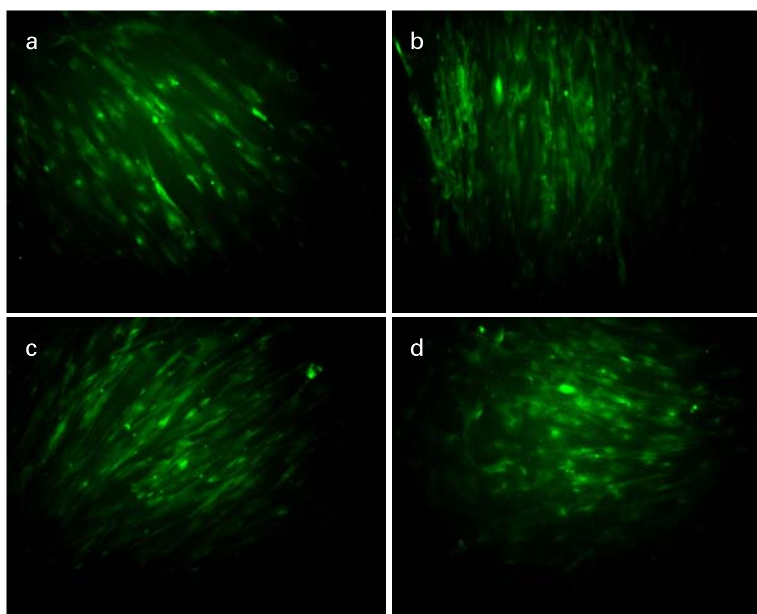


Fig. 10. Expression of LOXL1 protein in HDFa after the different treatments: a) Basal, b) TGF-β1, c) IL-1β, d) UPLEVITY™ .

As the images demonstrated, the tetrapeptide **augmented** the **expression** of **LOXL1 protein by 1.7-fold** versus the cells only cultured with medium.

UPLEVITY™ increased LOXL1 proteins levels.

MICROARRAY ANALYSIS

This assay was developed to detect the genes that were upregulated in HDFa in presence of UPLEVITY™ using an ASurePrint G3 Human Gene Expression Microarray v2.

HDFa were seeded and after 7 days cells were ready to be incubated with UPLEVITY™ (0.05 mg/mL) in supplemented medium for 24 h. Afterwards, cells were lysed directly in the cell-culture flasks following the kits protocol. Then, RNA samples were obtained and their quality was verified before microarray processing.

After analysing and normalising the arrays, microarray data were used to obtain the genes with differential and more altered expression.

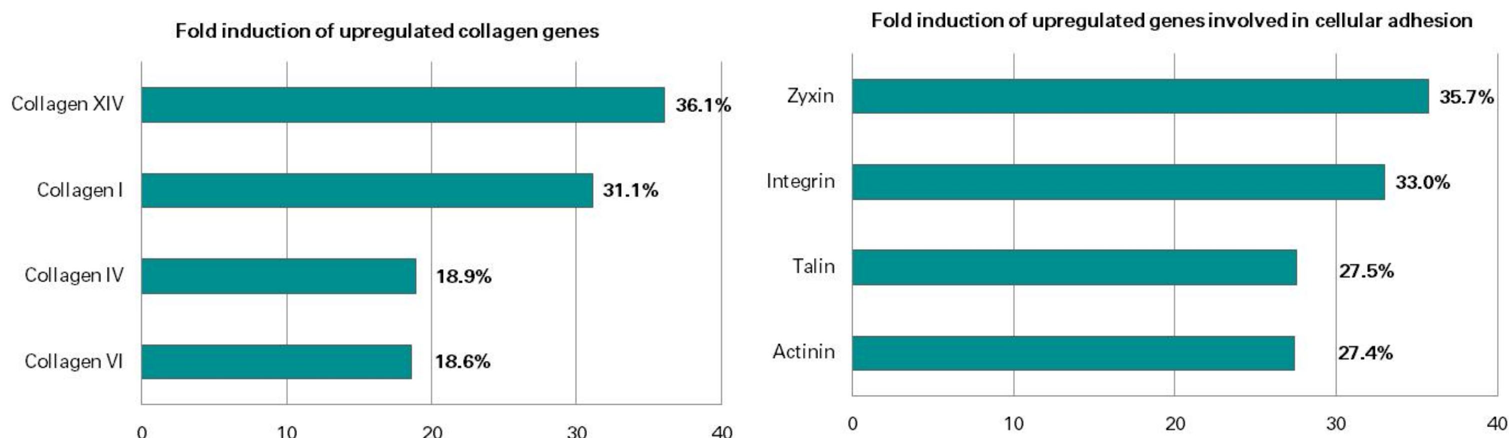


Fig. 11. Percentage of fold induction of significantly overexpressed collagen genes and genes involved in cellular adhesion.

UPLEVITY™ upregulated the expression of genes involved in collagen synthesis and focal adhesions, all of them implied in skin firmness.

Elastin induction

The aim of this study was to study the effect of UPLEVITY™ on the induction of elastin synthesis on HDFa by the Fastin Elastin Assay, a quantitative dye-binding method for the analysis of soluble elastin based on the release of this bond-specific dye upon treatment with a destaining reagent and measurement of its absorbance.

HDFa were grown until confluence in medium with specific growth factors. After cells were seeded into well plates and incubated for 72 h, fresh medium containing TGF-1β (10 ng/mL, positive control) or UPLEVITY™ (0.1 mg/mL) was added and plates were incubated for 48 h more. Non-treated cells were used as negative control. Afterwards, elastin was extracted from cells.

Absorbance was read at 540 nm in a microtiter plate reader, determining elastin concentration using a linear regression of the elastin standard curve.

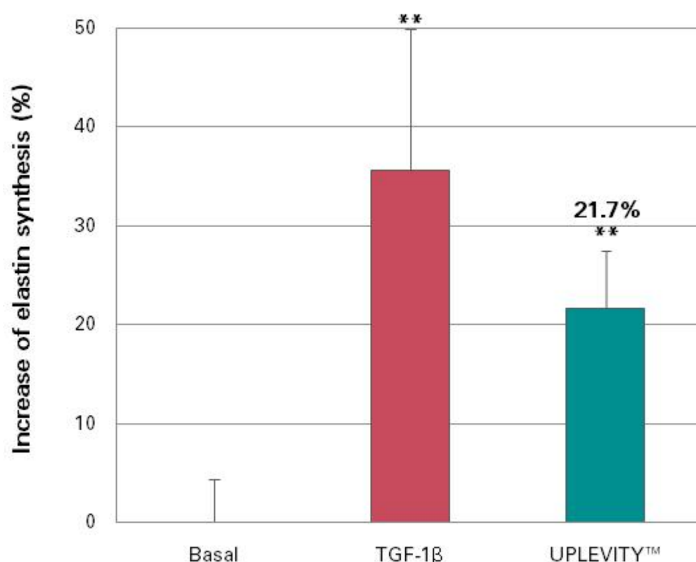


Fig. 12. Elastin increase after different treatments, including the tetrapeptide (**p<0.01).

The active peptide **increased elastin synthesis** by **21.7%** compared to non-treated cells.

UPLEVITY™ caused a statistically significant raise of elastin synthesis.

Type I collagen induction

To analyse the effect of UPLEVITY™ on the induction of type I collagen synthesis, an Enzyme-Linked Immunosorbent Assay (ELISA) was carried out on HDFa.

HDFa were grown until confluence in medium with specific growth factors. After cells were seeded into well plates and incubated for 24 h, fresh medium containing UPLEVITY™ (0.01 µg/mL) was added and plates were incubated for 48 h more. Non-treated cells were used as control. Then, well medium was collected and 50 µL was analysed by an ELISA.

Absorbance values were read at 490 nm in a microtiter plate reader and collagen concentrations were determined using a linear regression of type I collagen standard curve.

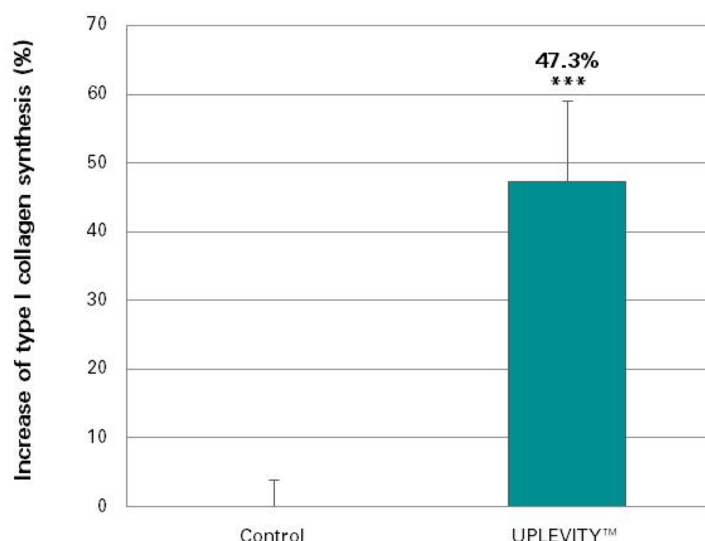


Fig. 13. Type I collagen synthesis versus non-treated cells (***p<0.0001).

The ingredient showed to **raise type I collagen synthesis** by **47.3%** versus non-treated cells.

UPLEVITY™ provided a clear statistically significant induction of type I collagen synthesis.

In vivo efficacy

INCREASE OF FIRMNESS

The objective was to examine the efficacy of UPLEVITY™ in ameliorating skin firmness by ballistometry. For this purpose, 19 female volunteers between 50-60 years old with a stable weight and presenting saggy facial skin applied an emulsion containing 2% UPLEVITY™ SOLUTION on the face twice a day for 55 days.

The principle of ballistometry is based on the use of an impacting mass (ballistometer hammer) on the skin surface to measure the mechanical properties of the skin through their interactions. Thus, a vibrational movement is imposed on the skin and the rebounds are transduced into quantifiable electrical signals.

Two parameters were selected: the indentation (mm), which is the peak penetration depth of the probe tip beneath the skin on its first impact, and the area between the bounce profile and skin zero datum (mm²). The higher the indentation or area value, the higher the skin flaccidity.

Measurements were taken from the cheek at the initial time and after 55 days in order to compare the efficacy of the active emulsion versus the initial time.

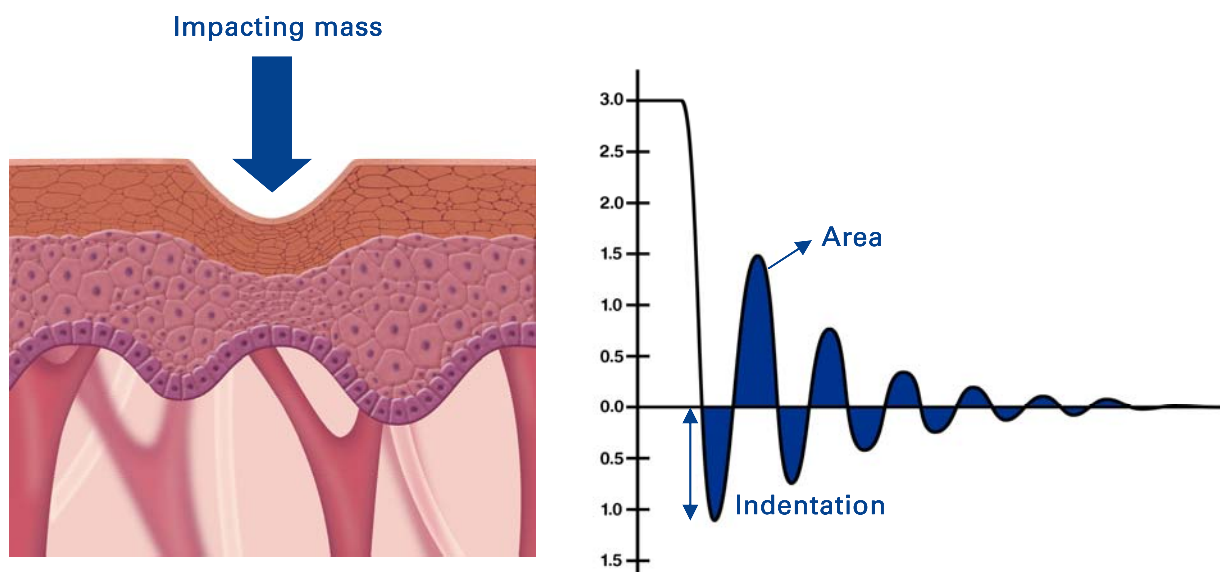


Fig. 14. The indentation and area parameters considering the direct effect of an impacting mass and the induced rebounds respectively.

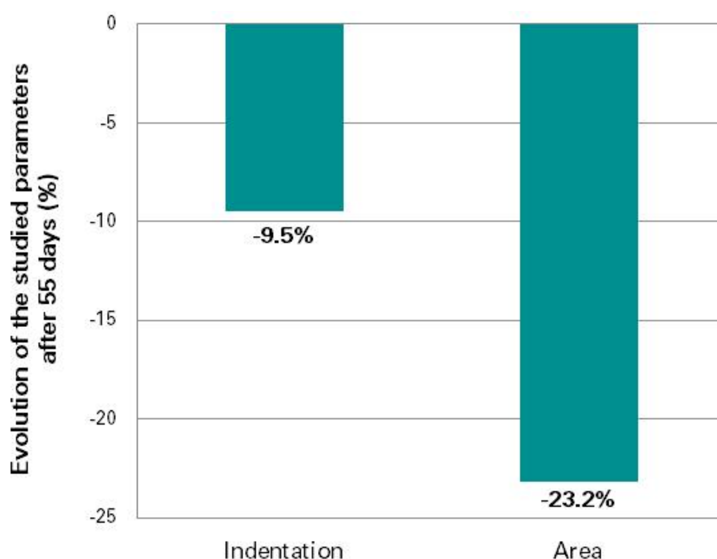


Fig. 15. The indentation and area values decrease after 55 days, which are related to an improvement of skin firmness.

The ingredient offered a statistically significant **diminution** ($p \leq 0.05$) of the **indentation** and the studied **area** (**-9.5%** and **-23.2%** respectively), characteristic of an **amelioration of skin firmness**, at the end of the treatment versus the initial time.

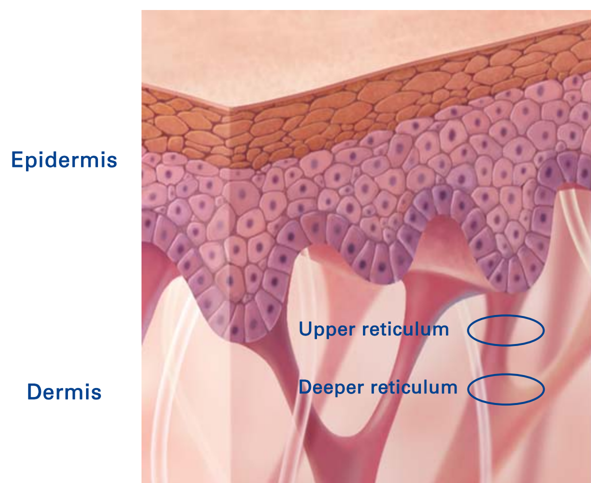
UPLEVITY™ improved skin firmness after 55 days.

RESTRUCTURATION OF THE DERMIS

In order to observe the efficacy of UPLEVITY™ in the dermal organisation, 19 volunteers (50-60 years old) with a stable weight and saggy skin applied a placebo emulsion on half of the face and an emulsion containing 2% UPLEVITY™ SOLUTION on the other half, twice a day for 55 days. The *in vivo* confocal microscopy was used to quantify the tissular structure of the superficial reticular dermis at two levels, facilitating the measurement of the fragmentation rates at different depths of the superficial reticular dermis.

Two stacks of each cheek were acquired at the beginning and at the end of the treatment. Two images were selected of each stack: one from the most superficial part of the reticular dermis and another one from 18 µm deeper. A region was defined in each image and two parameters were studied: the fragmentation rate of the upper reticulum and the deeper reticulum. The decrease of these parameters demonstrates an improvement of the reticular dermis.

A VivaScope® was used to carry out the acquisitions and specific software to analyse the digital images, permitting to characterise and quantify the fibres network. The more and smaller "objects" (in red) represent a higher fragmentation of such fibres.



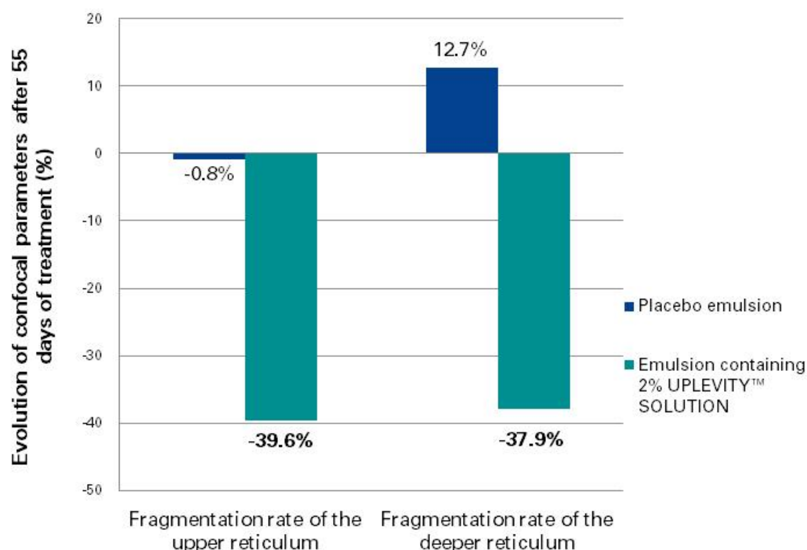


Fig. 15. Changes in the studied parameters comparing their values before and after the different treatments.

The active treatment caused a **statistically significant reduction of both parameters** (-39.6% and -37.9%), while the placebo did not. Additionally, the difference between the effect of the placebo and the active treatment was also found to be statistically significant for both parameters ($p \leq 0.05$).

UPLEVITY™ proved to restructure the dermis at the studied depths, improving skin inner cohesion.

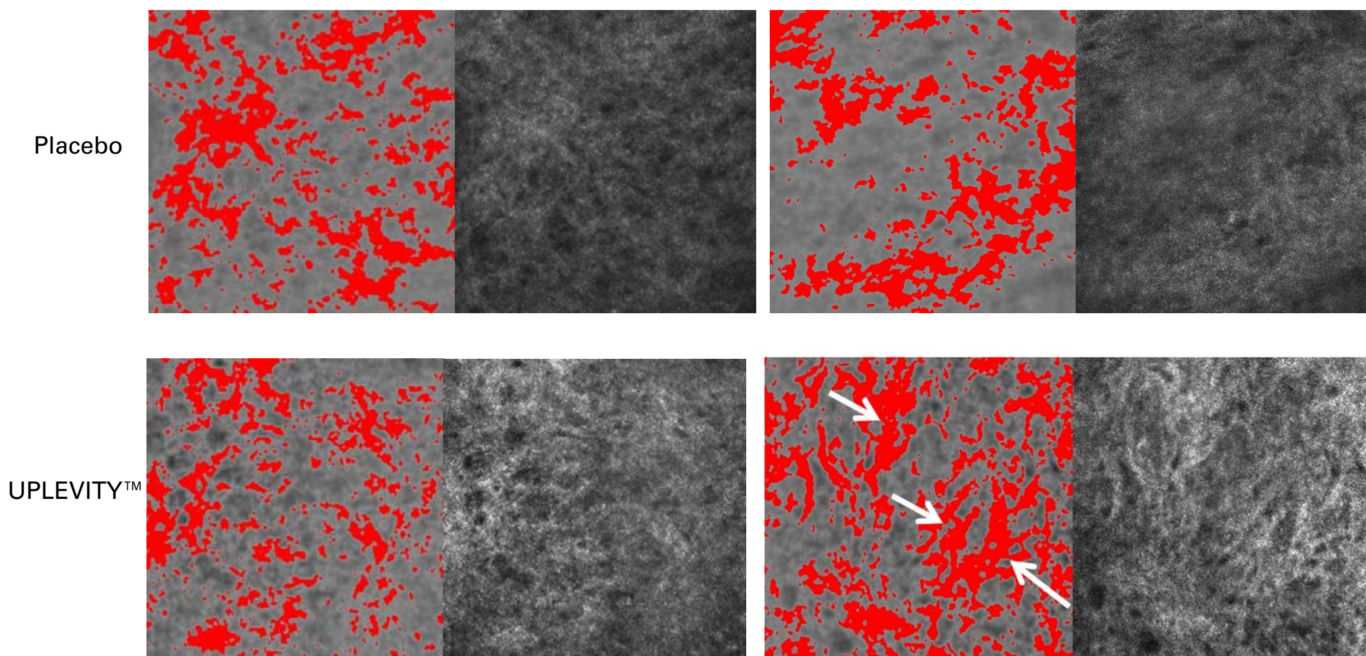


Fig. 15. Processed and non-processed images (from the upper reticulum) of a volunteer before (2 left images) and after the treatments (2 right images), highlighting the fibres network.

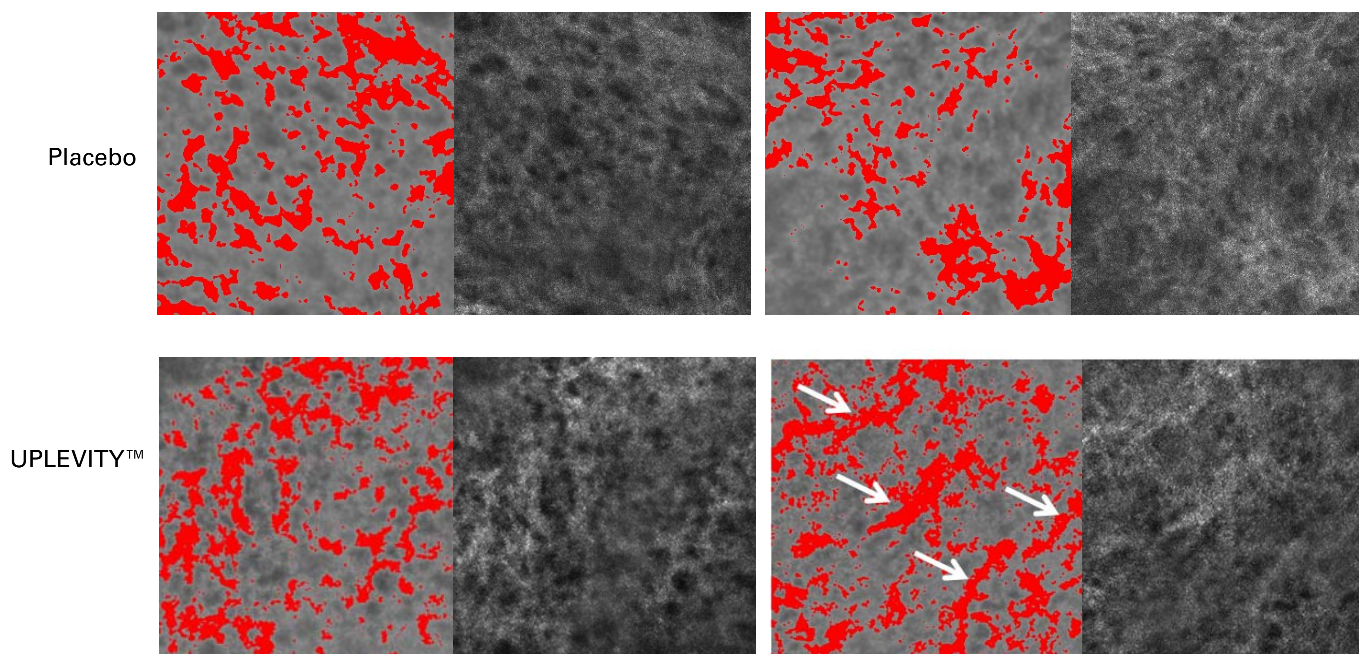


Fig. 15. Processed and non-processed images (from the upper reticulum) of another volunteer before (2 left images) and after the treatments (2 right images), highlighting the fibres network.

The images of the actively treated areas showed larger red objects at the end of the treatment, which implied minor fragmentation rate compared to the initial time but also to the placebo treatment.

UPLEVITY™ reduced the fragmentation of the fibres network.

Cosmetic properties

UPLEVITY™ :

- innovative tetrapeptide to increase skin firmness, avoiding sagginess and flaccidity.
- raised the activity of FBLN5 and LOXL1 promoters by 1.2-fold and 1.3-fold respectively (at 1 mg/mL), promoting the expression of these key elements and the correct assembly of elastin fibres.
- augmented FBLN5 and LOXL1 protein levels by 2.3-fold and 1.7-fold respectively, which help elastin fibres to be assembled accurately.
- upregulated the expression of genes involved in collagen synthesis and FAs (talin and zyxin among others), all of them beneficial elements that improve skin cohesion.
- provided a statistically significant induction of elastin synthesis (21.7%), protein directly linked to skin elasticity and recoil.
- increased type I collagen synthesis by 47.3% (statistically significant value), helping to improve skin firmness.
- improves skin cohesion, as *in vivo* (at 2%) it reduced the indentation (-9.5%) and the area (-23.2%) parameters, that are directly linked to lower firmness, and the fragmentation rate of the upper and deeper reticulum (-39.6 and -37.9% respectively), whose decreases are associated to an improvement of skin restructuration.

Cosmetic applications

UPLEVITY™ is an ideal ingredient to improve skin firmness by enhancing the natural elements that manage to maintain these properties in the skin, including elastin and collagen. Thus, it can be incorporated in firming and anti-aging formulations for both facial and body care, where skin cohesion and resilience wants to be increased to minimise sagginess and flaccidity.

Moreover, it would be also useful to add in slimming formulations to avoid flaccidity after losing weight.

Technical data

INCI NAME OF THE ACTIVE INGREDIENT

Active ingredient	INCI name
UPLEVITY™	Acetyl Tetrapeptide-2

PRESENTATION AND PRESERVATIVE

Solution containing 0.05% of active ingredient.

Code	Product presentation	Preservative
PD250	UPLEVITY™ SOLUTION	Preservative free

Application data

PROCESSING

UPLEVITY™ SOLUTION needs to be incorporated in the aqueous phase in case of cold gels, lotions or emulsions. In case of warm emulsions, it should be added once the emulsion is formed and at temperatures below 40 ºC.

UPLEVITY™ is stable at a pH range between 5.0 and 8.0. Please ask for further details if formulating under pH 5.0.

INCOMPATIBILITIES

Not expected.

SOLUBILITY

Soluble in water.

DOSAGE

A dosage of 2% of UPLEVITY™ SOLUTION is recommended in final cosmetic formulations.

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The specific situation of the trademark in each country may vary and we recommend that you contact us for updated information.

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Care Creations™

Syniorage™

High definition skin effect

Beauty Creations

The Passion for Beauty

Beautiful at each age

With numerous examples of seniors demonstrating with flair that it is entirely possible to age with beauty, old age is no longer to be feared, and can be approached with serenity.

The high activity of retired people these days has in fact made many of those still employed quite envious! Free, with much spare time, financially secure and independent, the baby-boomers of today do not hesitate to travel around the world full of energy. They are the opposite of the classic role model of traditional grandparents.

Not only do they accept their age, but they are taking their age and appearance to a higher level by notably altering the perception of the inevitable signs of skin aging. What was once thought to be a negative sign of age, wrinkles are now carried with pride as signs of experiences acquired during life.

One sign of aging remains less accepted: sallow skin. Seniors expect their skin to mirror their joy in life and not to betray their age. They prefer to project a youthful image, reflected by a radiant complexion.

In order to achieve this, it is necessary to have a specific anti-age approach for the epidermis, the outermost part of the skin that becomes more fragile with age and thins. The cohesion of the epidermal cells diminishes, the epidermis loses its resistance and radiance, resulting in dry and slack skin that is easily damaged with even the lightest friction or shock.

All these outward signs particular to the epidermis betray a person's age, as well as wrinkles and sagging of the skin and the face contour, which are more specific to the dermis.

To enhance the epidermal cohesion, Laboratoires Sérobiologiques has targeted two epidermal proteins:

- syndecan-1, a small proteoglycan, the production of which diminishes with age (exclusive LS fundamental research study), resulting in a lack of cohesion at the level of the epidermis.

- collagen XVII, a fundamental protein of the hemidesmosomes that are responsible for the adhesion between the epidermis and the dermo-epidermal junction (DEJ).

To rejuvenate the epidermis and restore its cohesion and resistance, LS has developed Syniorage™.

By acting on the production of syndecan-1 and collagen XVII in the epidermis, Syniorage™ supports the cohesion between its constituent cells as well as its adhesion to the DEJ.

With Syniorage™, an active peptide targeting the epidermis specifically, the skin recovers cohesion, resistance and a refined skin texture.

By its radiant appearance, the skin of seniors is finally able to reflect their joy in life and pride in aging gracefully.

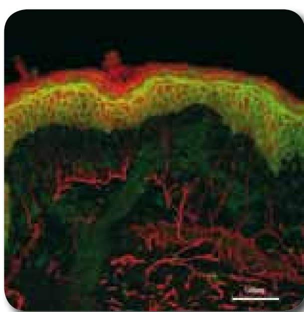


Fig. 1 - Visualization of syndecan-1 on human skin (immunohistochemistry, confocal microscopy). Presence in suprabasal layers.

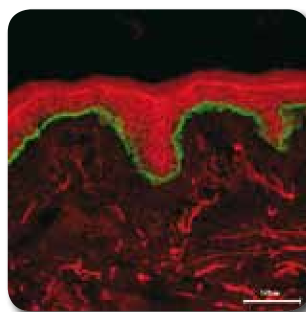
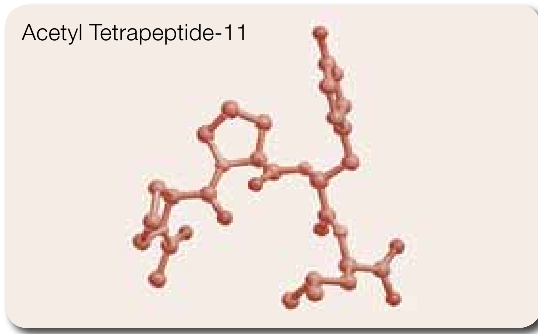


Fig. 2 - Visualization of collagen XVII on human skin (immunohistochemistry, confocal microscopy). Presence in the dermo-epidermal junction.

Definition / Composition

Syniorage™ is a white powder containing an acetylated tetrapeptide **(N-acetyl-Pro-Pro-Tyr-Leu)**. Concentration: ~ 1350 ppm.



Skin benefits

• Improvement of epidermal cohesion *via* the stimulation of the synthesis of:
- syndecan-1, a small proteoglycan involved in the cohesion of epidermal keratinocytes, and
- collagen XVII, a fundamental protein of hemidesmosomes.

• Increase of skin firmness and elasticity.
• Improvement of epidermal cohesion for a more radiant and uniform skin.

Cosmetics use

• Anti-age face care.
• Specific care for mature skin.
• Radiant senior skin care.

Dosage / Solubility / Mode of incorporation

1. Dose of use: 1 - 3%.
2. Solubility: soluble in water, insoluble in oils and fats.
3. Mode of incorporation: Syniorage™ is incorporated at the end of the process, below 60°C, or at room temperature for cold processing. Optimal pH: 4 - 8.

Analytical characteristics

1. Aspect: white powder with a characteristic odor.
2. Specifications: upon request.

Tolerance

Good.

Efficacy

Efficacy tests hereafter.

Storage

In its original packaging, at 15 - 25°C.

Regulatory data

Syniorage™ PW LS 9847
INCI name: Mannitol (and) Acetyl Tetrapeptide-11.

Efficacy tests

First of all, the overall effects of Syniorage™ were established by using the DNA-array technology. This test allowed to evaluate its influence on the general gene expression profile of human primary epidermal keratinocytes. Subsequently the action of Syniorage™ was checked *in vitro*:
- stimulation of syndecan-1 synthesis,
- stimulation of COL17A1 gene expression.

Both proteins are primordial to epidermis structure and functionality. Syndecan-1 is a cutaneous small proteoglycan. It plays a role in cellular adhesion, epidermal cohesion and is a co-receptor for growth factors. Collagen XVII, a hemidesmosomal component, mediates the adhesion of epidermal keratinocytes to the underlying basement membrane.
The effect of Syniorage™ was subsquentely confirmed by an *in vivo* evaluation:
- visible and measurable results on skin: improvement of skin firmness, elasticity and appearance.

These tests are described below. The *in vitro* tests were performed with the acetylated peptide (Acetyl Tetrapeptide-11), whereas the *in vivo* test were performed with Syniorage™.

Influence on gene expression (*in vitro* test on keratinocytes)

Aim

To evaluate the effect of Acetyl Tetrapeptide-11 on the overall gene expression profile of normal human primary epidermal keratinocytes, in order to identify the main positive modifications of cell physiology.
Keratinocytes from four different donors were pooled together, to take into account the inter-individual variability. Analyses using a skin-specific DNA-array[1] were performed. The expression of each gene was analyzed by four spots on the DNA-array slide to evaluate the hybridization quality.

Protocol

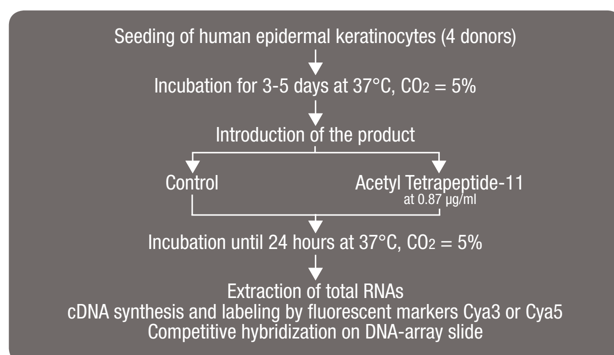


Fig. 3 - Protocol of evaluation of gene expression profile by human epidermal keratinocytes.

Results

Two strategic genes were identified to be modified by Acetyl Tetrapeptide-11 treatment.

The **collagen XVII** encoding gene (COL17A1) expression is potentially increased after treatment with Acetyl Tetrapeptide-11.

The collagen XVII or BP180 protein is implicated in the hemidesmosome structure that forms a bridge between cytoskeleton of basal epidermal keratinocytes and the extra-cellular matrix of the dermo-epidermal junction[2]. This collagen is strongly implicated in the cohesion of the different skin layers.

In addition, Acetyl Tetrapeptide-11 treatment has strongly repressed expression of the **DDR1 gene** (discoidin domain receptor 1).

This gene codes for a tyrosine kinase receptor for extra-cellular collagens and its activation induces a decrease of cell growth[3] and modulates expression of many genes of the extra-cellular matrix, including a decrease of syndecan-1 proteoglycan expression[4]. So, by repression of the DDR1 gene expression, Acetyl Tetrapeptide-11 may induce cell growth and may stimulate the production of the syndecan-1 proteoglycan, implicated in the cohesion between keratinocytes of the upper layers of the epidermis.

Conclusion

According to the gene expression profile analyzed by DNA-array, Acetyl Tetrapeptide-11 may potentially stimulate keratinocyte cell growth and the cohesion of skin layers by the stimulation of both collagen XVII and syndecan-1 proteins.

These effects have been confirmed by others *in vitro* tests.

Stimulation of keratinocytes growth (*in vitro* test)

Aim

To evaluate the capacity of Acetyl Tetrapeptide-11 to stimulate the growth of human keratinocytes. Fetal calf serum (FCS) was used as the reference substance.

Protocol

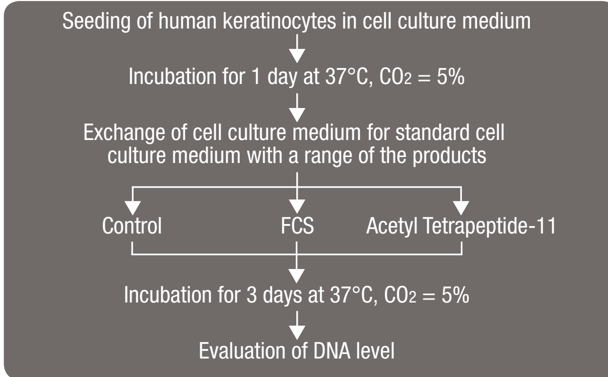
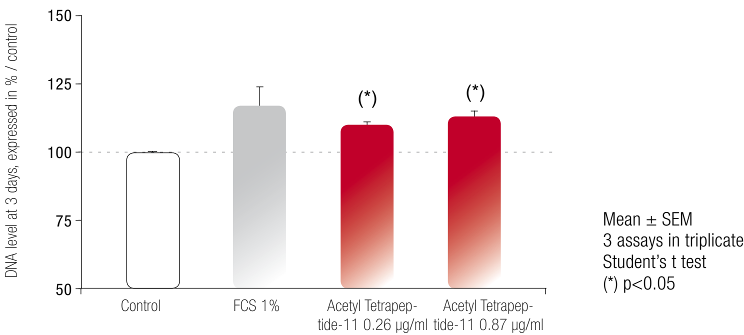


Fig. 4 - Protocol of evaluation of the stimulation of the growth of human keratinocytes.

Results



Mean ± SEM
3 assays in triplicate
Student's t test
(*) $p<0.05$

Fig. 5 - Stimulation of growth of human keratinocytes.

Conclusion

Acetyl Tetrapeptide-11 has significantly increased the growth of human keratinocytes (+13% at 0.87 µg/ml).

Stimulation of syndecan-1 synthesis (*in vitro* test on keratinocytes)

Aim

To evaluate the capacity of Acetyl Tetrapeptide-11 to stimulate the syndecan-1 synthesis by human keratinocytes in culture. Keratinocyte growth factor (KGF) was used as the reference substance[5].

Protocol

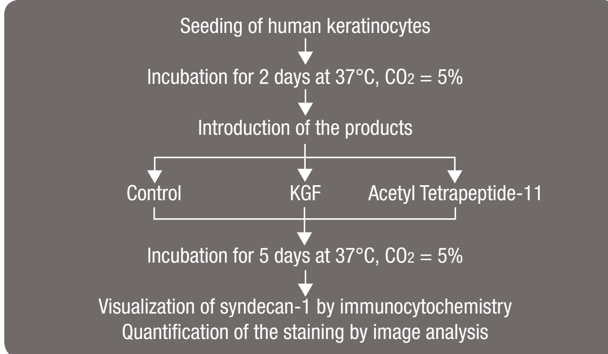


Fig. 6 - Protocol of evaluation of syndecan-1 synthesis by human keratinocytes.

Results

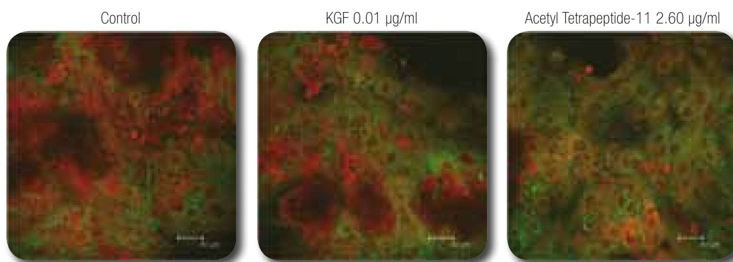
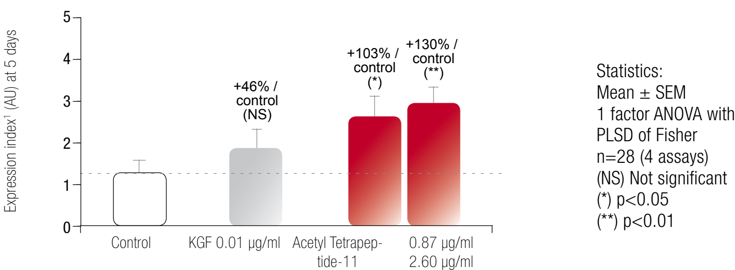


Fig. 7 - Stimulation of syndecan-1 synthesis by human keratinocytes: visualization at 5 days (syndecan-1 in green).



Statistics:
Mean ± SEM
1 factor ANOVA with PLSD of Fisher
n=28 (4 assays)
(NS) Not significant
(*) $p<0.05$
(**) $p<0.01$

[1] Number of stained pixels x fluorescence intensity in green channel in arbitrary unit (AU)

Fig. 8 - Stimulation of syndecan-1 synthesis by human keratinocytes: quantification.

Conclusion

Acetyl Tetrapeptide-11 has significantly increased the synthesis of syndecan-1 by human keratinocytes in culture, in a dose dependant way. These results confirm one of the levels of action of Syniorage™: stimulation of a specific skin component, the small proteoglycan, syndecan-1.

Stimulation of syndecan-1 synthesis (*in vitro* test on human reconstructed skin)

Aim

To confirm the capacity of Acetyl Tetrapeptide-11 to stimulate the synthesis of syndecan-1, as already demonstrated on keratinocytes, by testing on human reconstructed skin.

Protocol

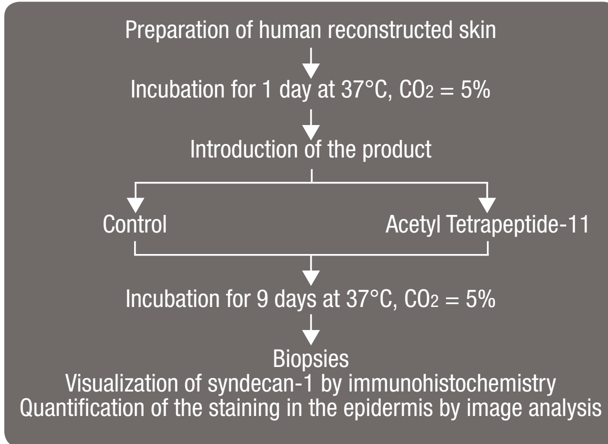


Fig. 9 - Protocol of evaluation of syndecan-1 synthesis by human reconstructed skin.

Results

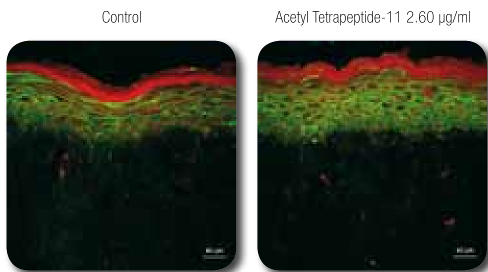
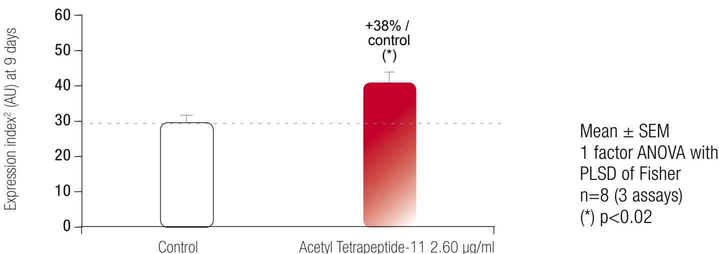


Fig. 10 - Stimulation of syndecan-1 synthesis by human reconstructed skin: visualization at 9 days (syndecan-1 in green).



Mean ± SEM
1 factor ANOVA with
PLSD of Fisher
n=8 (3 assays)
(*) $p<0.02$

[2] Number of stained pixels x fluorescence intensity in green channel/epidermal thickness in arbitrary unit (AU)

Fig. 11 - Stimulation of syndecan-1 synthesis by human reconstructed skin: quantification.

Conclusion

Acetyl Tetrapeptide-11 has clearly boosted the synthesis of syndecan-1 in this full thickness model, confirming the results obtained in the previous test on keratinocyte cultures and the targeted action of Syniorage™ on the small proteoglycan, syndecan-1.

Stimulation of the expression of collagen XVII gene (*in vitro* test on keratinocytes)

Aim

To evaluate the capacity of Acetyl Tetrapeptide-11 to stimulate the production of collagen XVII by human epidermal keratinocytes. The quantitative reverse transcriptase-polymerase chain reaction (qRT-PCR) for COL17A1 gene and the immunocytochemical visualization of collagen XVII protein were performed.

Protocol

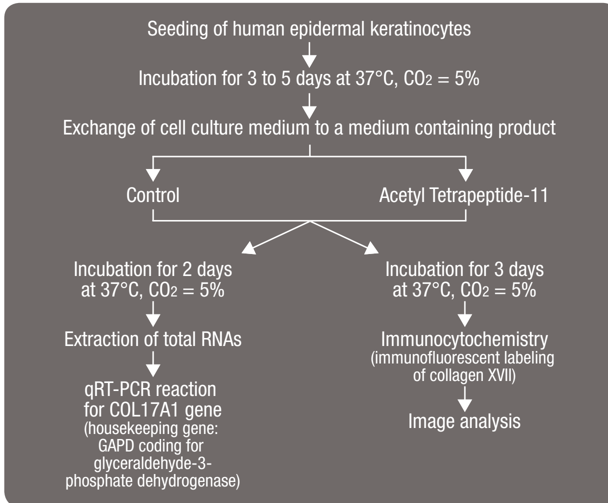


Fig. 12 - Protocol of evaluation of synthesis of collagen XVII at mRNA and protein levels.

Results

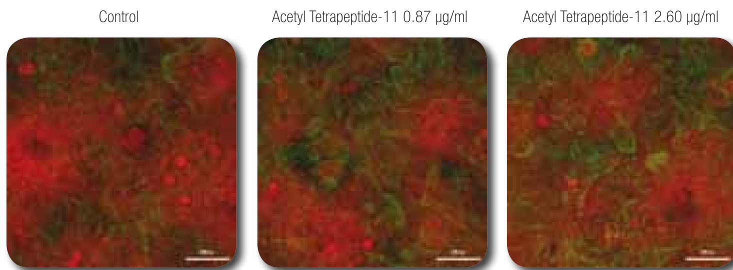
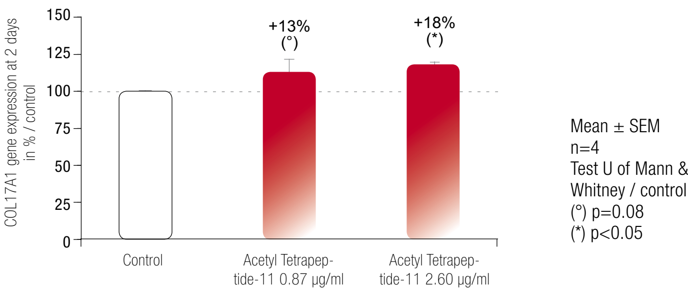


Fig. 13 - Stimulation of the synthesis of collagen XVII protein by human epidermal keratinocytes: visualization at 3 days.



Mean ± SEM
n=4
Test U of Mann & Whitney / control
(°) p=0.08
(*) p<0.05

Fig. 14 - Stimulation of the expression of collagen XVII COL17A1 gene by human epidermal keratinocytes: quantification.

Conclusion

Acetyl Tetrapeptide-11 has significantly increased the COL17A1 gene expression by human epidermal keratinocytes in culture. This result has been confirmed by visualizing the production of collagen XVII protein on cell culture.

Evaluation of the anti-aging effect (clinical test)

Aim

To evaluate, *in vivo*, the anti-aging effect of a cream with 1% Syniorage™ in comparison to placebo cream on human volunteers after 56 days of treatment (D56) (with check point at D28 (after 28 days of treatment)).

Method

The biomechanical properties of the skin were measured using a torquemeter DTM 310 on the face. The torquemeter is designed to measure the angular displacement of skin in response to torsional forces applied by the torque motor incorporated into the probe. The gap between the central rotating disk and the external stationary ring of the probe determines the depth of measurement into the skin. A gap of 1 mm was used for the characterization of the biomechanical behaviour of the superficial layers of epidermis[6].

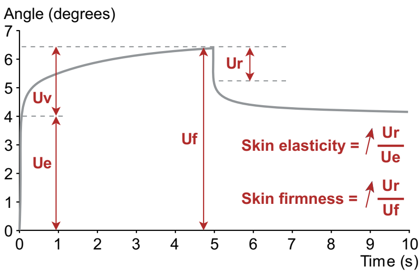


Fig. 15 - Curve of skin deformation obtained with a torquemeter.

The following parameters were measured:

- immediate extensibility Ue,
- maximal extensibility Uf,
- visco-elasticity Uv,
- elastic deformation rate Ur/Ue,
- elastic recovery rate Ur/Uf.

The Ur/Uf and Ur/Ue ratios were used to evaluate the antiaging efficacy. An increase in the Ur/Ue ratio corresponds to an improvement in skin elasticity. An increase in the Ur/Uf ratio corresponds to an improvement in skin firmness.

Protocol

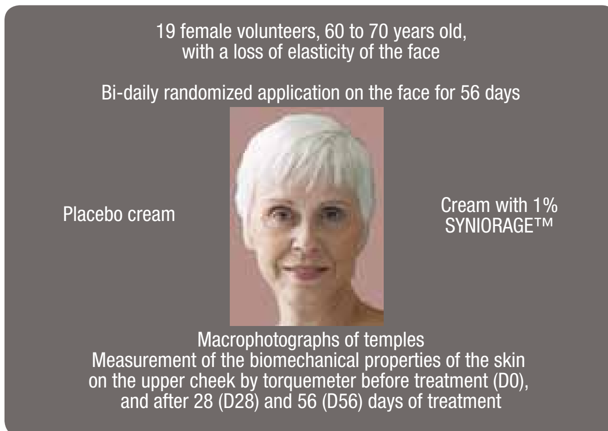


Fig. 16 - Protocol of the clinical evaluation of the anti-aging effect.

Results

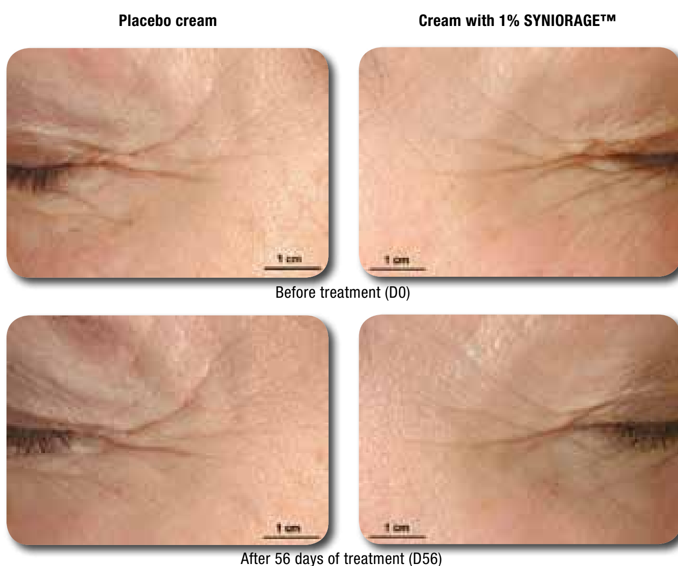


Fig. 17 - Evolution of cutaneous relief, *in vivo*, after treatment (D56) with the cream with 1% SYNIORAGE™ versus placebo cream.

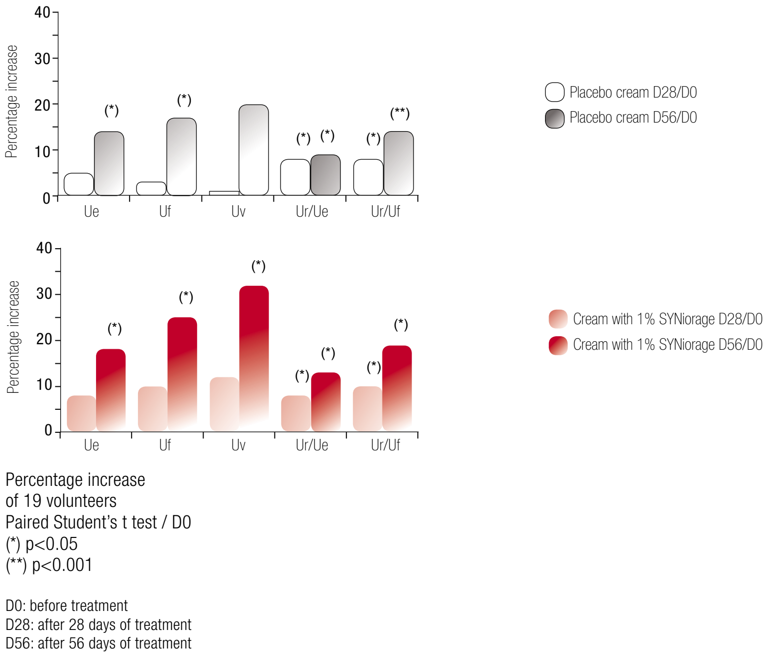


Fig. 18 - Effect of treatment on the biomechanical properties of the skin.

Conclusion

The significant increase of the biomechanical parameters of the superficial layers of the epidermis, *i.e.* firmness and elasticity, reflects an improvement of epidermal cohesion and consequently an anti-aging effect.

The cream with 1% SYNIORAGE™ has a 5 - 10% better effect than the placebo cream.

Skin texture was improved, skin relief was smoothed and skin radiance was increased after 56 days of treatment.

By increasing the production of syndecan-1, SYNIORAGE™ has allowed to increase skin elasticity and firmness, and thus to improve skin resistance. By stimulating the production of collagen XVII, SYNIORAGE™ allows to improve the cohesion of the different skin layers, for more uniform and thus more radiant skin.

General conclusion

There is a discrepancy between the spirit of seniors and the appearance of their skin. Whereas with age they acquire strength and serenity, their skin on the contrary becomes more fragile and blemished. By targeting 2 specific constituents of the epidermis responsible for its cohesion, syndecan-1 and collagen XVII, SYNIORAGE™ helps to reestablish the parallel between the life of seniors and the appearance of their skin: more resistant and radiant, it reflects their wisdom acquired by experience and their joy in life. For an optimal anti-age approach, it is recommended to use SYNIORAGE™, specific for the epidermis, in conjunction with DERMICAN™, which specifically targets aging of the dermis.

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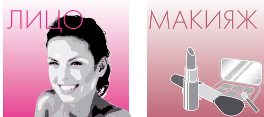


Патент N° WO 00/43417

RIGIN™

Пептид Pal-GQPR

Улучшает качество кожи всего за две недели

Действие:
Замедляет преждевременное старение. Повышает эластичность и тонус. Увлажняет, защищает и разглаживает кожу.

Описание:
Липопептид с последовательностью Palmitoyl-Gly-Gln-Pro-Arg, эфир в водно-гликолевом растворе

Свойства:
Регулирует синтез цитокинов (Интерлейкин 6), влияющих на многие признаки старения. Восстанавливает баланс цитокинов в зрелой коже.

Характеристика:
Rigin™ по последовательности аминокислот соответствует фрагменту иммуноглобулина G (иммунитет против инвазивных патогенов).

INCI Name:
Aqua – Glycerin – Steareth-20 – Palmitoyl Tetrapeptide 7*

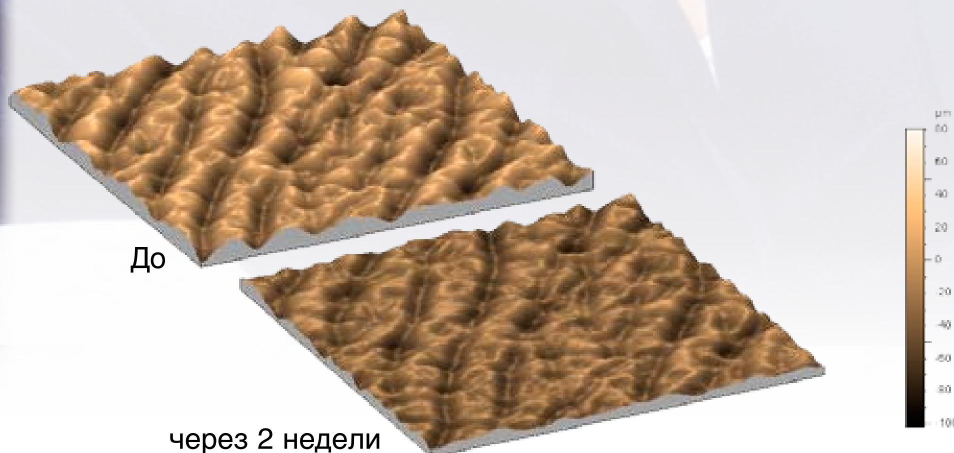
* изначально INCI name: Palmitoyl Tetrapeptide-3

Применение:
Продукты для ухода за кожей лица и шеи.

Введение в рецептуру:
Растворим в воде. Вводить при температуре 45°C или при комнатной температуре.

Рекомендуемый процент ввода:
3%

Значительное уменьшение (56%) числа глубоких морщин через 2 недели



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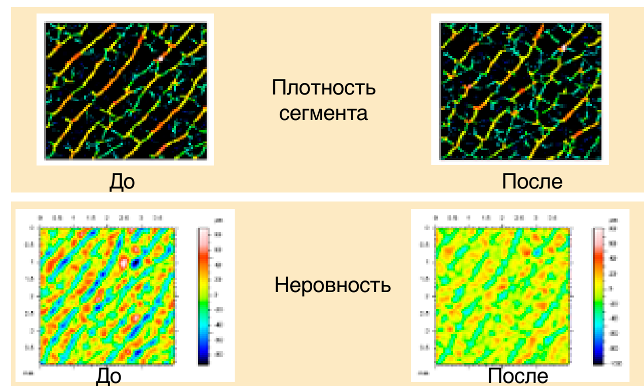
In vivo тесты

Дважды в день применение на области предплечья геля, содержащего 3% Rigin™ против плацебо в течение 14 дней.

Оценка разглаживания кожи – Анализ микрорельефа

Изучение методом анализа изображений

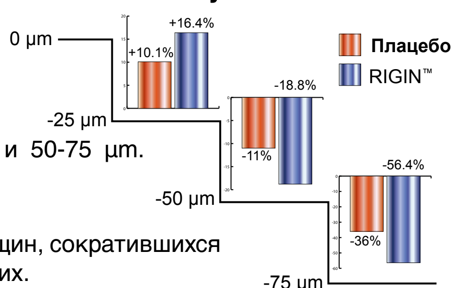
	Плацебо		Rigin™ 3%	
	T0	T15	T0	T15
Средняя изотропия (%) (n=15)	18,0±12,1	21,5±8,9	15,6±8,0	19,2±9,2
Отклонение (%)	+19,4		+23,3	
Значимость	Не значимо		p<0,05	
Средняя плотность сегмента (μm/cm²) (n=15)	0,079±0,019	0,086±0,019	0,079±0,02	0,092±0,022
Отклонение (%)	+9,5		+16,6	
Значимость	Не значимо		p<0,05	
Средняя неровность (μm) (n=15)	20,6±4,4	18,5±3,3	20,3±4,0	17,5±4,0
Отклонение (%)	-10,5		-14,2	
Значимость	Не значимо		p<0,05	

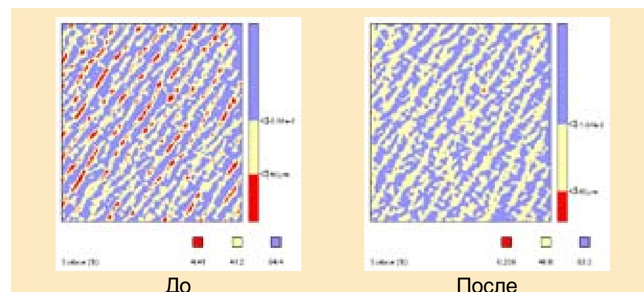


Распределение линий по глубине

Было выбрано три зоны глубины: 0-25 μm, 25-50 μm и 50-75 μm. 15 волонтеров.

Число глубоких морщин, сократившихся до уровня не глубоких.





Увлажнение

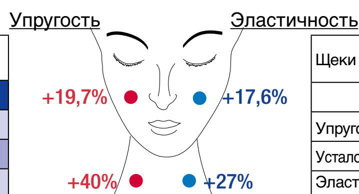
Измерения корнеометром Corneometer®

Увлажнение	Плацебо	Rigin™ 3%
Среднее значение (n=16)	-0,9±10	+24,1±18
Значимость	Не значимо	p<<0,0001

Упругость и эластичность

17 волонтеров. Дважды в день применяли на область щек и шеи крем, содержащий 3% Rigin™ против плацебо в течение 28 дней. Проводили измерения кутометром.

Шея	Изменения (%) T28/T0	
	Плацебо	Rigin™ 3%
Упругость	+22,4 p<0,05	+39,9 p<0,01
Усталость кожи	-14,0 p<0,01	-37,8 p<0,01
Эластичность	+8,1 Не значимо	+27,5 p<0,05



Щеки	Изменения (%) T28/T0	
	Плацебо	Rigin™ 3%
Упругость	+4,9 Не значимо	+19,7 p<0,01
Усталость кожи	-14,9 Не значимо	-40,0 p<0,01
Эластичность	+5,8 Не значимо	+17,6 p<0,01

In vitro Тесты

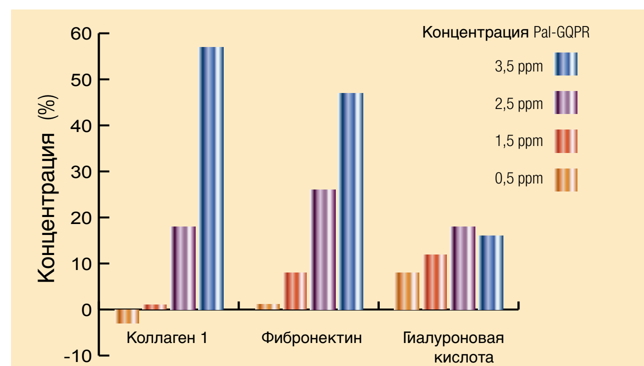
Стимулирование синтеза молекул матрикса

Пептид Pal-GQPR способен стимулировать синтез Коллагена I, Фибронектина и Гиалуроновой кислоты фибробластами дермы.

Регулирование уровня интерлейкинов

Тесты на культурах кератиноцитов, при помощи метода Elisa определение базального и УФ индуцированного уровня IL

	Положительный контроль	Rigin™ 3%
Базальный уровень IL6	-11%	-20%
IL6 индуцированный УФ	-34%	-37%
Базальный уровень IL8	-	-46%



- **Ежедневное применение Rigin™ 3% восстанавливает кожу за две недели, придает коже длительное увлажнение, разглаживает и выравнивает кожу. К концу первого месяца упругость и эластичность возрастают, и кожа лица и шеи становится более плотной.**
- **Rigin™ стимулирует синтез коллагена 1, фибронектина и гиалуроновой кислоты фибробластами.**
- **Rigin™ понижает уровень интерлейкинов в кератиноцитах.**

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