BASF
We create chemistry

Care Creations™

Nephoria™

The natural youth booster

by Beauty Creations
another Care Creations™ product group Inspired by Life

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SUMMARY FILE

Nephoria	**BC10044**
Origin - Description	Natural extract of rambutan leaves, titrated in corilagin, from a sustainable sourcing program
Regulatory data	
INCI	Maltodextrin (and) Nephelium Lappaceum Leaf Extract
China	Each component is listed in “Inventory of Existing Cosmetic Ingredient in China” (IECIC 2015). Nephelium Lappaceum Leaf Extract is listed as Nephelium Lappaceum Extract in IECIC 2015
CAS#	9050-36-6 ; 93165-68-5 / 999999-99-4
EINECS#	232-940-4 ; 296-955-8 / 310-127-6
Appearance	Powder
Preservative	None
Natural labels	Raw material conforms to COSMOS standard of natural and organic cosmetics
Naturalness content (ISO 16128)	100% from natural origin
Cosmetic use	
Properties	Stimulation of key dermal components, elastic and collagen I fibers Contributes to the functional organization of the extracellular matrix Contributes to increase dermal elasticity and firmness Anti-wrinkle
Applications	Performance skin care Anti-aging skin care Skin firming Organic formulation – natural cosmetics Eco-responsible face care formulations
Formulation data	
Concentration of use	0.1%
Incorporation method	Nephoria is dissolved at 20% w/w in water at room temperature and then incorporated during the final process below 30°C, or at room temperature for cold processing
Optimal temperature of use	15-30°C
Optimal pH	3-7
Patent family	Application filed

SUSTAINABLE UPCYCLING OF RAMBUTAN IN THE SERVICE OF BEAUTY

Responsible living is a daily challenge. Women and men want to give their skin special care to counter environmental impacts, but not to the detriment of the planet. Consumers are now searching for more ethical cosmetic products, which are as healthy for their skin as they are for the earth. Consequently, the cosmetic industry has taken up the trends of the demand of modern consumers and their growing environmental awareness to continue developing sustainable solutions. This industry expects more responsible cosmetic ingredients from suppliers who can ensure a reliable supply chain and social commitment, and who will not compromise on the level of effectiveness. Therefore, we have embedded sustainability in our corporate purpose: “We create chemistry for a sustainable future.”

This is the starting point of our work. Capitalizing on our experience acquired with a previous Argan program, we have discovered a plant and built a new specific supply chain in cooperation with a long-standing local partner in Vietnam. We have identified rambutan, also called *Nephelium lappaceum*, a well-known tree in Asia, that grows in the humid tropics. Out of the fruit itself, we have found that other by-products of the rambutan plant possess interesting properties for our skin’s health and beauty (Figure 1).

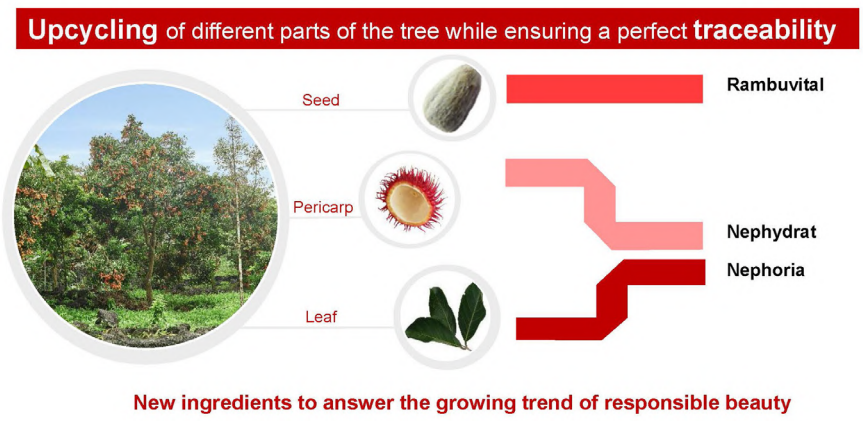


Figure 1 - Upcycled active ingredients from rambutan tree.

Nephoria, our unique active ingredient extracted from the evergreen leaves of the rambutan tree, has been created to help us to preserve the capital of our skin's youthfulness while having a positive impact on the planet through our skin care routine.

COLLAGEN, ELASTIN AND SKIN AGING

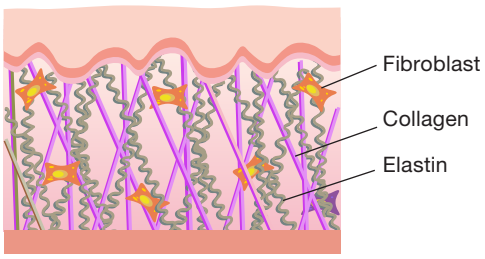


Figure 2 - Network of interlaced elastic and collagen fibers in the dermis.

One side effect of the aging process is the loss of collagen and elastin in the skin. Collagen I (COL I) and elastin (ELN) are both important proteins responsible for keeping the skin aging well and free of sagging and wrinkles (Figure 2) and to have it age well. As these proteins are affected by aging (Quan and Fisher, 2015), there are several ways of increasing their content in the skin, such as the stimulation of their synthesis and/or the inhibition of their degradation. Not only the quantity but also the quality of the 3D-structure of the collagen and elastic fibers are important for dermal architecture. Stimulating collagen I and elastin synthesis while keeping proper fiber assembly, is the anti-aging recipe to reduce and prevent the appearance of wrinkles and aging signs.

Collagen I: a complex 3D assembly for perfect functionality; CCN1: a negative regulator of its homeostasis

Dermal collagen fiber bundles are the major structural elements in the dermis and are responsible for skin firmness. The dermis contains predominantly type I collagen, responsible for keeping skin firm, plump, smooth and young-looking.

Collagen prolyl 4-hydroxylase plays a central role in the synthesis of collagens. It catalyzes the formation of 4-hydroxyprolines through hydroxylation of the proline residues in collagen which are essential for the formation and stabilization of the collagen triple helical domain (Myllyharju, 2003; Zou *et al.* 2017).

Prolyl 4-hydroxylase is a tetramer composed of two identical alpha subunits and two beta subunits. Prolyl 4-hydroxylase subunits alpha 1 (P4HA1) and alpha 2 (P4HA2) provide the major part of the catalytic site of the active enzyme.

Reduced synthesis of collagen I is characteristic of chronologically aged skin. Consequently, 3D organization and functionality are progressively deteriorated. The collagen network loses its mechanical strength, the skin of the face sags and wrinkles appear (Varani *et al.* 2006).

Moreover, in chronologically aged skin *in vivo*, an elevated CCN1 expression (cysteine-rich protein 61, corresponding to the gene CYR61) was reported, dramatically increasing this phenomenon (Quan *et al.* 2006). CCN1 modulates collagen I homeostasis by down-regulating its production and promoting its degradation via the up-regulation of collagenases such as matrix metalloproteinases-1.

Elevated CCN1 content is involved in collagen loss, which is observed in aged human skin.

Elastin and its multiple partners in a functional architecture

Although the extracellular matrix of the dermis is composed primarily of collagen fibers, the 3 or 4% content of elastic fibers are just as important. Elastic fibers, after being straightened by stretching forces, use their property of elasticity to return the tissue to its normal position when forces are no longer present (Langton *et al.* 2010).

Mature elastic fibers synthesis is complex and involves multiple components (Baldwin *et al.* 2013).

Elastin is synthesized as soluble tropoelastin by fibroblasts and acquires its physicochemical properties (insolubility, elasticity) after its cross-linking by enzymes of the lysyl oxidase family (LOX and LOXL) and its deposit on fibrillin-rich microfibrils in the extracellular matrix to form the mature elastic fibers (Figure 3).

To summarize, mature elastic fiber organization could be briefly described in two key phases, which occur outside of the cell at the same time: a tropoelastin coacervation step (a crucial step before elastic fiber assembly) and an assembly step onto the microfibrillar network.

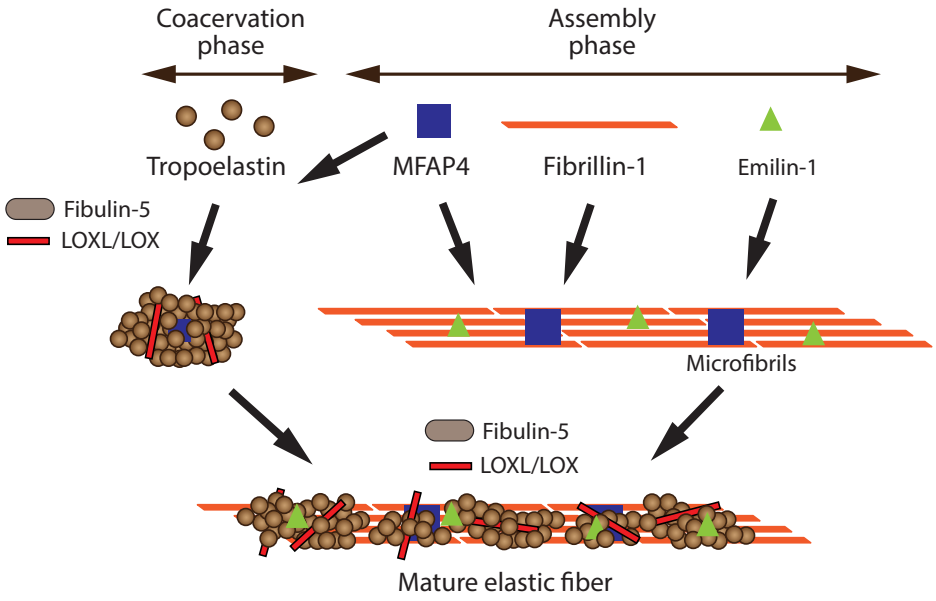


Figure 3 - Schematic representation of the formation of mature elastic fibers (according to Kasamatsu *et al.* 2011).

Among the main partners involved in mature elastic fiber formation, some are particularly relevant:

- Fibulin-5 (FBLN5) contributes to the formation of elastic fibers in the 2 phases (Figure 3). During coacervation, it facilitates the cross-linking of tropoelastin by tethering LOXL enzymes (Hirai *et al.* 2007). Fibulin-5 also inhibits excessive maturation of tropoelastin coacervates thereby allowing for the integration of micro-assemblies of tropoelastin into the microfibrillar scaffold (Cirulis *et al.* 2008, Choi *et al.* 2009). In addition, as shown in Figure 4, Fibulin-5 contributes to the formation of mature elastic fibers by binding to structural components including tropoelastin and fibrillin-1, and by helping cross-linking enzymes (LOX/LOXL), aiding elastic fiber assembly (Yanagisawa *et al.* 2009). Finally, FBLN5 content in the reticular dermis was described as decreasing with age (Kadoya *et al.* 2005).

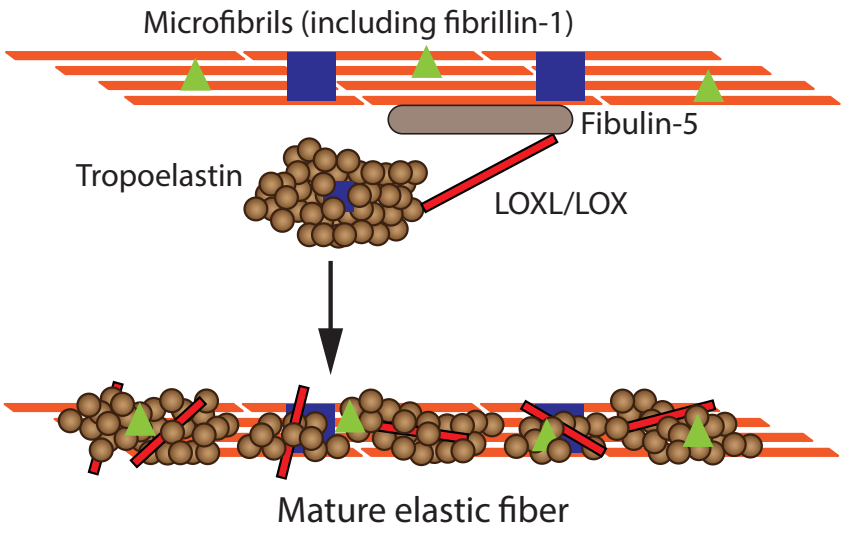


Figure 4 - LOXL binds to a specific domain of fibulin-5 to activate tropoelastin. A mature elastic fiber is then formed by covalent cross-linking of tropoelastin (according to Northington, 2011).

- Microfibrillar-associated protein 4 (MFAP4) is involved in the 2 phases of elastic fiber formation (Figure 3). MFAP4 was found as a tropoelastin binding protein and promoting tropoelastin coacervation (Pilecki *et al.* 2016) which is a crucial step before elastic fiber assembly. Additionally, MFAP4 interacts with fibrillin-1, contributing to the development of microfibrils involved in proper elastic fiber organization (Kasamatsu *et al.* 2011). These results show that MFAP4 is an important elastic fiber component.
- Elastin microfibril interface–located protein 1 (EMILIN-1) plays a role in the assembly phase by aiding the fibrillin-microfibril fibers to be more ordered (Figure 3) (Randell *et al.* 2017). Little is known about the exact function of EMILIN-1. However, this protein seems to be important as it is involved into microfibril strengthening and its deficiency leads to serious skin disorders (Schiavinato *et al.* 2006).

Aged skin has an atrophied extracellular matrix with a reduced amount of mature elastic fibers (Kadoya *et al.* 2005). In addition, as 3D architecture is lost because of elastic fiber fragmentation, a reduction in skin suppleness and elasticity is observed (Bonta S, 2013).

RETINOL-LIKE EFFICACY: GETTING INSPIRATION FROM RETINOL, WHILE GETTING RID OF ITS DRAWBACKS

Retinol is a well-known molecule, widely used in the cosmetic field for its anti-aging properties.

This molecule was demonstrated as enhancing epidermal proliferation, dermal collagen production and also elastin production and assembly, particularly through tropoelastin and fibrillin-1 stimulation (Rossetti *et al.* 2010). In addition, retinol significantly reduced elevated CCN1 concentration in aged skin (Quan *et al.* 2011). This suggests that the mechanism by which retinol improves collagen homeostasis in aged skin involves a decrease of CCN1 expression.

Although retinol shows promise in the treatment of skin aging, irritant reactions such as burning, scaling or dermatitis limit its use in cosmetics (Mukherjee *et al.* 2006). Moreover, its stability depends on environmental factors such as temperature, oxygen and light (Ji and Choi, 2009).

Developing a natural active ingredient with some pathways similar to retinol (elastin and collagen stimulation, CCN1 inhibition) without its drawbacks (stability, tolerability) is a target for visible anti-aging actions.

Nephoria

A sustainable ingredient for a rejuvenated skin

Description of the plant

Family: Sapindaceae

Species: *Nephelium lappaceum* L.

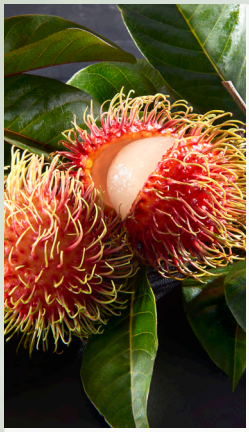
Common name: the name "rambutan" comes from the Malay word “rambut” meaning "hair", a reference to the numerous hairy protuberances on the fruit. In Vietnam, rambutan is called chôm chôm (meaning "messy hair").

Description: *Nephelium lappaceum* is an evergreen tree that reaches 12 to 20 meters high in nature and 4 to 12 meters when cultivated clonaly. Its main trunk has an open crown of large branches. Its bark is slightly rough and greyish or red. The hairy fruit is mainly red in color, but may also can be also yellow, orange or pink. The tree has a life spend of up to 100 years.

Distribution: its origin, possibly the Malay Archipelago, is undeterminable because wild growth from cultivation has blurred the contours of its primary distribution. It was then disseminated to the South Asian countries of Vietnam, Thailand and China. Nowadays, the extend of rambutan cultivation ranges in South China to the Philippines and is found in tropical areas of South America.

Habitat: Rambutan trees grow in humid tropics, especially in elevation of up to 700 meters, with temperatures comprised between 22 and 30°C, in areas exposed to the sun and subjected to heavy rains (between 2000 and 5000 mm/year).

Bibliography available upon request.



Nephelium lappaceum: traditional and modern uses

Rambutan, whose fruit is edible, is already known for its significant benefits to health and is widely used in Asia (Hernandez-Hernandez *et al.* 2019).

The fruits have long been used to quell dysentery while the peels (pericarps) contain a variety of beneficial compounds that demonstrate antioxidant and anti-cancer properties. The leaves are used to treat headaches and the bark is used for tongue diseases.

The sweet-tasting fruit is consumed fresh or canned. It is appreciated for its refreshing flavor and exotic appearance. Naturally highly rich in iron, vitamin C, fibers and antioxidants, rambutan is also reported to have some benefits similar to superfruits. For example, it is reported to diminish fat, to act against free radicals, to boost immunity, to prevent diseases, and so on.

The responsible rambutan program: upcycling for greater social impact and sustainable supply chain

Origin: Vietnam

Part used: Leaf, for Nephoria
Other parts, pericarp (peel) and seed, are also used for other active ingredients, Nephydrat and Rambuvital (scientific brochures also available).

Variety: Java

Supply and cultivation: in 2015, a specific supply chain was set up in cooperation with our long-term supplier in Vietnam. Rambutan trees are cultivated in organic-certified gardens in Southern Vietnam. Our supplier and the network of farmers involved in production promote sustainable agricultural practices, respecting the local ecosystem and improving working conditions including safety higher incomes for workers and specific on-the-job training.

Harvesting and processing: the main harvest of rambutan occurs from July to September. A tree produces up to 200 kg of fruit per year. Fruit is gathered in clusters at maturity and leaves are removed for later use. The premium quality fruit is then processed according to a specific technic know-how.

Seeds, pericarps and leaves are then processed to produce active ingredients for use in cosmetics.

Processing and Composition

Nephoria is obtained through a nature-friendly extraction process using water as the sole solvent. Following a first step of aqueous extraction from the crushed leaves, the unextracted insoluble matter is removed and the product is concentrated and standardized to obtain Nephoria as a preservative-free powder with maltodextrin (10-30% *Nephelium lappaceum* leaf extract; 70-90% maltodextrin), titrated in corilagin (0.7-1.3%).

**No involvement of animal genes or animal-derived substances; unlikely cross-contamination from animal substances; no animal testing has been carried out by or on behalf of BASF on the ingredients of the product after 11th March 2009 and/or after the extended deadline 11th March 2013 for the purposes of the Cosmetic Regulation (EU) 1223/2009 (statement available upon request).

Nephelium lappaceum leaf extract, i.e. the plant matter, contains mostly carbohydrates, proteins and polyphenols. Among the polyphenols, the main compound is corilagin (Figure 5A and 5B) belonging to the ellagitannin family (Li *et al.* 2018). This phytochemical compound was proven to stimulate the synthesis of collagen I (Figure 6) as Nephoria does.

Our process concentrates the active corilagin molecule naturally present in rambutan leaves, around 15-fold, to obtain the titrated Nephoria (corilagin: 0.7-1.3%).

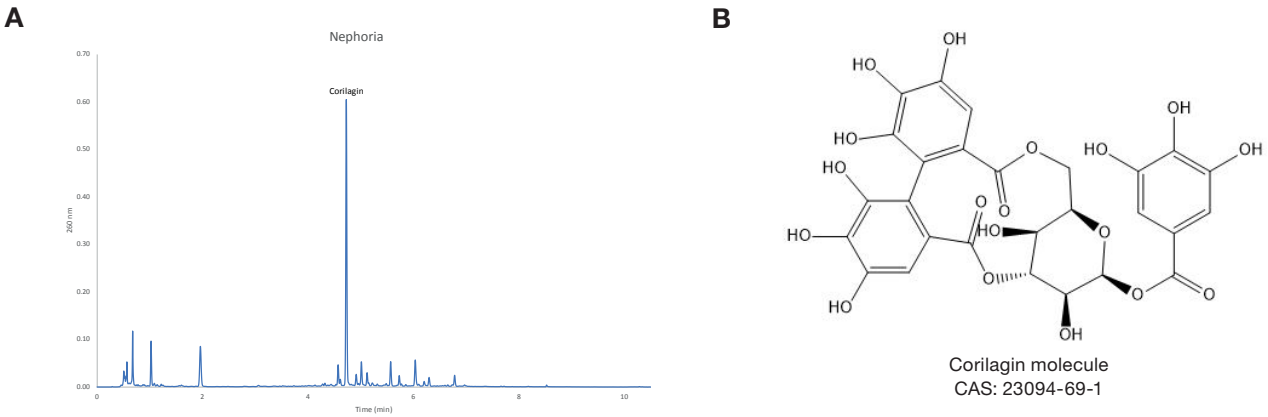


Figure 5 - **A** - Example of HPLC-PDA typical chromatogram profile (260 nm). **B** - Molecular structure of corilagin.

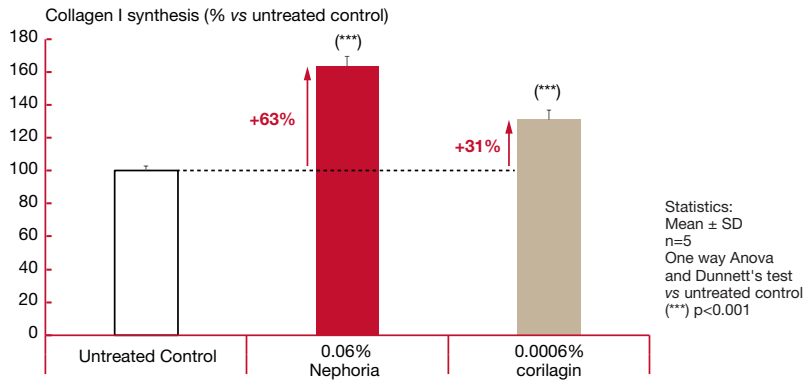


Figure 6 - Effect of Nephoria and its biomarker corilagin on collagen I synthesis by human fibroblasts. The dose of corilagin corresponds to its content in the tested sample of Nephoria. Detailed material & methods in the *in vitro* test part (Delfia method, page 16).

Safety / tolerability of the product

Nephoria was tested to ensure its safety under the recommended conditions of use. Nephoria does not irritate the eyes nor skin and no indication of skin sensitization was observed.

Description

Nephoria is a natural preservative-free extract of rambutan leaves, titrated in corilagin, from a sustainable sourcing program.

INCI name: Maltodextrin (and) Nephelium Lappaceum Leaf Extract

Naturalness content (according to ISO 16128): 100% from natural origin

Dose of use: 0.1%

China IECIC listed

Approved by ECOCERT RAW MATERIAL COSMOS APPROVED

Vegan Friendly**

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Example: illustration of a commercial sample of Nephoria, with an emulsion and hydrogel containing 0.1%

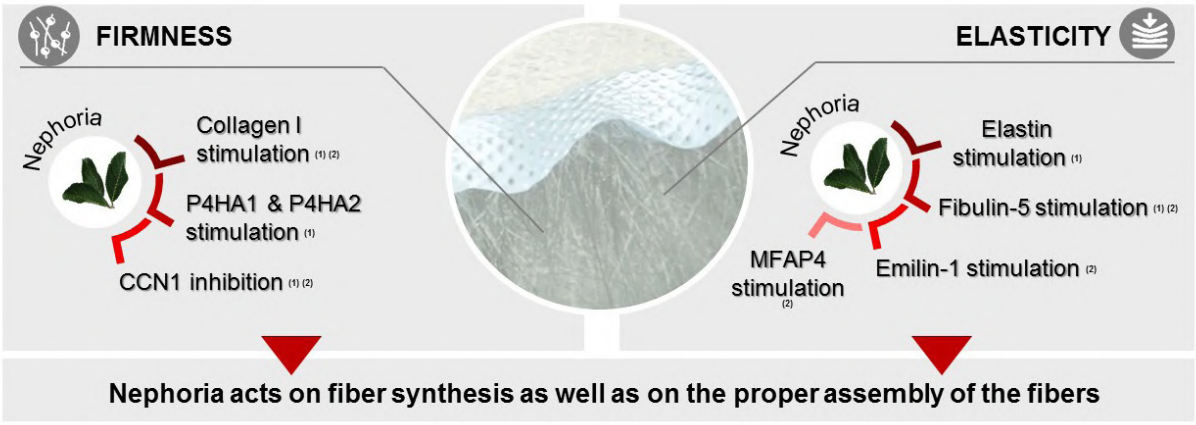
**No involvement of animal genes or animal-derived substances; unlikely cross-contamination from animal substances; no animal testing has been carried out by or on behalf of BASF on the ingredients of the product after 11th March 2009 and/or after the extended deadline 11th March 2013 for the purposes of the Cosmetic Regulation (EU) 1223/2009 (statement available upon request).

DEMONSTRATED EFFICACY

Nephoria has been proven to increase skin elasticity and to reduce wrinkles, two crucial criteria that help us age well.

Proven *in vitro* performance

Evaluated both on gene and protein level, Nephoria proved its efficacy *in vitro* to stimulate both elasticity and firmness targets (Figure 7).



(1) Genomics
(2) Proteomics

Figure 7 - Summary of firmness and elasticity targets stimulated by Nephoria (1) Genomic analysis (2) Proteomic analysis.

Nephoria's efficacy was then confirmed on 4D bioprinted skins, showing a significant increase of extracellular collagen fibers density.

Proven *in vivo* performance

In vivo, Nephoria treatment significantly decreased peaks and valleys of crow's feet, while improving skin elasticity.
Nephoria consequently reduces these signs of skin aging.

EFFICACY

DERMAL-MATRIX RELATED GENE EXPRESSION PROFILE

in vitro

OBJECTIVE

Gene expression analysis by PCR arrays is considered to be one of the most effective and cost-efficient methods for studying a panel of targeted genes.
A particular PCR array focused on 88 genes involved in the dermal aging process was specifically designed. This method allowed us to quickly draft a initial "profile" of activity and to identify the main modulated metabolic pathways (Figure 8). Then, the expression of each modulated gene was confirmed by a specific qRT-PCR assay.

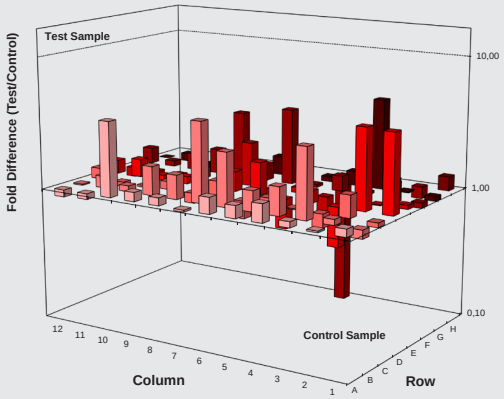
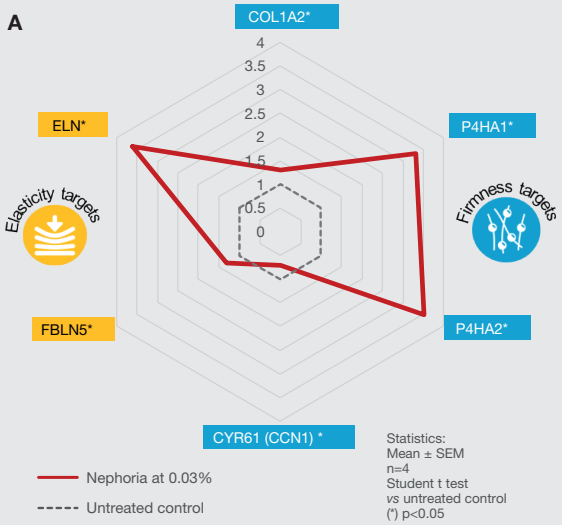


Figure 8 - Illustrative graph showing Nephoria PCR array results on 88 genes. Each modulated gene was subsequently confirmed by a qRT-PCR assay.

RESULTS & DISCUSSION

Figures 9A&B show that Nephoria significantly modulated the expression of many genes involved in skin firmness and elasticity. We noticed up-regulations of COL1A2 gene coding for the major structural protein type I Collagen (x1.3), P4HA1 (x3.3) and P4HA2 (x3.5), two genes encoding subunits of Prolyl-4 Hydroxylase, an essential enzyme for the proper three-dimensional folding of the collagen triple helix. In addition, CYR61 (CCN1) gene expression was down-regulated (x0.7), limiting the signaling inducing the collagen degradation process.
Furthermore, Nephoria significantly stimulated the expression of ELN coding for elastin (x3.6) and FBLN5 coding for fibulin-5 (x1.3), key components involved in proper elastic fiber synthesis and assembly.

A



B

Symbol	Gene Name	Function
COL1A2	Collagen Type I Alpha 2 Chain	Component of dermal collagen fibers
P4HA1	Prolyl 4-Hydroxylase Subunit Alpha 1	Hydroxylation of collagen alpha-chain prolines
P4HA2	Prolyl 4-Hydroxylase Subunit Alpha 2	Hydroxylation of collagen alpha-chain prolines
CYR61 (CCN1)	Cystein rich	Down-regulator of collagen homeostasis
ELN	Elastin	Component of dermal elastic fibers
FBLN5	Fibulin-5	Component of dermal elastic fibers

Figure 9 - **A** - Spider graph showing the effect of Nephoria at 0.03% on the expression of elasticity and firmness markers. The *in vitro* gene expression ratio between Nephoria treatment and the untreated control are represented by the continuous line. The dashed line is the baseline representing no expression modulation (ratio=1). Genes were first screened by qPCR-array test (88 genes evaluated, results not shown) and their modulations were then confirmed by dedicated qRT-PCR assays. Only the significantly modulated genes are represented on the graph, (*) $p < 0.05$. **B** - Name and function of the significantly modulated genes evaluated by PCR array method.

CONCLUSION

Nephoria acts on the *in vitro* expression of genes involved in both elasticity and firmness, helping the skin fight against wrinkles and look younger.

MATERIALS&METHODS

Cell culture

qPCR-array test: Four different human primary fibroblasts strains were obtained from surgical skin biopsies from women donors (between 42 and 59 years old). Fibroblasts with passages between 5 and 9 were cultured in Dulbecco's modification of Eagle medium (DMEM) with fetal calf serum (FCS) and incubated at 37°C with 5% CO_2.

Dedicated qRT-PCR assays: Fibroblasts were isolated from 4 abdominal skin samples of women donors (aged between 42 and 60 years old) obtained after aesthetic surgery and grown at 37°C, 5% CO_2 in a complete medium (DMEM/Ham F-12 (3/1) + FCS 10%) until post-confluence.

Treatment

After confluence, cells were treated with *Nephelium lappaceum* leaf extract at 0.006% - dose equivalent to Nephoria at 0.03% - and incubated for 24 or 48 hours at 37°C with 5% CO_2. The control condition corresponds to the culture of fibroblasts without product added to the basal culture medium. Absence of cytotoxicity induced by the treatment was verified using the blue trypan method.

Total RNAs from fibroblast cultures were extracted with NucleoSpin miRNA kit (Macherey-Nagel), according to the instructions in the manual. Quantification and quality control of total RNAs were performed by measurement of optical densities at 260 and 280 nm.

Identification of genes modulated by Nephoria and validation of expression variation

For the identification of genes whose expression is modulated by Nephoria treatment, we designed a PCR-array dedicated to 88 strategic genes involved in dermal extra-cellular matrix quality (Prime PCR Custom Plate 384 Wells-96 genes, Bio-Rad). The same quantity of RNA extracted from 4 treated fibroblast cultures was pooled and used for PCR-array analysis. Reverse transcriptions and quantitative PCRs were performed using commercial kits (iScript Advanced cDNA Synthesis kit and SsoAdvanced Universal SYBR Green Supermix, Biorad) and (SsoAdvanced Universal SYBR Green Supermix, Bio-Rad). The method of $\Delta\Delta$Ct was used to calculate the expression of each of the 88 targeted genes under each analyzed condition. Finally, we selected a panel of genes whose expression is modulated by the Nephoria treatment and decided to validate these gene expression modulations by dedicated quantitative PCR methods.

To validate the identified gene modulations, specific qRT-PCR analyses focused on the selected target genes were performed on each fibroblast culture. Reverse transcriptions were performed on 0,1 to 1 µg of RNAs, according to the relative expression of each target gene, in 20 µl at the final mix (Thermoscript RT-PCR System kit, Invitrogen). Quantitative PCRs were performed on 2 µl of RT mix diluted to 1/2 in 10 µl final reaction mix, according to instruction in the manual (LC480 SYBR Green I Master system, Roche) in a LC480™ thermocycler (Roche).

Analysis of housekeeping genes (ACTB: Actin B; SDHA: succinate dehydrogenase; RPL13A: Ribosomal Protein L13A; GAPDH: Glyceraldehyde 3-phosphate dehydrogenase) was performed in parallel with target genes. Each analysis was performed twice. Specificity of amplification was validated after qPCR by fusion curve analysis and the Ct means used for calculation. The most conserved combination of housekeeping genes was used to calculate the relative expression of each target gene, using the $\Delta\Delta$Ct method.

Results and statistics

Results were expressed as a percentage of target gene expression in the Nephoria treated condition compared to the untreated condition for each culture (n=4) and expressed as the mean ± standard error of the mean. The statistical analysis was carried out via the Student t test versus the untreated condition. The threshold of significance was set to 5% ($p<0.05$).

EFFICACY

DERMAL PROTEIN PROFILE BY MULTI-TARGET WESTERN BLOT ASSAY

in vitro

OBJECTIVE

A fully automated western blot method overcomes the obstacles related to reproducibility, sensitivity, quantifiability, and speed seen in traditional western blotting.

A multi-target western blot assay focused on proteins involved in skin elasticity and firmness was specifically designed. This method allowed us both to confirm the protein expression of genes previously selected and to discover new targets stimulated by our active ingredient. For collagen I synthesis, the deposited collagen was quantified (Delfia method).

For this purpose, normal human fibroblasts were grown *in vitro* in the presence or absence of Nephoria and a protein expression profile on these dermal targets was established.

RESULTS & DISCUSSION

Figure 10 shows the effects of Nephoria on firmness targets. We confirmed that Nephoria was able to significantly increase protein synthesis of collagen I in a dose-dependent manner up to 63% at 0.06% (Figure 10A). In addition, CCN1 synthesis significantly decreased up to -48% at 0.04% (Figure 10B).

These results suggested that Nephoria stimulated collagen I synthesis and positively regulated its homeostasis by the inhibition of CCN1 synthesis.

As shown in figure 11, Nephoria stimulated the synthesis of key partners involved in elastic fiber formation. Fibulin-5, a key component involved in tropoelastin and elastic fiber assembly, was significantly stimulated up to 82% at 0.04% (Figure 11A). Emilin-1 and MFAP4, two ligands of microfibrils involved in proper elastic fiber organization, were respectively stimulated up to 267% and 27% at 0.01% (Figure 11B &C).

The significant increase in Fibulin-5, Emilin-1 and MFAP4 synthesis suggests that Nephoria favored the elastic fiber assembly and consequently a strong elastic network.

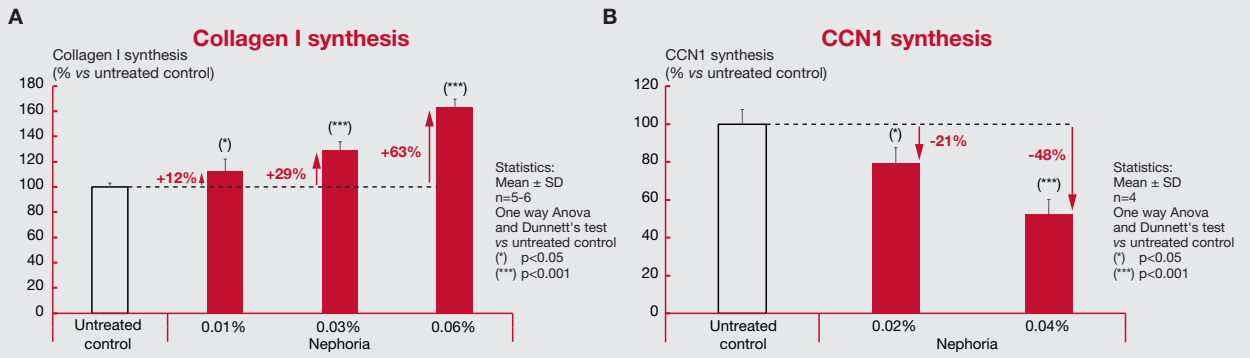


Figure 10 - Effect of Nephoria on the protein expression of firmness targets. **A** - Collagen I synthesis. **B** - CCN1 synthesis.

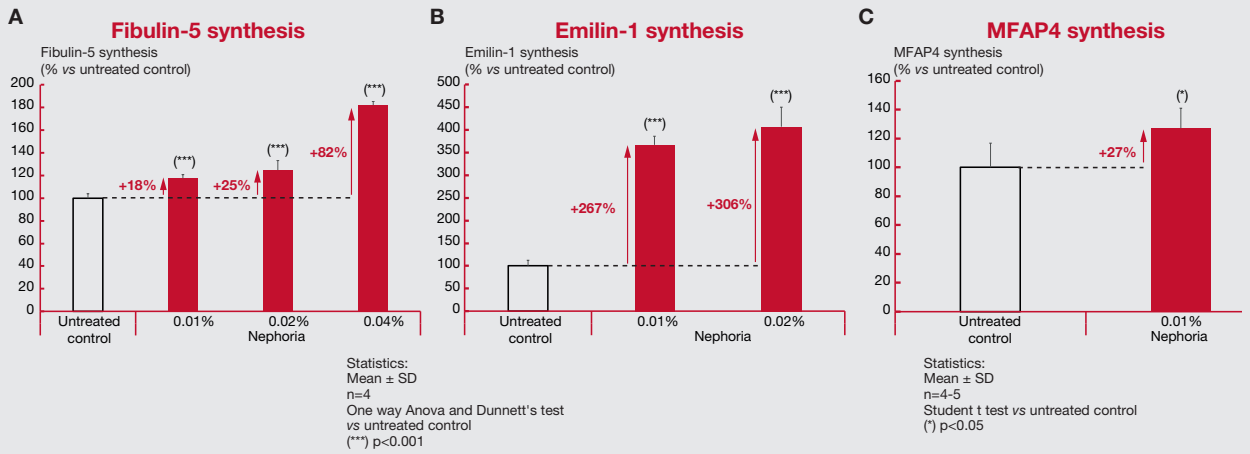


Figure 11 - Effect of Nephoria on the protein expression of elasticity targets. **A** - Fibulin-5 synthesis. **B** - Emilin-1 synthesis. **C** - MFAP4 synthesis.

CONCLUSION

At the protein level, Nephoria stimulates *in vitro* both firmness and elasticity-related targets, two important criteria which are dramatically impacted during the skin aging process.

MATERIALS&METHODS

Cell culture

Normal human fibroblasts (woman 19 years old for collagen dosage and 34 years old for CCN1, Fibulin-5, MFAP4, Emilin-1 dosages) were cultured in a defined medium (Fibroblast Growth Medium, FGM) for 48 hours in the presence or absence of different final concentrations of *Nephelium lappaceum* leaf extract at a dose equivalent to Nephoria from 0.01% up to 0.06%.

Western blot on dermal targets (CCN1, MFAP4, Emilin-1 and Fibulin-5)

After treatment, culture media were recovered to perform a western blot on CCN1, MFAP4 and Emilin-1 and the cells were harvested and lysed with a specific lysis buffer to evaluate Fibulin-5 content. Protein concentration was determined by BCA assay and then the samples were kept frozen at -80°C until use. All the samples were adjusted to the same protein concentration to deposit the same quantities in each capillary. A biotinylated molecular weight ladder, streptavidin-HRP, DTT, molecular weight fluorescence standards, luminol-S, hydrogen peroxide, sample buffer, running buffer, stacking matrix, separation matrix, wash buffer, and matrix removal buffer were purchased from ProteinSimple (Santa Clara, CA, USA). Antibody diluent, goat-anti rabbit secondary antibody, and goat-anti mouse secondary antibody were also purchased from ProteinSimple. The capillaries were obtained from ProteinSimple containing a proprietary UV-activated chemical linked coating. Target proteins were identified by a capillary electrophoresis-based protein analysis system (ProteinSimple Sally Sue Instrument, ProteinSimple, San Jose, California, USA) using primary antibodies and immunoprobed using a horseradish peroxidase-conjugated secondary antibody and chemiluminescent substrate. The resulting chemiluminescent signal was detected and quantified by Compass Software version 2.7.1 (ProteinSimple).

Delfia method (collagen I dosage)

Following incubation with the active for 48 hr, the medium (Complete FGM) was discarded and the dedicated lysis solution was added onto the monolayers. This solution allows the cell membranes to be disrupted without solubilizing the deposited matrix. The cell lysates obtained were recovered for DNA assay (Life Technologies SAS, Saint Aubin, France). In parallel, a PBS/BSA saturation solution (Perkin Elmer, Courtaboeuf, France) was added onto the deposited matrix before reaction with the primary anti-collagen I antibody (Interchim/ Acris, Montluçon, France, LH0284/R1038). After rinsing in PBS, the Europium-conjugated secondary antibody (Perkin Elmer) was added. Finally, a specific enhancement solution (Perkin Elmer) was added. Fluorescence intensity was read (λexc. 340 nm / λem. 615 nm) using an EnVisionλ multilabel plate reader (Perkin Elmer). All data are normalized to DNA. Percentage of stimulation is related to the untreated control.

Results and statistics

The results are expressed in percentage, as the mean ± standard deviation (SD) compared to the untreated control standardized to 100%. Each condition was carried out n=4-6. Statistical analysis versus the untreated control was done after normal distribution comparison of the values (Shapiro-Wilk test) following Sigmaplot® software recommendations (Systat Software Inv. USA). The threshold of significance was set to 5% ($p<0.05$).

EFFICACY

IMPROVEMENT OF THE EXTRACELLULAR MATRIX NETWORK BY NEPHORIA ON 4D BIOPRINTED SKIN

in vitro

OBJECTIVE

3D bioprinted skin provides a fully automated and advanced platform that facilitates the simultaneous and highly specific deposition of multiple types of skin cells (keratinocytes, fibroblasts etc…), a process that is lacking in conventional skin tissue-engineering (Ng WL *et al.* 2016). Therefore, "4D bioprinting" has emerged recently, where "time" is integrated with 3D bioprinting as the fourth dimension, and the printed objects can change their shapes or functionalities when an external stimulus is imposed or when cell fusion or postprinting self-assembly occurs (Gao B *et al.* 2016).

The aim of the study was to evaluate the effect of Nephoria on the extracellular matrix network in 4D bioprinted skin (Cadau *et al.* 2017).

Laser Assisted Bioprinting combined with innovative second harmonic generation (SHG) microscopy methods were associated respectively to produce skin equivalents in less than 3 weeks and to provide advanced 3D-structural information on the fibrillar skin network with Nephoria treatment.

RESULTS & DISCUSSION

In this study, we demonstrated that the quality of the dermis treated with Nephoria was dramatically improved (Figure 12). The network of neosynthesized collagen fibers evidenced by SHG microscopy is denser and more intense in the dermis treated with Nephoria (Figure 12B and 12D) compared with the untreated control (Figure 12A and 12C). In the untreated condition, printed collagen is defined as light grey layers one over the others. Neo-synthetized collagen followed those layers all along and appeared as whiter lines. In the samples treated with Nephoria, any collagen layers are visible due to high collagen neo-synthesis. We observed newly synthetized homogeneous collagen throughout the dermis.

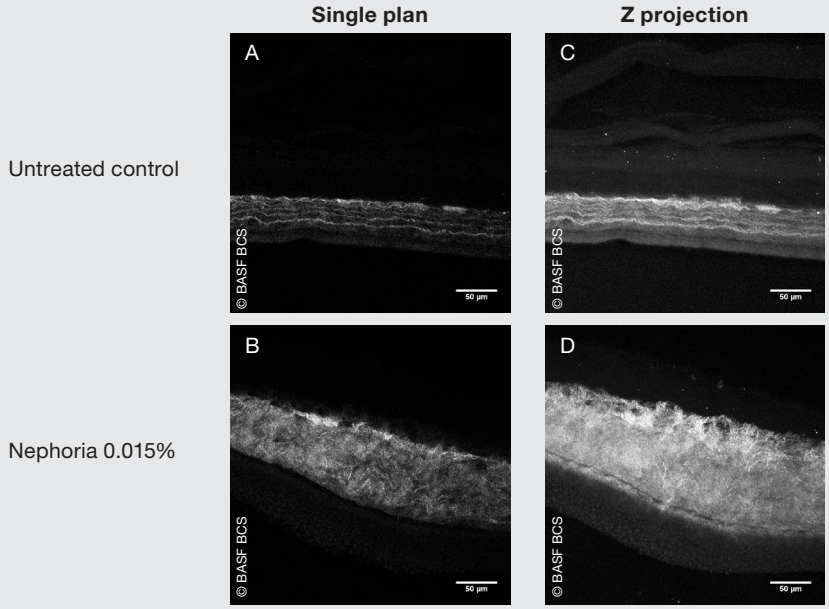


Figure 12 - Visualization by second harmonic generation (SHG) of the effect of Nephoria at 0.015% (B) and (D) versus control (A) and (C) on the collagen network in 4D bioprinted skins. Collagen fibers were visualized in grey levels, scale bar: 50 µm. (A) and (B) images were obtained from a single plan (C) and (D) images were obtained from a 3D stack acquisition of a depth of 30 layers of the upper part of the control dermis (C) and treated dermis (D).

CONCLUSION

As shown in 4D bioprinted skins, Nephoria dramatically improves the extracellular collagen fiber density in the dermis for firmer skin.

MATERIALS&METHODS

4D bioprinted skin

Reconstructed fully bioprinted skins are alternatively composed of multilayers of bovine collagen type I and III and of human fibroblasts using a microvalve and laser technology respectively. Bioprinted dermis were matured for 5 days in DMEM/F12 medium with 10% bovine calf serum, 100 µg/ml normocine and 5 µg/ml ascorbic acid. Human keratinocytes were printed on top of the dermis and matured for 10 days in modified Green mediums 0.8% BSA, 0.12 UI/ml insulin, 0.4 µg/ml hydrocortisone and 5 µg/ml ascorbic acid. The cultures were made at 37°C and 5% CO_2.
Treatments with a solution of *Nephelium lappaceum* leaf extract, at a dose equivalent to Nephoria at 0.015%, were done every 2 days except when cells were seeded.

Second harmonic generation (SHG) microscopy

Second-harmonic generation (SHG) is a non-linear second order optical process combining the advantages of a non-linear microscopy approach with a coherent modality able to probe the molecular organization of fibrillar collagens in normal human skin and 4D reconstructed models without exogenous staining. We used confocal microscopy (LSM 780, Zeiss, France) associated with a multiphoton laser (Spectra Physics) to generate a second harmonic signal specific to fibrillar collagen. The acquisition was done with histological sections of 4D bioprinted skins. The images (30) were acquired in depth of the histological section to create a 3D stack. One image from this stack is used to compare the effect of the treatment with Nephoria *vs*. the untreated control condition.

Conclusions *in vitro*

We demonstrated the effects of Nephoria on:

- **modulation of expression of genes involved in dermal matrix quality**
  Up-regulation of COL1A2, P4HA1 and P4HA2, ELN and FBLN5.
  Down-regulation of CYR61 (CCN1).
- **modulation of protein synthesis involved in dermal matrix quality**
  Stimulation of Collagen I, Fibulin-5, Emilin-1, MFAP4.
  Inhibition of CCN1.
- **improvement of the collagen extracellular matrix network demonstrated on a 4D bioprinted skin.**

As a retinol-like ingredient, Nephoria stimulates *in vitro* both collagen and elastin fiber formation and organization. In addition, CCN1 synthesis is decreased, assuring good collagen I homeostasis.

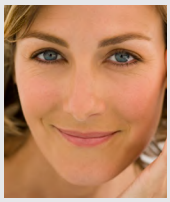
EFFICACY

IMPROVEMENT OF SKIN ELASTICITY AND WRINKLE REDUCTION WITH NEPHORIA FOR ANTI-AGING EFFICACY

in vivo

OBJECTIVE

In a double-blind, randomized, split-face, placebo-controlled clinical study, we evaluated the ability of Nephoria to improve the major signs of aging (Figure 13).



Cheek elasticity measurement (R5, R7) using Cutometer
Crow's feet wrinkle evaluation using AEVA imaging

Figure 13 - Clinical study on the signs of aging with Nephoria *vs.* placebo.

The study was performed on 28 females aged from 55 to 65, having grade 3-4 crow's feet wrinkles according to the Bazin Atlas (Bazin and Doublet, 2007) and considering themselves to have a loss of skin elasticity and firmness.
Nephoria at 0.1% and a placebo formulation were applied twice a day for a period of 28 days. The measurements were done at D0 and D28.

RESULTS & DISCUSSION

Elasticity improvement

Nephoria at 0.1% showed significant improvement ($p<0.05$) as compared to baseline in both the R5 Immediate elasticity parameter and the R7 Elasticity recovery parameter (Figure 14 A&B). Immediate elasticity and Elasticity recovery increased by 19% and 12.5% respectively. These changes are higher than those obtained with the placebo, even though the difference between the two products' application is not statistically significant.

An increase in these elasticity parameters as compared to baseline demonstrated that, after 28 days, Nephoria application promoted an improvement in the elasticity of the skin of the cheek.

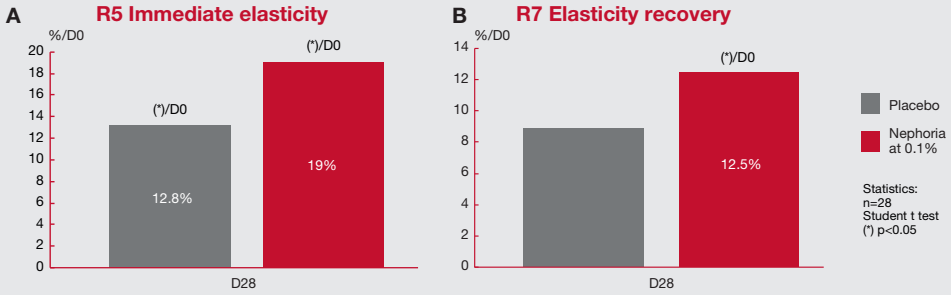


Figure 14 - Percentage of change of cheek elasticity *vs.* baseline using Cutometer. **A** - R5 Immediate elasticity. **B** - R7 Elasticity recovery.

Crow's feet wrinkle reduction

At 28 days, Nephoria showed a significant decrease (14.8%, $p<0.05$) in max wrinkle depth as compared to placebo (Figure 15A), as well as a significant decrease (9.1%, $p<0.05$) in mean wrinkle depth as compared to placebo (Figure 15B). These maximum and mean wrinkle depths were also significantly improved after Nephoria application *vs.* baseline.

At 28 days, Nephoria also showed a significant decrease (18%, $p<0.05$) in roughness of the crow's feet area as compared to the placebo (Figure 15C).

Nephoria promoted a significant decrease in the depth of prominent crow's feet wrinkles, as well as an overall significant decrease in average crow's feet wrinkle depth after only 4 weeks of treatment. In addition, Nephoria prevented the development of roughness on the crow's feet area.

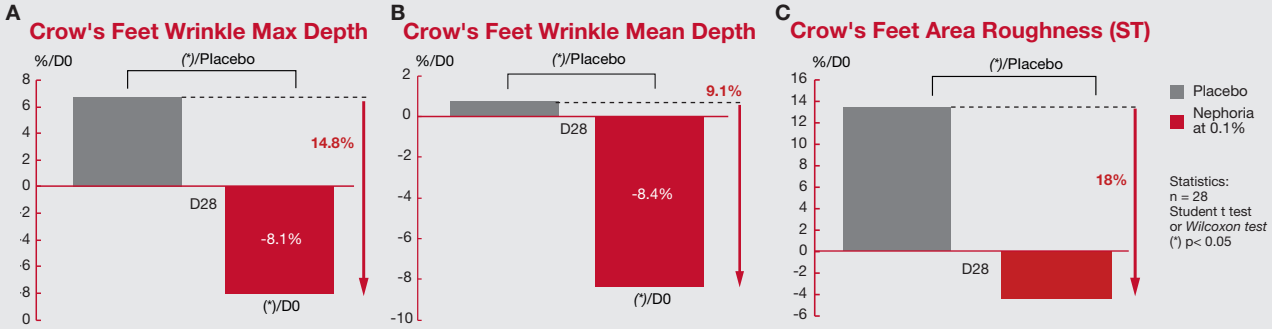


Figure 15 -Percentage of change of crow's feet wrinkle *vs.* baseline. **A** - Crow's feet wrinkle max depth. **B** - Crow's feet wrinkle mean depth. **C** - Crow's feet area roughness (ST).

in vivo

Pictures in figure 16 illustrate the improvement of wrinkles with Nephoria.

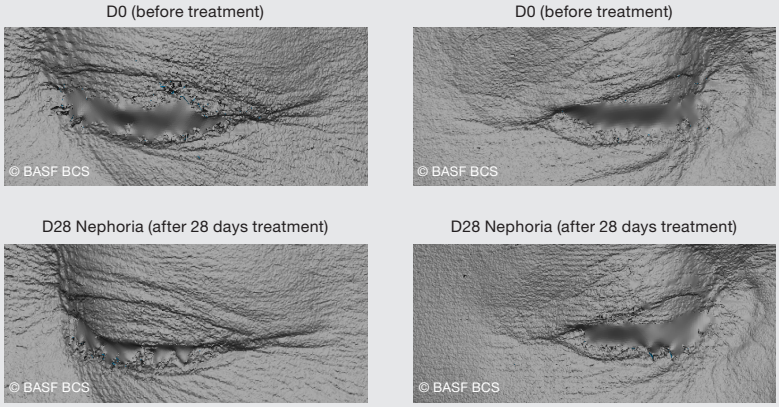


Figure 16 - Crow's feet wrinkle fringe projection images (AEVA) from 2 volunteers, before (D0) and after treatment (D28) with Nephoria at 0.1% for 28 days.

CONCLUSION

In vivo, Nephoria has demonstrated efficacy to fight against aging signs:

- immediate elasticity and elasticity recovery are increased as compared to baseline,
- crow's feet wrinkle maximum depth and mean depth are reduced *vs* baseline and *vs.* placebo, and crow's feet area roughness is reduced *vs.* placebo.

Nephoria at 0.1% improves skin elasticity and reduces wrinkle depth to give a younger skin appearance !

MATERIALS&METHODS

Study design

The clinical study was carried-out randomized double blind *versus* placebo. The efficacy of the formulation containing Nephoria at 0.1% was compared to the baseline (before treatment, D0) and to the half of the face treated with the placebo formulation. The formulation is detailed in Annex 2. The study was conducted for a period of 28 days with check points at D0 and D28.

Inclusion criteria

The study was done on 28 healthy female volunteers, Fitzpatrick skin type I, II or III, age 55 to 65, considering themselves to have a loss of skin elasticity and firmness, having visible crow's feet wrinkles of grade 3-4 according to the Bazin Atlas (Bazin and Doublet, 2007) assessed by a clinical scientist.

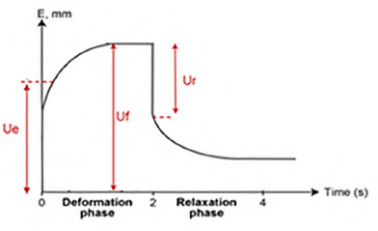
Application modality

The products (a formulation containing Nephoria at 0.1% or a placebo formulation) were applied by the volunteers twice a day on each half of the face for 28 days, under normal conditions of use.

Evaluation methods

Skin elasticity study

The Cutometer dual MPA 580 is used to measure the elasticity of the upper skin layer. It mechanically deforms the skin using negative pressure; Suction is created in the device and the skin is drawn into the aperture of the probe for a set period of time before it is released again. Inside the probe, the penetration depth is determined by a non-contact optical measuring system. This optical measuring system consists of a light source and a light receptor, as well as two prisms facing each other, which project the light from the transmitter to the receptor. The light intensity varies according to the penetration depth of the skin. The resistance of the skin to the negative pressure (firmness) and its ability to return into its original position (elasticity) are displayed as curves (penetration depth in mm/time) in real time during the measurement. This measurement principally allows information about the elastic and mechanical properties of the skin surface to be obtained and enables the quantification of changes in elasticity caused by aging. The measurements were performed on the cheek.



R5 (Ur/Ue) Immediate elasticity: Net elasticity without viscous deformation, decreases with age (Krueger *et al.* 2011).
R7 (Ur/Uf) Elasticity recovery: Elastic recovery to distensibility ratio, decreases with age (Krueger *et al.* 2011).

AEVA study (wrinkle depth and roughness)

The AEVA is an imaging system which uses stereo imaging to create three dimensional topographical images of the face. The system can then analyze these images to assess changes in facial topography, such as wrinkle depth and skin roughness.

The wrinkle depth of various facial wrinkles is calculated from the topographical images created. The instrumentation software assesses the images and calculates max and mean wrinkle depth. The software can also assess skin roughness by calculating the roughness parameter ST as the the maximum height deviation of the wrinkle from the surface of the skin.

VISIA images

The VISIA has a multi-point positioning system and ghost imaging capability that captures well registered images to document changes in the face over time. The VISIA captures and automatically analyzes left, right and frontal facial views.

Statistics

Results are expressed as the mean percentage of change compared to the baseline measurement.

The statistical analysis of the evolution of the parameters as a function of time and of the differences in the studied parameters between the treatment groups, was done after verifying the normality of distribution using Shapiro-Wilk test. The following tests were used afterwards:

- for those comparisons where the normality of both data sets was validated, a paired t-test was used,
- if the normality validation failed, then the Wilcoxon test was used.

GENERAL CONCLUSION

Beauty is a global concern that arose thousands of years ago and will always continue. However, our lifestyles have evolved, and we must not forget that our day-to-day choices could potentially impact the future of our planet. Taking up the trends of modern consumer demand and their growing environmental awareness, has prompted the cosmetic industry to develop more sustainable solutions, while keeping the same high level of demonstrated *in vitro* biological efficacy and clinical performance.

Building on the experience acquired with our previous sustainable and responsible argan program in Morocco, we have created a new socially responsible supply chain in cooperation with a long-standing local partner in Vietnam. We identified rambutan (*Nephelium lappaceum*) as the most promising resource.

Exploring the different parts of the rambutan tree, we have discovered that a corilagin-titrated extract of rambutan leaves, Nephoria, was able to act on two main signs of skin aging: loss of elasticity and wrinkles.

We have demonstrated *in vitro* that Nephoria is able to boost the major dermal structural protein, collagen I, and the prolyl 4-hydroxylase playing a central role in the formation and stabilization of its triple helical structure. Furthermore, CCN1 synthesis, a down-regulator of collagen homeostasis, is inhibited. On 4D bioprinted skin, Nephoria confirmed its efficacy by improving the density of the extracellular collagen fibers for a denser dermis.

Additionally, Nephoria stimulated *in vitro* gene expression and the protein synthesis of several partners involved in elastic fiber assembly, such as Fibulin-5, MFAP4 and Emilin-1.

All these *in vitro* results show that Nephoria acts both on elasticity and firmness targets through biological pathways like those of the gold standard retinol.

In vivo, in a placebo-controlled clinical study, Nephoria visibly improved skin elasticity and the appearance of wrinkles, decreasing the maximum wrinkle depth by 15% within one month.

Nephoria, our unique active ingredient extracted from the evergreen leaves of rambutan tree, has been created to help us to preserve our skin's youth capital while having a positive impact on the planet through our beauty routine.

ANNEXES

Annex 1 - Technical data - Available upon request

- Quality and Regulatory Product Information
- Composition sheet
- Specifications
- Formulation Data Sheet

Annex 2 - Clinical test formula

Trade name	INCI name	Placebo formulation %	Nephoria formulation %
Emulgade® 165	Glyceryl Stearate (and) PEG-100 Stearate	4.00	4.00
Cutina® PES	Pentaerythrityl Distearate	1.50	1.50
Cetiol® Sensoft	Propylheptyl Caprylate	5.00	5.00
Cetiol® SN	Cetearyl Isononanoate	3.00	3.00
Cetiol® C5	Coco-Caprylate	2.00	2.00
Cetiol® CC	Dicaprylyl Carbonate	3.00	3.00
Xiameter PMX-200 Silicone Fluid 50 CS (Dow Corning)	Dimethicone	1.00	1.00
Elestab™ 388	Propylene Glycol (and) Phenoxyethanol (and) Chlorphenesin (and) Methylparaben	2.50	2.50
1-3 Butanediol	Butylene Glycol	2.00	2.00
Rheocare® XGN	Xanthan Gum	0.20	0.20
NaOH Solution 16%	Sodium Hydroxide (and) Water	0.15	0.15
Rheocare® C Plus	Carbomer	0.15	0.15
Nephoria BC 10044	Maltodextrin (and) Nephelium Lappaceum Leaf Extract	0.00	0.10
Water, demin	Aqua	qsf 100	qsf 100

Annex 3 - Formulation examples

Face care emulsion (SC-FR-19-BC-50721-09)

Phase	Ingredients	INCI	% by weight	Function
A	Emulgade® 165	Glyceryl Stearate, PEG-100 Stearate	4.00	Emulsifier (O/W)
	Cutina® PES	Pentaerythrityl Distearate	1.50	Consistency agent
	Cetiol® SN	Cetearyl Isononanoate	3.00	Emollient
	Cetiol® Sensoft	Propylheptyl Caprylate	5.00	Emollient
	Cetiol® C 5	Coco-Caprylate	2.00	Emollient
	Cetiol® CC	Dicaprylyl Carbonate	3.00	Emollient
	Xiameter PMX-200 Silicone Fluid 50CS *(Dow Corning)*	Dimethicone	1.00	Skin feel modifier
B	Water, demin.	Aqua	64.40	
	Elestab® 388	Propylene Glycol, Phenoxyethanol, Chlorphenesin, Methylparaben	2.50	Preservative
	Rheocare® XGN	Xanthan Gum	0.20	Stabilizer
	1,3-Butanediol	Butylene Glycol	2.00	Humectant
	Sodium Hydroxide (18% solution)	Sodium Hydroxide	0.15	pH Adjustment
C	Rheocare® C Plus	Carbomer	0.15	Rheology modifier
	Water, demin.	Aqua	10.00	
D	Nephoria™ BC10044	Maltodextrin, Nephelium Lappaceum Leaves Extract	0.10	Active ingredient
	Water, demin.	Aqua	1.00	

Chaq boi toi booster – SPF 10 (SC-DE-18-150-5)

Phase	Ingredients	INCI	% by weight	Function
A	Water, demin.	Aqua	52.50	
	Rheocare® XGN	Xanthan Gum	0.30	Rheology modifier
	Glycerin	Glycerin	8.00	Humectant
B	Eumulgin® SG	Sodium Stearoyl Glutamate	0.50	Emulsifier (O/W)
C	Lanette® O	Cetearyl Alcohol	3.00	Consistency agent
	Cegesoft® HF 62	Hydrogenated Vegetable Oil	2.00	Consistency agent
	Cetiol® MM	Myristyl Myristate	1.00	Emollient
	Cetiol® RLF	Caprylyl Caprylate/ Caprate	3.00	Emollient
	Cetiol® LC	Coco-Caprylate/Caprate	8.00	Emollient
	Eutanol® G	Octyldodecanol	3.00	Emollient
D	Veegum Pure *(Vanderbilt Minerals LLC)*	Magnesium Aluminum Silicate	1.50	Stabilizer
E	Ethanol	Alcohol	5.00	Solvent
	Covi-ox® T 90 EU C	Tocopherol	0.50	Antioxidant
	Perfume*	Parfum	0.20	Fragrance
F	Nephoria™ BC10044	Maltodextrin, Nephelium Lappaceum Leaves Extract	0.10	Active ingredient
	Water, demin.	Aqua	9.90	
G	Sodium Benzoate	Sodium Benzoate	0.50	Preservative
H	Citric Acid (50% solution)	Citric Acid	1.00	pH Adjustment

*** Quitte & Litschi Natura (Düllberg) INCI: Parfum, Citral, Geraniol, Linalool, Citronellol, Limonene**

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