# ALULA PEREGRINA™

## PRODUCT PORTFOLIO

# UNCOVER THE SECRETS OF THE PEREGRINA TREE

The Peregrina tree is an extremophile : it grows in arid, rocky regions and applies specific drought-stress adaptative strategies. This environment is undoubtedly the cause for its unique chemical signature and properties.

Yet, what biological mechanisms and metabolic pathways allow this majestic tree to collect and preserve water in one of the most arid places on earth? How can a seed remain fully functional under heat and UV rays without genetic drift or alteration for many years? And what are the chemical pathways allowing a botanical oil to self-preserve for more than 30 years ?

Nature showed us how active skin cell DNA integrity protection could be the ultimate key to delaying aging and reversing cell damage. AlUla Peregrina™ oil and actives reveal the biological mechanisms uncovered in the Peregrina seeds to provide multifunctional skincare with unparalleled skin cell DNA integrity protection.

# DESCRIPTION OF THE PLANT

## Family

*Moringaceae*

## Species

*Moringa peregrina (Forssk.) Fiori*

## Common names

*Peregrina, al bân, ben*

## Distribution

Peregrina is a genetically different species from Moringa oleifera Lam. Compared to all the other species in the genus, it grows in arid and rugged environments.

Peregrina is indigenous to Yemen, Oman, Saudi Arabia, the Eastern Horn of Africa, Egypt, Jordan, and the Sinai Peninsula. In many countries today - especially in Egypt and the Levant – the species is classified as rare and endangered due to overgrazing and ecosystem degradations. In Saudi Arabia, wild trees stand in northern and central wadis and Asir.

Within AlUla (Kingdom of Saudi Arabia), Peregrina thrives in the southern part of the region, in wild wadis, at an intermediate elevation. Local farmers started cultivating Peregrina 40 years ago to green the area while earning income from this traditional tree.

## Description

The compound leaves on the Peregrina tree appear in February before disappearing very rapidly. Only the rachis remains in its place, making the tree look somewhat like a Tamarisk.

The five-petal pink, whitish flowers come into full bloom in March-April and release a sweet, honeydew-like fragrance. The fruit is a long pod containing several globular to ovoid brown, grey, or whitish seeds. The seeds present specific qualities ascribable to the harsh environment. Germination can be delayed for long until finding favorable conditions; thus, the seed has developed unique mechanisms to maintain its integrity and capacity to grow over time.

## Plant part used

Due to its challenging environment, the seeds present specific nutrients and exceptional metabolites, passed over to the virgin Peregrina oil and the actives.

# GROUNDBREAKING INGREDIENT SUPPLY FROM ALULA

## An exclusive and sustainable sourcing

In AlUla, Peregrina is already cultivated sustainably by local farmers, including many women. Peregrina farming has become a landmark of the local ecology, with low water requirements and a positive environmental impact through a no waste and clean agriculture with a minimal footprint. Peregrina seeds are carefully harvested at maturity, then hand-sorted and dried in the shade. Producers decant the oil naturally for sustainable and superior quality.

## ISO 9001 certified factory pioneering R&D and quality control in AlUla

The Peregrina Center was created in 2019 in AlUla to develop local quality insurance, innovative research & development. The laboratory operates high-end analytical equipment driven by nine scientists, including eight women. The center plays a significant and leading role in all aspects of the Peregrina supply chain to warrant capacity, quality control, traceability, standardization of the production, and fair trade and sustainable practices.

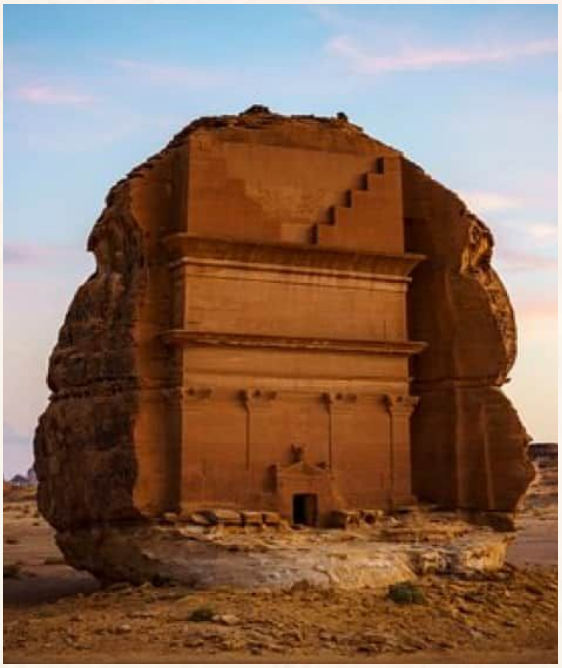
## Local development meets international industry standards

The Royal Commission for AlUla (RCU) safeguards the natural and cultural landscape, celebrates local heritage, promotes balanced agriculture, and enables the development of local communities.

In line with this strategy, AlUla Peregrina Trading Company supports the AlUla Peregrina supply chain by actively promoting a social development model that takes pride in the emergence of a local industry of the highest quality. It favors the ethical employment & empowerment of women.

## The unique heritage of the AlUla Peregrina™ oil

Peregrina is an essential element of nature and heritage in the AlUla region. From the Harrat canyons to the wadis and sandy desert, AlUla is home to fascinating archeological sites covering more than 200,000 years of human history, unique ecological systems, and wild landscapes.



With oases dotting the area, AlUla became a vital crossroad along the famous incense-trading routes, running from southern Arabia to Egypt and beyond. AlUla was a hub of the ancient kingdoms of Dadan and Lihyan, dominating the caravan trade; later on, Hegra was the principal southern city of the Nabataean kingdom, famed for its spectacular monumental tombs.

We found proof of the ancestral use of Peregrina oil in ancient texts and archaeology, back to ancient Egypt, through the Hellenistic & Roman periods, and in the Middle Ages in Abassid times (9th-13th c.). The oil was renowned for preserving and enhancing fragrances. Peregrina oil, then called bān oil, was a crucial ingredient in the most expensive, complex, sought-after perfumes like the so-called King of Parthia and the Ghaliya.

In the 14th century, the best bān was found in Hejjaz, corresponding to today's AlUla region.

# PRODUCT PORTFOLIO

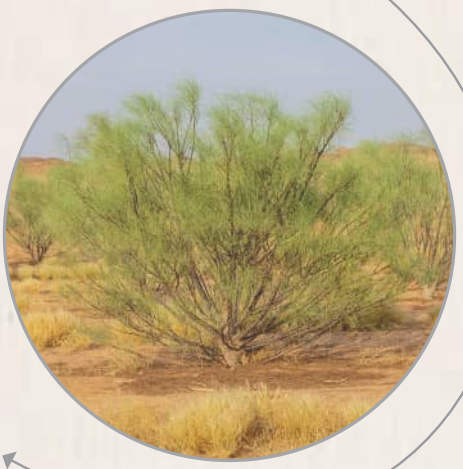
## Peregrina Seeds

Harvested in July-August

## Virgin AlUla Peregrina™ Oil

*Cold press*

Light and dry oil with deep hydration action and nourishing properties

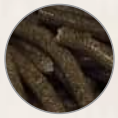


## Hydrolyzed AlUla Peregrina™ Paste Extract

*Hydrolysis from AlUla Peregrina ™ paste*

Innovative upcycled ingredient with proven smoothing, tightening, tensor and film-forming effects on the skin

## AlUla Peregrina™ Press Cake



## Hydrolyzed AlUla Peregrina™ Extract

*Hydrolysis from AlUla Peregrina™press cake.*

Multifunctional brightening and anti-aging natural active with unparalleled skin cell DNA integrity protection

## Lipophilic AlUla Peregrina™ Extract

*Ethanolic extraction and lipidic vectorization from AlUla Peregrina™ press cake.*

Instant skin soothing and protection with long-term skin cell DNA repair.

# VIRGIN ALULA PEREGRINA™ OIL

PATENT N°WO2024/03378

COSMOS APPROVED

**Light and dry oil with deep hydration action and nourishing properties, and proven hair density enhancement.**

**The oil offers a perfect affinity with the skin, hair and scalp with penetrating and nourishing properties.**

## COSMETIC BENEFITS

The Virgin AlUla Peregrina™ oil is a light and dry oil with deep hydration and nourishing properties.

The Virgin Peregrina oil has a neutral odor, is a fragrance booster, and is a long-term natural preservative.

Recent clinical tests have demonstrated an impressive 18% increase in hair density after 56 days and a 29% increase after 84 days, significantly outperforming traditional solutions like Minoxidil.

## KEY FEATURES

The Virgin AlUla Peregrina™ oil is liquid at room temperature. It contains fatty acids of interest, primarily gondoic acid, rarely present in plants and close to the composition of sebum.

The Peregrina oil is also rich in unsaponifiable matter: around 0,45%, including β-sitosterol, stigmasterol, and squalene.

## SENSORY ANALYSIS

The first study panel consisted of 11 women. The panel training was carried out in two sessions, 1 hour each. The evaluation of the products on all the descriptors was carried out instantly after the two training sessions.

The Virgin AlUla Peregrina™ oil is soft, runny in texture, with a medium greasy residue, light yellow, and odorless. The absorption, penetration, and playtime are moderate to long, leaving supple skin.

A second panel consisted of 26 women. Over 84 days, the panel provided further insights into the AlUla Peregrina™ Oil's efficacy, with unanimous feedback on its ability to rejuvenate the appearance of the skin, enhance hydration, and even out complexion. The panel also observed improvements in skin elasticity and a reduction in visible signs of fatigue, suggesting that the oil's sensory benefits are matched by its restorative actions.

**ORIGIN AND DESCRIPTION**

Family: Moringaceae
Renewable botanical origin: seeds
Geographic origin: AlUla, Saudi Arabia
Extraction: cold press

**REGULATORY DATA**

English name: Virgin AlUla Peregrina™ oil
Inci: Moringa peregrina (seed) oil
CAS: 68956-68-3
EINECS: 273-313-5
Natural ingredient (ISO 16128)
Cosmos: Approved

**PHYSICOCHEMICAL CHARACTERISTICS**

Form: Liquid
Color: Light Yellow
Odor: Very light smell

**COSMETIC USE**

Dry oil / light oil phase

**COMPOSITION**

Peregrina oil fatty acid profile

| | Fatty acid | % |
|---|---|---|
| Saturated C14:0 | Myristic acid | 0,1 |
| Saturated C16:0 | Palmitic acid | 9,6 |
| Monounsaturated C16:1 | Palmitoleic acid | 2,3 |
| Saturated C17:0 | Margaric acid | 0,1 |
| Saturated C18:0 | Stearic acid | 5,2 |
| Monounsaturated C18:1 | Oleic acid | 72,5 |
| Polyunsaturated (ω6) C18:2 | Linoleic acid | 0,6 |
| Saturated C20:0 | Arachidic acid | 2,9 |
| Monounsaturated C20:1 | Gadoleic (Gondoic) acid | 2,2 |
| Saturated C22:0 | Behenic acid | 3,7 |
| Saturated C24:0 | Lignoceric acid | 0,8 |

**SPECIFICATIONS**

| | |
|---|---|
| Density at 20 °C | 0,905 ≤ d ≤ 0,925 |
| Refractive index | 1,450 - 1480 |
| Solubility | liposoluble |

**FORMULATION DATA**

Preservatives: -
Use level in formula: between 3% to 25%
Solubility: in any oil phase
Incorporation method: anytime in oil phase using a cold process, after cooling at the end of hot process
Rancimat: >10 years
Storage: 36 months, unopened vial protected from light and temperature between 16 and 25 °C
Shelf life: 36 months

**TOXICOLOGY**

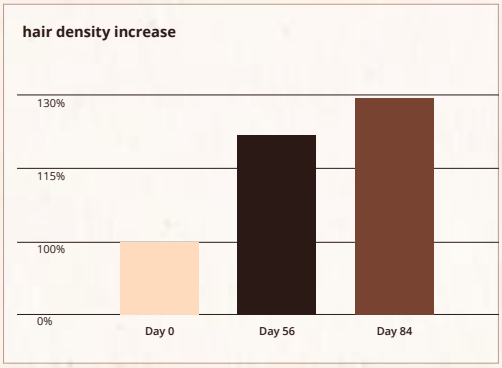
Cutaneous patch test: non-irritating (concentration of 50%)

# VIRGIN ALULA PEREGRINA™ OIL

## EFFICACY

Carried out on 21 men and women
- 58-year-old average, ranging from 43 to 72
- presenting sensitive scalps
- presenting dry, normal or oily scalps
- hair density average 98,8 hair/cm$^2$ ranging from 85 to 115 hair/cm$^2$.

The volunteers applied 3 drops of Virgin AlUla Peregrina™ Oil daily for 84 days.
After 56 and 84 days, the measurement of hair density using Aramo SG® ASG 200F showed a statistically significant increase in the hair density of the volunteers. The Virgin AlUla Peregrina™ Oil improves the hair density.




**Day 0** → **Day 56** → **Day 84**

After 56 and 84 days, hair density significantly increased.

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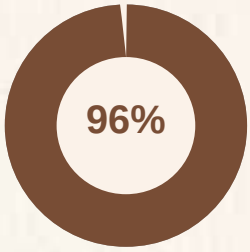
# BIOLOGICAL ACTIVITY

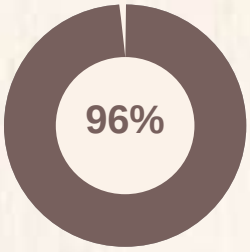
## CLINICAL STUDIES

Evaluation of the Virgin AlUla Peregrina™ Oil by 26 volunteers over 84 days.

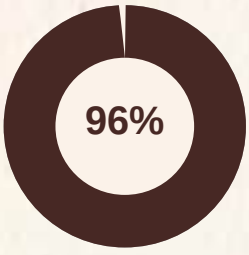

**Gives the appearance of younger skin**




**Visibly reduces signs of fatigue**



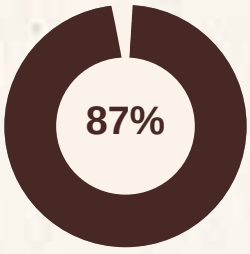

**Visibly improves the elasticity of the skin**



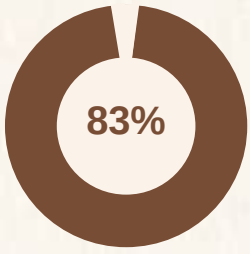

**Enhances the feeling of hydratation the skin**


**Gives a feeling of repairing the skin**

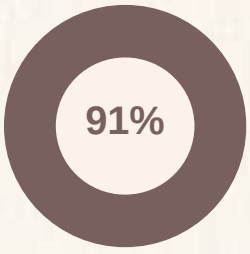

**Gives a feeling of nourished skin**




**Visibly brightens the skin**




**Visibly makes the complexion more even**




**Visibly smoothes fine line and wrinkles**

# VIRGIN ALULA PEREGRINA™ OIL - FORMULATION BOOK

## AlUla Peregrina™ Hair & Body Dry oil

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Ephyster MCR | Brassica napus extract | 50 |
| A | Sunflower oil | Helianthus annuus seed oil | 44 |
| A | Virgin AlUla Peregrina™ Oil | Moringa peregrina (seed) oil | 2 |
| B | Fragrance | Parfum | 2 |
| B | Lipophilic AlUla Peregrina™ Extract | Caprylic/capric triglyceride & Moringa peregrina seed oil extract | 1 |
| B | Vitamin C Tetra E | Ascorbyl tetraisopalmitate | 1 |
| | | | 100 |

**Protocol**
Prepare A and heat slightly to homogenize. When the temperature is below 35°C, add B and homogenize

**1.** Prepare and heat A slightly to homogenize
**2.** Decrease temperature to 35°C, add B and homogenize

## AlUla Peregrina™ Nourishing Light Cream

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Water | Aqua | 69,5 |
| A | Geogard ultra | Gluconolactone & Sodium benzoate & Calcium gluconate | 1 |
| A | Sodium benzoate | Sodium benzoate | 0,3 |
| B | Frametime CXG | Bentonite & Xanthan gum & Sodium stearoyl glutamate & Citric acid | 5 |
| B | Xanthan gum FF | Xanthan gum | 0,2 |
| C | Cetearyl alcohol | Cetearyl alcohol | 1,5 |
| C | Ephyster ECR | Brassica napus extract | 10 |
| C | Virgin AlUla Peregrina™ Oil | Moringa peregrina (seed) oil | 12 |
| D | Fragrance | Parfum | 0,5 |
| | | | 100 |

**Protocol**
Prepare phase A and heat to 45°C to obtain a homogeneous mixture. Add phase B and mix. Melt C to 70°C, add to the previous mixture and mix until obtain a homogeneous product. Wait for the temperature to drop to 30°C before adding D.

**1.** Prepare and heat A slightly to homogenize
**2.** Decrease temperature to 35°C, add B and homogenize

## AlUla Peregrina™ Regenerating Hair Mask

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Ephyltec A | Aqua & Anacardium occidentale extract* & Sodium citrate & Sodium benzoate | 50 |
| A | Frametime CX | Bentonite & Xanthan gum & Citric acid | 2 |
| B | Virgin AlUla Peregrina™ Oil | Moringa peregrina (seed) oil | 45,4 |
| C | Fragrance | Parfum | 0,5 |
| D | Lipophilic AlUla Peregrina™ Extract | Caprylic/Capric triglyceride & Moringa Peregrina seed oil extract | 1,5 |
| E | Benzyl alcohol | Benzyl alcohol | 0,6 |
| | | | 7 |

**Protocol**
Prepare A and heat slightly to homogenize. When the temperature is below 35°C, add B and homogenize

**1.** Prepare and heat A slightly to homogenize
**2.** Decrease temperature to 35°C, add B and homogenize

## AlUla Peregrina™ Hair Oil Serum

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Ephyster MCR | Brassica napus extract | 42,5 |
| A | Virgin AlUla Peregrina™ Oil | Moringa peregrina (seed) oil | 42 |
| B | OLO 3D | Stearalkonium bentonite | 12 |
| B | Unipure red LC320 | CI 75470 | 0,01 |
| C | Lipophilic AlUla Peregrina™ Extract | Caprylic/Capric triglyceride & Moringa peregrina seed oil extract | 1 |
| C | Fragrance | Parfum | 2 |
| C | Vitamin C Tetra E | Ascorbyl tetraisopalmitate | 0,5 |
| | | | 100 |

**Protocol**
Prepare A and heat to 35°C. Prepare B and add to A. mix until the temperature reaches 45°C. Add C phase and homogenize.

**1.** Prepare and heat A to 35°C
**2.** Prepare B and add to A
**3.** Mix until the temperature reaches 45°C
**4.** Add C and homogenize

# OTHER PEREGRINA ACTIVES

**The cold press of the Peregrina seeds reveals a precious virgin Peregrina oil. The patented activity on hair density increase puts the Virgin AlUla Peregrina™ Oil in the category of oil actives. The by-product of this extraction is a cake traditionally used for its nutritional properties. Recent analytical and clinical studies uncovered the unparalleled skin cell DNA integrity protection of the AlUla Peregrina™ Press Cake, contributing to the outstanding durability of the Peregrina seeds.**

**Hydrolyzed AlUla Peregrina™ Extract and Lipophilic AlUla Peregrina™ Extract are two synergistic actives extracted from the AlUla Peregrina™ press cake. The first boosts the cell metabolism while the second shields and maintains the vital well-being of the cell. Both prevent skin cell DNA degradation.**

**A further noteworthy derivative of the oil press process is AlUla Peregrina™ paste, which exhibits surprising efficacy. Subjected to hydrolysis, this initially soft and nourishing paste is transformed into a highly potent and stable active ingredient. Its remarkable properties render it an excellent option for inclusion in advanced skincare formulations.**

# HYDROLYZED ALULA PEREGRINA™ EXTRACT

PATENT N°WO2021234166

## A multifunctional brightening and anti-aging natural active with unparalleled cell DNA integrity protection.

**The Hydrolyzed AlUla Peregrina™ Extract visibly and safely brightens and unifies the skin while protecting skin cell DNA integrity.**

## COSMETIC BENEFITS

The Hydrolyzed AlUla Peregrina™ Extract:

- protects skin cell DNA integrity
- fights photoaging with a visible reduction in dark spots and a global brightening action
- lifts the skin and fights wrinkles
- regulates hydration and provides a plumping effect

## MECHANISMS OF ACTION

The Hydrolyzed AlUla Peregrina™ Extract protects skin cell DNA integrity by lengthening telomeres while preserving the integrity of stem cells.

The Hydrolyzed AlUla Peregrina™ Extract regulates the process of skin pigmentation with activity on three known mechanisms of action:

- It regulates skin pigmentation through DKK1 stimulation and DKK3 inhibition; these are glycoproteins involved in controlling the differentiation & activation of melanocytes in the basal layer at the bottom of the epidermis.
- It regulates melanin production through stimulation of Zinc α-2-glycoprotein (ZAG), a protein involved in the regulation of melanogenesis decrease.
- It decreases melanin synthesis by inhibiting Endothelin-1, a potent vasoconstrictor peptide involved in the regulation of melanogenesis.

Hydrolyzed AlUla Peregrina™ Extract provides tensing, anti-wrinkle, and second-skin effects through strong film-forming and tensor action.

The Hydrolyzed AlUla Peregrina™ Extract promotes a youthful complexion, lifts the skin, and regulates hydration by stimulating bleomycin hydrolase, the leading natural factor in NMF (Natural Moisturizing Factor) hydration.

The Hydrolyzed AlUla Peregrina™ Extract provides a plumping effect through inhibition of Endothelin-1, providing vasodilatation in the skin.

**ORIGIN AND DESCRIPTION**
Family: Moringaceae
Renewable botanical origin: seeds
Geographic origin: AlUla, Saudi Arabia
Extraction: Hydrolysis

**REGULATORY DATA**
English name: Hydrolyzed AlUla Peregrina™ Extract
Inci: Aqua & sodium citrate & Moringa peregrina seed extract & propionic acid
Natural ingredient Index = 0,995 (ISO 16128)
China: pending (2024)

**PHYSICOCHEMICAL CHARACTERISTICS**
Form: Liquid
Color: Yellowish to orange
Odor: characteristic

**FORMULATION DATA**
Preservatives: propionic acid (1.00%)
Use level in formula: 0.50% - 2.00%
Solubility: Water soluble
Shelf life: 36 months

**PACKAGING MATERIALS**
Food grade polyethylene bags, polyethylene drums

**BIOLOGICAL ACTIVITY**

**IN VITRO**
**Long-term anti-aging action through active protection of skin cell DNA integrity**
- Telomere length increase by 16.60% at a concentration of 0.50%
- The survival rate of stem cells increased by 30.50% at a concentration of 0.05%

**A radiant complexion**
- DKK1 increased by 131.50% at a concentration of 0.50%
- DKK3 inhibition by 20.70% at a concentration of 0.50%
- Zinc-α2-glycoprotein increased by 337.80% at a concentration of 2.00%
- Endothelin-1 inhibition by 34.90% at a concentration of 2.00%
- Melanin inhibition by 71.40% at a concentration of 0.10%

**Physiological hydration**
Bleomycin hydrolase increased by 147.20% at a concentration of 0.50%

**Tensor activity**
Collagen discs contracted by 51.10% at a concentration of 0.50%

**Plumping effect**
Endothelin-1 inhibition by 34.90% at a concentration of 2.00%

**CLINICAL STUDIES**
Evaluation of the depigmenting potential results available under one month

# BIOLOGICAL ACTIVITY

**The cellular metabolism of our skin cells is the pathway to global and multifunctional skincare, targeting the signs of aging, fatigue, and stress. The genes in our cellular DNA control it. However, the expression of these genes deteriorates over time, resulting in aging. Active protection of the genetic material is the ultimate key to delaying the effects of aging and reversing cell damage.**

**The Hydrolyzed AlUla Peregrina™ Extract acts, at the level of the skin tissue, on the signs of aging to provide instant action. At the cellular level, it strengthens and maintains with lasting results the quality of the central metabolic pathways involved in the appearance of one of the most significant stigmas of aging, the hyperpigmentation with dark spots.**

## LONG-TERM ANTI-AGING ACTION THROUGH ACTIVE PROTECTION OF SKIN CELL DNA INTEGRITY

**The Hydrolyzed AlUla Peregrina™ Extract preserves skin cell DNA integrity over time, prevents genetic drift due to aging and preserves the integrity of stem cells to promote a youthful and beautiful skin.**

### Action on telomere length

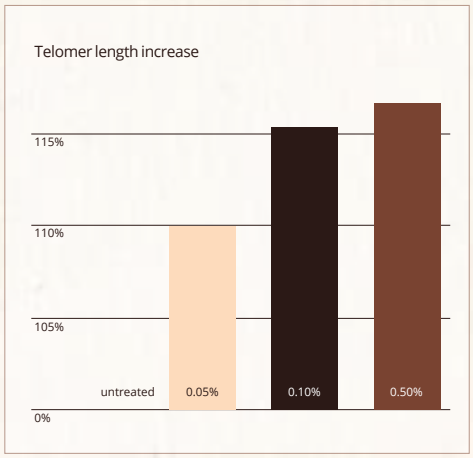
Telomeres act as chromosome caps protecting against genome instability. Increasing the length of telomeres preserves skin cell DNA integrity over time.

**Telomere length increase (in vitro)**

Fibroblasts from a normal donor's skin were treated during three consecutive passages with 0.05%, 0.10%, and 0.50% The Hydrolyzed AlUla Peregrina™ Extract or left untreated during three consecutive passages.

The Hydrolyzed AlUla Peregrina™ Extract at 0.10% and 0.50% significantly lengthens telomeres.

The Hydrolyzed AlUla Peregrina™ Extract has a strong ability to preserve skin cell DNA integrity.



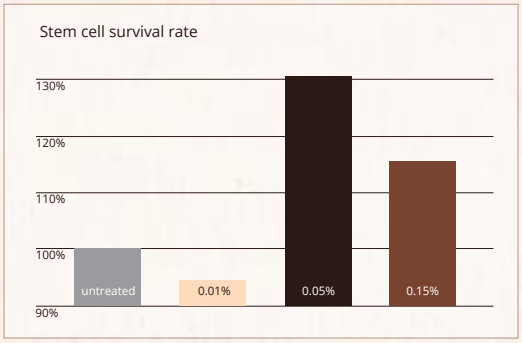
## Action on the integrity of stem cells

Stem Cells are the source of tissue regeneration. The protection of stem cells is correlated with protecting cell DNA integrity and preserving the skin's potential over time.

**Stem cells protection (in vitro)**

Keratinocytes from a normal donor's skin were treated with 0.01%, 0.05%, and 0.15% The Hydrolyzed AlUla Peregrina™ Extract for 24 hours or left untreated, then incubated for six days at 37°C.

The Hydrolyzed AlUla Peregrina™ Extract at 0.05% and 0.15% significantly increase stem cell survival rate.
The Hydrolyzed AlUla Peregrina™ Extract at 0.05% significantly preserves the integrity of stem cells.




## ACTION ON CELLULAR METABOLISM TO PREVENT AND REVERSE SKIN PIGMENTATION AS WELL AS TO PROMOTE A YOUTHFUL HYDRATION

**The Hydrolyzed AlUla Peregrina™ Extract safely brightens and unifies the skin through three different mechanisms of action, acting on cellular metabolism to brighten the skin and reduce the appearance of age spots.**

**The Hydrolyzed AlUla Peregrina™ Extract improves or repairs the skin's hydration mechanisms and prevents mixed skin from experiencing dryness.**

## A radiant complexion

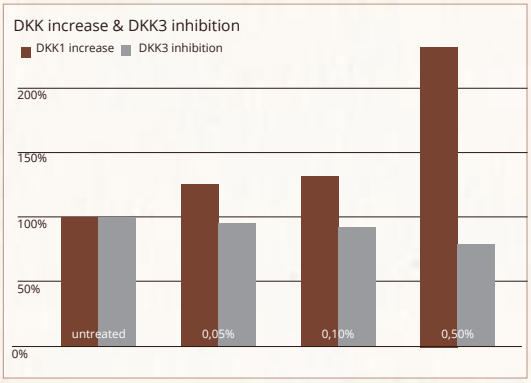
The Hydrolyzed AlUla Peregrina™ Extract acts on three metabolic pathways involved in hyperpigmentation:
- DKK1 increase and DKK3 inhibition to regulate skin pigmentation;
- Stimulation of Zinc α-2-glycoprotein (ZAG) to regulates melanin production;
- Endothelin-1 inhibition to decrease in melanin synthesis resulting into a significant melanin inhibition in vitro

**Action on the DKK1/ DKK3 ratio (in vitro)**

Fibroblasts from a normal donor's skin were treated with 0.05%, 0.10%, and 0.50% of Hydrolyzed AlUla Peregrina™ Extract for 48 hours or left untreated.

The Hydrolyzed AlUla Peregrina™ Extract at 0.50% significantly increases the production of DKK1 and significantly decreases the production of DKK3 in human cells.

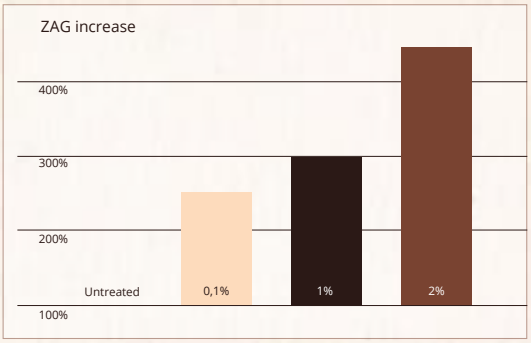
The Hydrolyzed AlUla Peregrina™ Extract has a strong ability to manage genes involved in melanocyte differentiation and decrease skin pigmentation based on the mechanism of palmoplantar inhibition.



**Action on the modulation of the ZAG (in vitro)**
Keratinocytes from a normal donor's skin were treated with 0.10%, 1.00%, and 2.00% of Hydrolyzed AlUla Peregrina™ Extract for 48 hours or left untreated.

The Hydrolyzed AlUla Peregrina™ Extract at 2.00% significantly increases the production of ZAG.

The Hydrolyzed AlUla Peregrina™ Hydrolyzed has a strong ability to brighten the skin.

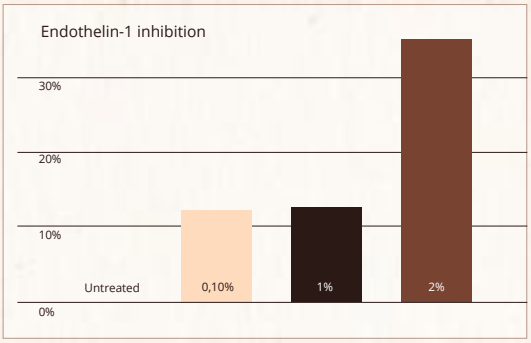



**Endothelin-1 inhibition (in vitro)**

Endothelial cells from a normal donor were treated with 0.10%, 1.00%, and 2.00% of Hydrolyzed AlUla Peregrina™ Extract for 24 hours or left untreated.

The Hydrolyzed AlUla Peregrina™ Extract at 2.00% significantly inhibits the production of Endothelin-1.

The Hydrolyzed AlUla Peregrina™ Extract has a strong ability to brighten the skin and soothe the skin.

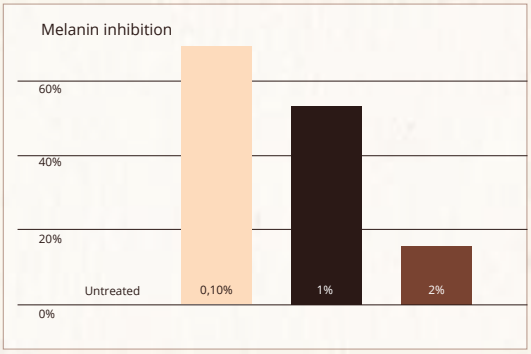



**Melanin inhibition (in vitro)**

Melanocytes from human cell culture were treated with 0.10%, 1.00%, and 2.00% of Hydrolyzed AlUla Peregrina™ Extract for 72 hours or left untreated.

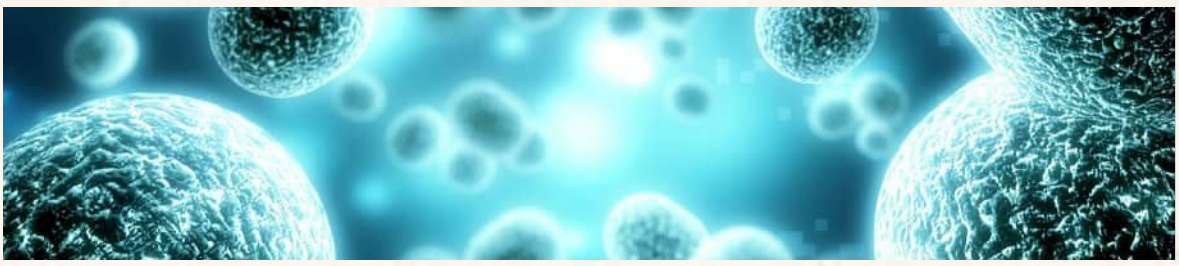
The Hydrolyzed AlUla Peregrina™ Extract at 0.10% and 1.00% significantly inhibits melanin production, with an inverse dose-dependence relationship indicating possible long-lasting activity.

The Hydrolyzed AlUla Peregrina™ Extract has demonstrated a strong ability to induce skin brightening.




## Physiological hydration

Stimulating the NMF (Natural Moisturizing Factor) improves or repairs the function of hydration at the level of our epidermis. The natural key enzyme involved in NMF hydration is bleomycin hydrolase. Stimulating bleomycin hydrolase promotes a youthful complexion.

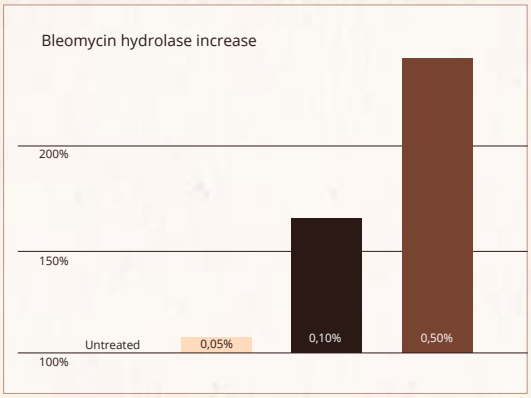


**Bleomycin hydrolase increase (in vitro)**

Keratinocytes from a normal donor's skin were treated with 0.05%, 0.10%, and 0.50% of AlUla Peregrina™ Hydrolyzed Extract for 48 hours or left untreated.

The Hydrolyzed AlUla Peregrina™ Extract at 0.10% and 0.50% significantly stimulates the production of bleomycin hydrolase.

The Hydrolyzed AlUla Peregrina™ Extract has a strong ability to regulate hydration, balance, and moisturize the skin's surface. The Hydrolyzed AlUla Peregrina™ Extract prevents mixed skin from experiencing dryness.




## INSTANT EFFECT ON SKIN TISSUE

**The Hydrolyzed AlUla Peregrina™ Extract provides strong film-forming and tensor action for lifting, anti-wrinkle, and second-skin effects.**

**The Hydrolyzed AlUla Peregrina™ Extract provides a plumping effect through vasodilatation.**

### Lifting effect

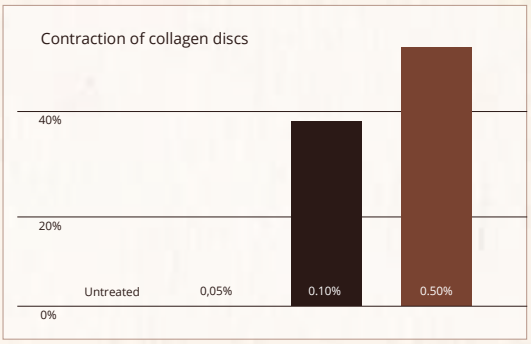
The contraction of collagen discs measures the tensor properties of an active ingredient.

**Tensor activity (in vitro)**

Lyophilized collagen discs were treated with 0.05%, 0.10% and 0.50% of Hydrolyzed AlUla Peregrina™ Extract for 30 minutes or left untreated.

The Hydrolyzed AlUla Peregrina™ Extract at 0.10% and 0.50% significantly contract collagen discs.

The Hydrolyzed AlUla Peregrina™ Extract has a strong ability to provide lifting, anti-wrinkle, and second-skin effects.




### Plumping effect (in vitro)

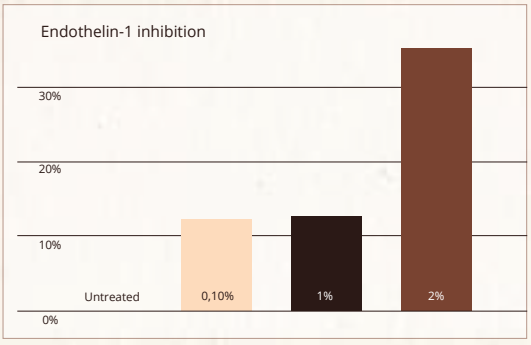
Endothelin-1 is the most potent vasoconstrictor in the human body. Inhibiting Endothelin-1 provides vasodilatation and a plumping effect.

**Endothelin-1 inhibition (in vitro)**

Endothelial cells from a normal donor were treated with 0.10%, 1.00%, and 2.00% of Hydrolyzed AlUla Peregrina™ Extract for 24 hours or left untreated.

The Hydrolyzed AlUla Peregrina™ Extract at 2.00% significantly inhibits the production of Endothelin-1 and triggers a skin vaso-dilator effect.

The Hydrolyzed AlUla Peregrina™ Extract has a plumping effect.

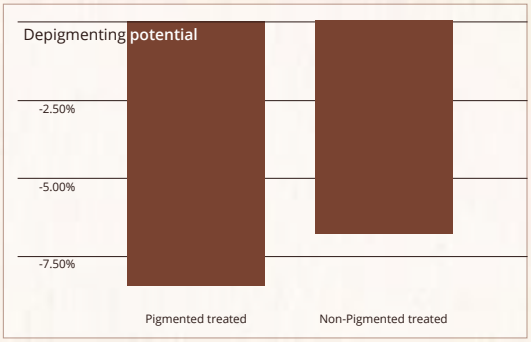


# EFFICACY

## Evaluation of the depigmenting potential under one month (in vivo)

Carried out on 23 women (64-year-old average, ranging from 44 to 70) presenting lentigos on the face, neck, décolleté, and hands. The volunteers applied a formula containing 2.00% of Hydrolyzed AlUla Peregrina™ Extract for 28 days.

After 28 days, the data analysis of mexametric measurements showed a statistically significant decrease in the melanin index on pigmented and non-pigmented areas.
The Hydrolyzed AlUla Peregrina™ Extract visibly reduces age spots.

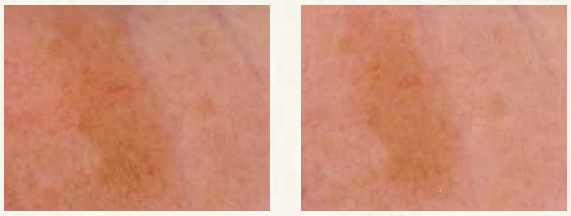



**Day 0** → **Day 28**

After 28 days, pigmentation of age spots decreased; fine lines are reduced.

**Day 0** → **Day 28**

After 28 days, pigmentation of age spots decreased.



**Day 0** → **Day 28**

After 28 days, pigmentation of age spots decreased; fine lines are reduced.

**Day 0** → **Day 28**

After 28 days, pigmentation of age spots decreased.

# THE HYDROLYZED ALULA PEREGRINA™ EXTRACT - FORMULATION BOOK

## AlUla Peregrina™ Dark Spot Cleanser

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Water | Aqua | 60,75 |
| A | Frametime LTX | Sodium magnesium silicate & Xanthan gum & Citric acid | 2,8 |
| B | NEOSORB P60 | Sorbitol | 15 |
| C | Propanediol - Massocare | Propanediol | 15 |
| C | Guar gum | Cyamopsis tetragonoloba gum | 0,4 |
| D | Sea salt | Maris sal | 0,6 |
| E | Hydrolyzed AlUla Peregrina™ Extract | Aqua & sodium citrate & Moringa peregrina seed extract & propionic acid | 1,5 |
| F | Skinperf LWG | Aqua & Glycolic acid & Lactic acid & Sodium magnesium silicate & Citric acid & Xanthan gum | 2,5 |
| G | Benzyl alcohol | Benzyl alcohol | 0,95 |
| H | Fragrance | Parfum | 0,5 |
| | | | 100 |

**Protocol**
Using the stator rotor, mix A until obtain a transparent gel. Add B and mix. Pre-mix C, add to AB and mix. Add D to H and mix between each ingredient.

**1.** Prepare and mix A with a rotor stator until it becomes a transparent gel
**2.** Add B and mix
**3.** Pre-mix C, add to A&B and mix
**4.** Add D, E, F, G & H and mix

## AlUla Peregrina™ Anti-Aging Light Cream

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Water | Aqua | 60,75 |
| A | Frametime LTX | Sodium magnesium silicate & Xanthan gum & Citric acid | 2,8 |
| A | NEOSORB P60 | Sorbitol | 15 |
| B | Propanediol - Massocare | Propanediol | 15 |
| B | Guar gum | Cyamopsis tetragonoloba gum | 0,4 |
| C | Sea salt | Maris sal | 0,6 |
| C | Hydrolyzed AlUla Peregrina™ Extract | Aqua & sodium citrate & Moringa peregrina seed extract & propionic acid | 1,5 |
| D | Skinperf LWG | Aqua & Glycolic acid & Lactic acid & Sodium magnesium silicate & Citric acid & Xanthan gum | 2,5 |
| E | Fragrance | Benzyl alcohol | 0,95 |
| | | | 0,5 |

**Protocol**
Prepare phase A and heat to 45°C to obtain a homogeneous mixture. Add phase B and mix. Melt C to 70°C, add to the previous mixture and mix until obtain a homogeneous product. Wait for the temperature to drop to 30°C before adding D then E.

**1.** Prepare and heat A to 45°C.
**2.** Add B to A and mix.
**3.** Melt C to 70°C and mix.
**4.** Add C and mix.
**5.** Wait for temperature to drop to 30°C.
**6.** Add D then E and mix.

## Brightening mask

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Water | Aqua | 38,5 |
| B | Unipure white LC987 EM | CI 77891 & Silica | 2 |
| B | White clay | Kaolin | 18 |
| B | Frametime CX | Bentonite & Xanthan gum & Citric acid | 6 |
| B | Sericite GMS-4C | Mica | 1 |
| C | Propanediol -Massocare | Propanediol | 5 |
| C | Palmera G995E | Glycerin | 7 |
| D | Fragrance | Parfum | 0,5 |
| D | Ephyster MCR | Brassica napus extract | 5 |
| D | Organic Palm Desert oil | Balanites roxburghii seed oil | 7 |
| D | HTR1 | Helianthus annuus seed oil & Protium heptaphyllum resin | 3 |
| D | DUB MCT 5545 MB | Caprylic / Capric triglyceride | 5 |
| E | Hydrolyzed AlUla Peregrina™ Extract | Aqua & sodium citrate & Moringa peregrina seed extract & propionic acid | 1 |
| F | Sepicide LD | Phenoxyethanol | 1 |

**Protocol**
**1.** Add B to A and mix
**2.** Add C and mix
**3.** Add D and mix
**4.** Add E and mix
**5.** Add F and mix

# LIPOPHILIC ALULA PEREGRINA™ EXTRACT

PATENT N°WO2021234159

## Instant skin soothing and protection with long-term cell DNA repair

**The Lipophilic AlUla Peregrina™ Extract protects the skin with long-lasting results.**

## COSMETIC BENEFITS

The Lipophilic AlUla Peregrina™ Extract:
- protects skin cell DNA integrity
- prevents and treats skin sagging
- provides soothing for the surface of the skin
- plumps the surface of the skin

## MECHANISMS OF ACTION

The Lipophilic AlUla Peregrina™ Extract provides long-term anti-aging action by activating telomerase. This enzyme repairs the telomeres of the chromosomes during successive rounds of replication to minimize the telomere shortening and extend the number of replications of the chromosomes.

The Lipophilic AlUla Peregrina™ Extract prevents and treats skin sagging by inhibiting collagenase. Collagenase degrades collagen in the skin.

The Lipophilic AlUla Peregrina™ Extract provides soothing and plumping effects for tired or aging skin by inhibiting phospholipase A2, a key enzyme promoting inflammation, and Endothelin-1, the most potent vasoconstrictor in the human body.

**ORIGIN AND DESCRIPTION**
Family: Moringaceae
Renewable botanical origin: seeds
Geographic origin: AlUla, Saudi Arabia
Extraction: Ethanol

**REGULATORY DATA**
English name: Lipophilic AlUla Peregrina™ Extract
Inci: Moringa peregrina seed oil extract and Caprylic/Capric Triglyceride
Natural ingredient index = 1 (ISO 16128)
China: pending (2024)

**PHYSICOCHEMICAL CHARACTERISTICS**
Form: Liquid
Color: Colorless to yellow
Odor: Almost odorless

**FORMULATION DATA**
Preservatives: -
Use level in formula: 2.0% - 5.0%
Solubility: Oil soluble
Shelf life: 36 months

**PACKAGING MATERIALS**
Food grade polyethylene bags, polyethylene drums

**BIOLOGICAL ACTIVITY**

***IN VITRO***

**Long-term anti-aging action through preventive protection of cell DNA integrity**
- Telomerase increased by 18.90% at a concentration of 2.0%

**Curative and preventive anti-aging**
- Collagenase inhibition by 87,71% at a concentration of 0.10%

**Soothing effect**
- Phospholipase A2 inhibition by 19.00% at a concentration of 2.0%

**Plumping effect**
- Endothelin-1 inhibition by 53.21% at a concentration of 5.0%

***IN VIVO CLINICAL STUDIES***

**TransEpidermal Water Loss**
- 81% of volunteers confirmed that their skin is nourished
- 86% had positive feedback on the results after 21 days of application.

# BIOLOGICAL ACTIVITY

**Our skin bears the stigmas of daily stress and progressive aging.**

**The Lipophilic AlUla Peregrina™ Extract provides active protection of the skin cell DNA integrity by improving telomere replication cycles. It prevents collagen degradation and skin sagginess, delivers instant relief by reversing stress-induced inflammatory mechanisms.**

## LONG-TERM ANTI-AGING ACTION THROUGH PREVENTIVE PROTECTION OF SKIN CELL DNA INTEGRITY

**The Lipophilic AlUla Peregrina™ Extract preserves skin cell DNA integrity over time and prevents genetic drift due to aging by significantly activating telomerase.**

### Prevent genetic drift

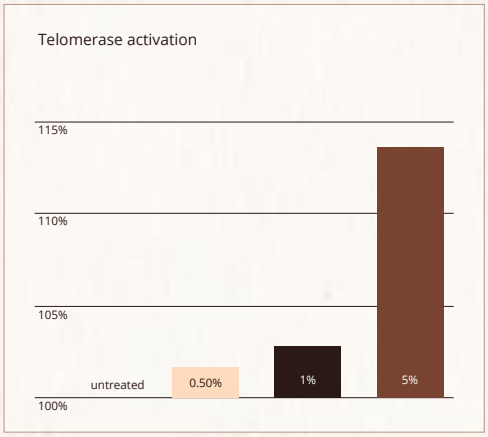
Telomerase builds and repairs the telomeres at the end of the chromosomes, and it can restore these natural caps shortened during successive rounds of chromosome replication. Activating telomerase preserves skin cell DNA integrity over time.

**Telomerase activation (in vitro)**

Keratinocytes from a normal donor's skin were treated with 0.50%, 1.00%, and 5% Lipophilic Peregrina Extract for 24 hours or left untreated.

The Lipophilic AlUla Peregrina™ Extract at 5% significantly activates telomerase.

The Lipophilic AlUla Peregrina™ Extract has a strong ability to preserve skin cell DNA integrity over time.

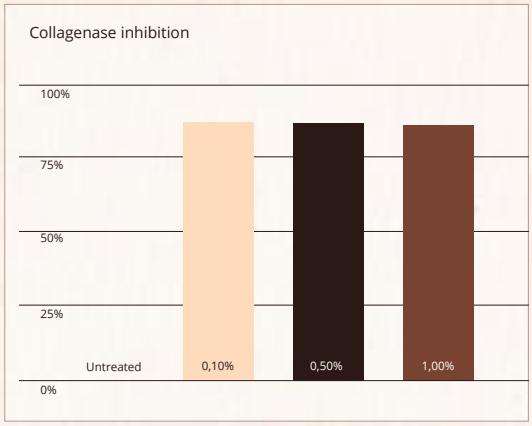



## CURATIVE AND PREVENTIVE ANTI-AGING

One of the main consequences of stress and aging is the acceleration of collagen degradation, leading to skin sagging. The Lipophilic AlUla Peregrina™ Extract prevents collagen degradation by significantly inhibiting collagenase.

## Prevent and treat skin sagging

Collagenase degrades collagen in the skin. Inhibiting collagenase prevents and treats skin sagging.




**Collagenase inhibition (in vitro)**

In vitro assay with 0.10%, 0.50%, and 1.0% of Lipophilic AlUla Peregrina™ Extract.

The Lipophilic AlUla Peregrina™ Extract at 0.10%, 0.50%, and 1% significantly inhibits collagenase.

The Lipophilic AlUla Peregrina™ Extract has a strong ability to prevent and treat skin sagging.

# INSTANT SOOTHING AND PLUMPING

**The Lipophilic AlUla Peregrina™ Extract provides soothing and plumping effects for tired, stressed, pollution-damaged, aging skin by inhibiting phospholipase A2, a key enzyme promoting inflammation, and Endothelin-1, the most potent vasoconstrictor in the human body.**

## Soothing effect

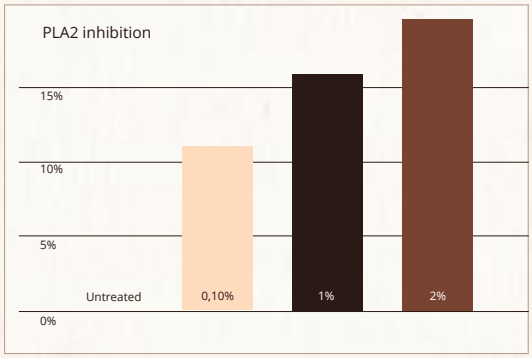
Phospholipase A2 is involved in the inflammation cascade by catalyzing the first step of the arachidonic acid pathway.

**Phospholipase A2 inhibition (in vitro)**

A phospholipase A2 enzyme solution is incubated in its substrate with 0.10%, 1.00%, and 5.00% of Lipophilic AlUla Peregrina™ Extract or left untreated, then mixed with chromogenic DTNB before a 15-minute incubation at 25°C.

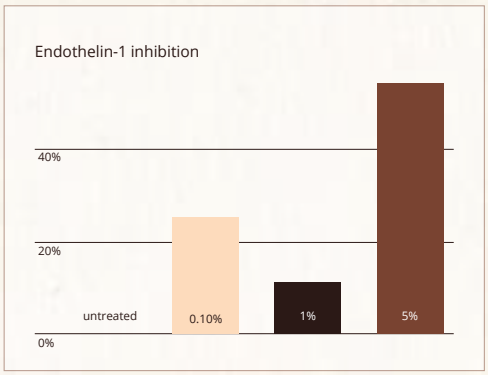
The Lipophilic AlUla Peregrina™ Extract at 2.00% can significantly inhibit the production of phospholipase A2.

The Lipophilic AlUla Peregrina™ Extract has a strong ability to soothe and relax the skin.




## Plumping effect (in vitro)

Endothelin-1 is the most potent vasoconstrictor in the human body. Inhibiting Endothelin-1 provides vasodilatation and a plumping effect.




**Endothelin-1 inhibition (in vitro)**

Endothelial cells from a normal donor were treated with 0.10%, 1.00%, and 5% of Lipophilic AlUla Peregrina™ Extract for 24 hours or left untreated. The Lipophilic AlUla Peregrina™ Extract at 1.00% and 5.00% significantly inhibits the production of Endothelin-1. The Lipophilic AlUla Peregrina™ Extract has a strong ability to soothe and plump the skin.

# EFFICACY

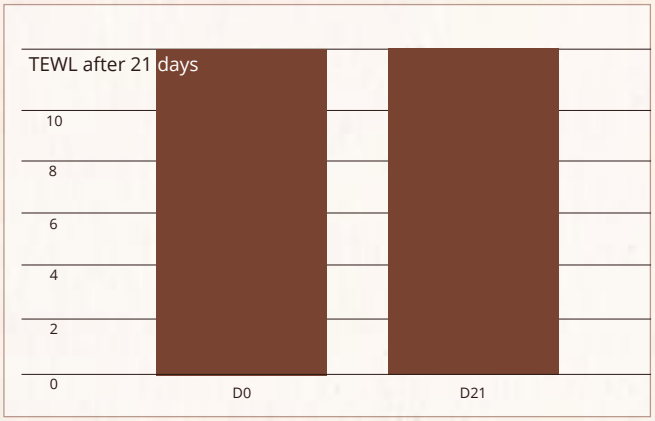
## TransEpidermal Water Loss (in Vivo)

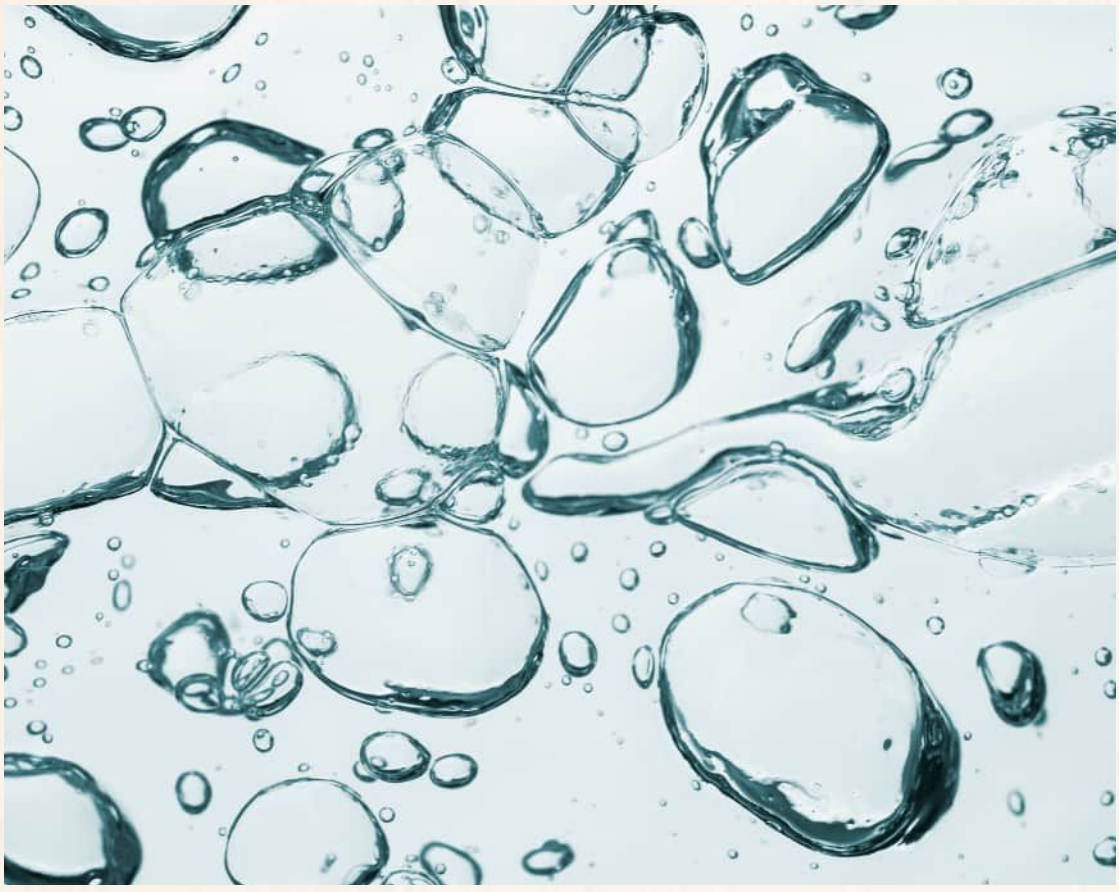
In this clinical study, twenty-one women (50-year-old average, ranging from 20 to 70) with all skin types applied the formula containing 3.00% of Lipophilic AlUla Peregrina™ Extract for 28 days.

After 21 days of application of Lipophilic AlUla Peregrina™ Extract, the average value of TEWL remained stable.

The Lipophilic AlUla Peregrina™ Extract has strong dermo-protective properties after 21 days of application.

81% of volunteers confirmed that their skin is nourished, and 86% had positive feedback on the results after 21 days of application.



# THE LIPOPHILIC ALULA PEREGRINA™ EXTRACT - FORMULATION BOOK

Soothing anti-stress shower gel

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Water | Aqua | 81,7 |
| A | Geoguard ultra | Gluconolactone & Sodium benzoate & Calcium gluconate | 1 |
| A | Sodium benzoate | Sodium benzoate | 0,3 |
| B | Frametime CXG | Bentonite & Xanthan gum & Sodium stearoyl glutamate & Citric acid | 4,5 |
| D | Elfan AT 84 | Sodium cocoyl isethionate | 4 |
| D | Sulfetal C90C | Sodium coco sulfate | 5 |
| C | DUB MCT 5545 | Caprylic / Capric triglyceride | 2 |
| C | Fragrance | Parfum | 0,5 |
| C | Lipophilic AlUla Peregrina™ Extract | Caprylic/Capric triglyceride & Moringa Peregrina seed extract | 1 |
| | | | 100 |

Protocol
**1.** Weigh water and preservatives, heat at 50°C and homogenize
**2.** Add B and mix
**3.** Add C and mix
**4.** Premix D with 31.7% water and heat at 65°C
**5.** Add D + water to ABC under soft agitation (pale)

AlUla Peregrina™ Hair & Body Dry oil

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Ephyster MCR | Brassica napus extract | 50 |
| A | Sunflower oil | Helianthus annuus seed oil | 44 |
| A | Virgin AlUla Peregrina™ Oil | Moringa peregrina (seed) oil | 2 |
| B | Fragrance | Parfum | 2 |
| B | Lipophilic AlUla Peregrina™ Extract | Caprylic/capric triglyceride & Moringa peregrina seed oil extract | 1 |
| B | Vitamin C Tetra E | Ascorbyl tetraisopalmitate | 1 |
| | | | 100 |

**Protocol**
Prepare A and heat slightly to homogenize. When the temperature is below 35°C, add B and homogenize
**1.** Prepare and heat A slightly to homogenize
**2.** Decrease temperature to 35°C, add B and homogenize

AlUla Peregrina™ Hair Oil Serum

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Ephyster MCR | Brassica napus extract | 42,5 |
| A | Virgin AlUla Peregrina™ Oil | Moringa peregrina (seed) oil | 42 |
| B | OLO 3D | Stearalkonium bentonite | 12 |
| B | Unipure red LC320 | CI 75470 | 0,01 |
| C | Lipophilic AlUla Peregrina™ Extract | Caprylic/Capric triglyceride & Moringa peregrina seed oil extract | 1 |
| C | Fragrance | Parfum | 2 |
| C | Vitamin C Tetra E | Ascorbyl tetraisopalmitate | 0,5 |
| | | | 100 |

**Protocol**
Prepare A and heat to 35°C. Prepare B and add to A. mix until the temperature reaches 45°C. Add C phase and homogenize.

**1.** Prepare and heat A to 35°C
**2.** Prepare B and add to A
**3.** Mix until the temperature reaches 45°C
**4.** Add C and homogenize

AlUla Peregrina™ Regenerating Hair Mask

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Ephyltec A | Aqua & Anacardium occidentale extract* & Sodium citrate & Sodium benzoate | 50 |
| A | Frametime CX | Bentonite & Xanthan gum & Citric acid | 2 |
| B | Lipophilic AlUla Peregrina™ Extract | Moringa peregrina (seed) oil | 45,4 |
| C | Fragrance | Parfum | 0,5 |
| D | Lipophilic AlUla Peregrina™ Extract | Caprylic/Capric triglyceride & Moringa Peregrina seed oil extract | 1,5 |
| E | Benzyl alcohol | Benzyl alcohol | 0,6 |
| | | | 7 |

**Protocol**
Prepare A and heat slightly to homogenize. When the temperature is below 35°C, add B and homogenize

**1.** Prepare and heat A slightly to homogenize
**2.** Decrease temperature to 35°C, add B and homogenize

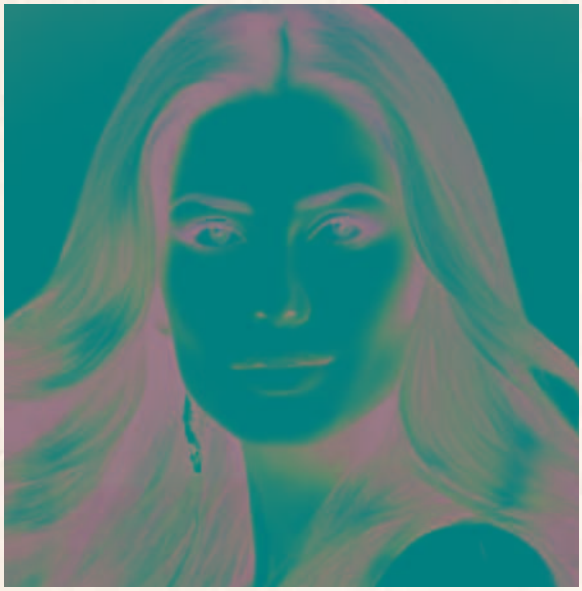
AlUla Peregrina™ Hair & Body Dry oil

| Phase | Commercial Name | INCI | % |
|---|---|---|---|
| A | Ephyster MCR | Brassica napus extract | 50 |
| A | Sunflower oil | Helianthus annuus seed oil | 44 |
| A | Virgin AlUla Peregrina™ Oil | Moringa peregrina (seed) oil | 2 |
| B | Fragrance | Parfum | 2 |
| B | Lipophilic AlUla Peregrina™ Extract | Caprylic/capric triglyceride & Moringa peregrina seed oil extract | 1 |
| B | Vitamin C Tetra E | Ascorbyl tetraisopalmitate | 1 |
| | | | 100 |

**Protocol**
Prepare A and heat slightly to homogenize. When the temperature is below 35°C, add B and homogenize
**1.** Prepare and heat A slightly to homogenize
**2.** Decrease temperature to 35°C, add B and homogenize

# HYDROLYZED ALULA PEREGRINA™ PASTE EXTRACT

## Innovative upcycled ingredient with proven smoothing, tightening, tensor and film-forming effects on the skin.



The Hydrolyzed AlUla Peregrina™ Paste Extract reveals unexpected potency within one of the most surprising by-products of the cold press of the Peregrina seeds. The soft and nourishing paste becomes a powerful and very stable active, making it a prime choice for cutting-edge skincare formulations.

**The Hydrolyzed AlUla Peregrina™ Paste Extract smooths and tightens the skin while providing film-forming and a tensor effect over time.**

## COSMETIC BENEFITS

The Hydrolyzed AlUla Peregrina™ Paste Extract:
- Smoothing effect on the skin
(reduction of skin microrelief) and tightens the skin
- Provides film-forming and a tensor effect over time

**ENGLISH NAME**
Hydrolyzed AlUla Peregrina™ paste extract

**RENEWABLE BOTANICAL ORIGIN**
Moringa peregrina seeds

**GEOGRAPHIC ORIGIN**
AlUla Saudi Arabia

**INCI**
Aqua, Sodium citrate, Moringa peregrina seed extract, Proprionic acid

**NATURAL INGREDIENT INDEX**
(ISO 16128) Natural Index 0.89,
Natural Origin Index 0.96

**PRESERVATIVE**
Propionic acid (1.00%)

**USE LEVEL IN FORMULA**
0,50% – 5,00%

**SOLUBILITY**
Water soluble

**PACKAGING MATERIALS**
Food grade polyethylene bags, polyethylene drums

**EXTRACTION METHOD**
Hydrolysis of the AlUla Peregrina™ paste obtained after cold press

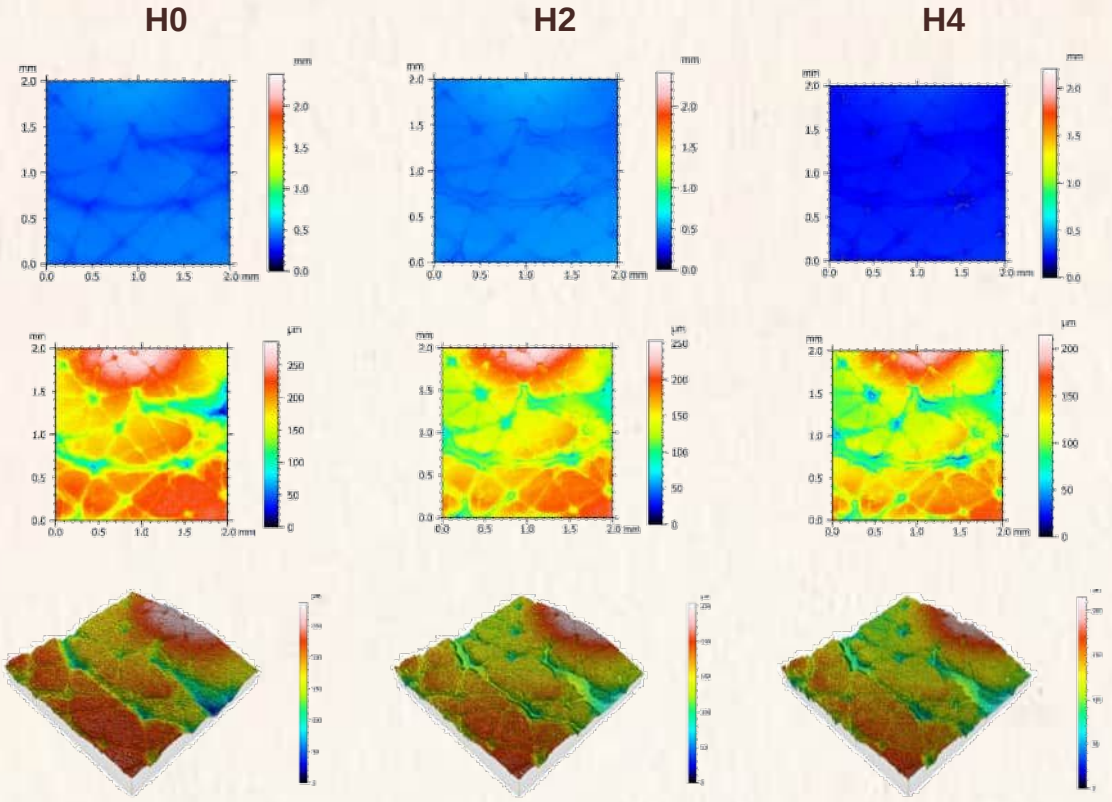
**CAS**
7732-18-5 ; 6132-04-3; ND ; 79-09-4

**EINECS**
231-791-2 ; 200-675-3 ; ND ; 201-176-3

# BIOLOGICAL ACTIVITY

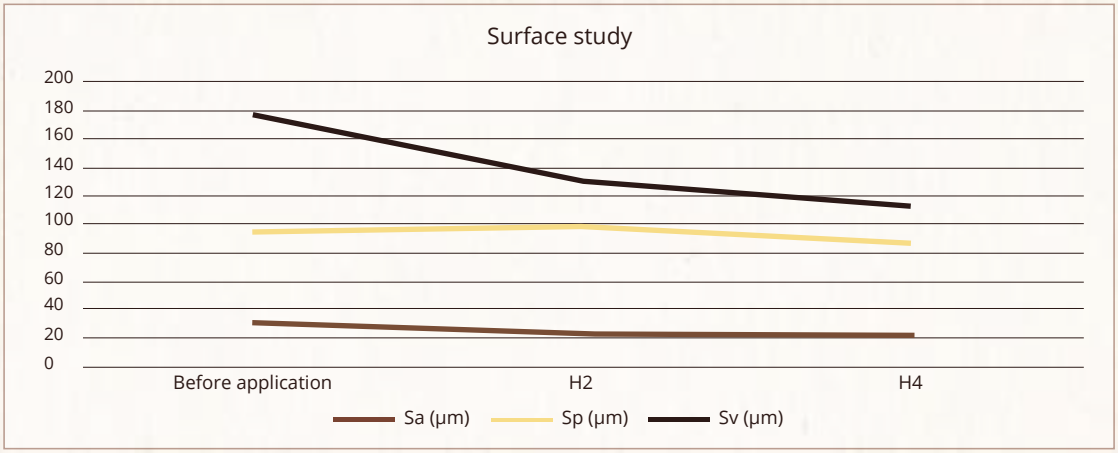
**PROVEN SMOOTHING AND TIGHTENING ACTIVITY**

The Hydrolyzed AlUla Peregrina™ Paste Extract shows a reduction in the surface roughness of skin explants 2 hours and 4 hours after application. The microrelief smoothing data collected during skin surface analysis shows a sharp decrease of the surface coefficient 2 and 4 hours after application.




**TENSOR AND FILM-FORMING EFFECTS ON THE SKIN FOR A YOUTHFUL AND REVITALIZED APPEARANCE**

Tensor and film-forming effects on the skin for a youthful and revitalized appearance
Arithmetic mean of the heights between peaks and lows value [Sa] decreases along with the maximum depth of the lows [Sv] by almost 26% in depth after 2 hours and 36% after 4 hours.



# SCIENTIFIC INFORMATION

## Telomeres

### BACKGROUND & LITERATURE

Telomere length dynamics are essential for regulating cell replicative life span, especially in long-lived species. Telomere shortening and telomerase activity are critical factors in aging and tumorigenesis [Te1].
Telomeres are complex nucleotide sequences that cap the end of chromosomes from degradation, unwanted recombination-fusion, and inappropriate activation of DNA damage response. They also play a critical role in cell division and chromosome stability. There is growing evidence that telomere stability can be affected by occupational and environmental exposure, as some of these factors are associated with an increase in inflammation, oxidative stress, DNA damage, chromosome aberration, and epigenetic alterations.
Telomerase is a ribonucleoprotein that catalyzes the addition of telomeric repeats to the ends of telomeres. Telomeres are typically 7-10 kb in length and include multiple repeats of the sequence -TTAGGG-.
Telomerase is not expressed in most adult cells, and telomere length decreases with successive rounds of replication. After a certain number of replication rounds, the progressive shortening of the telomeres results in the cells entering a telomeric crisis stage, leading to cellular senescence. Certain diseases are associated with rapid telomeric loss, resulting in premature cell senescence. Expression of the gene encoding the human telomerase protein in human cells has been shown [Te2] to confer a «long-lasting» phenotype, presumably bypassing the cells' natural senescence pathway. In addition, expression of the telomerase gene in aging cells with short telomeres increases telomere length and restores a phenotype typically associated with younger cells.

### REFERENCES

[Te1] Shay J. W., Senescence and Immortalization: Role of Telomeres and Telomerase, Carcinogenesis 26 5, pp. 867-874, 2005.
[Te2] Blasco M., Telomere Length, Stem Cells, and Aging, Nature Chemical Biology 3, pp. 640-649, 2007.

## Stem cells

### BACKGROUND & LITERATURE

Adult tissues, including the skin epidermis, gastrointestinal epithelium, and the hematopoietic system, have a high cell turnover rate. The physiological process of maintaining tissue homeostasis is attributed to a constant number of cells in renewing organs to sustain their functions and integrity. Endothelial stem cells (ESCs) are essential for the maintenance and regeneration of skin tissues. Adult skin is composed of a diverse organized array of cells from different embryonic origins; epidermis and dermis are developed respectively from ectoderm and mesoderm.
The epidermis develops from the embryonic surface ectoderm. It starts as a single layer of unspecified progenitor cells covering the embryo after neurulation and grows into the epidermal basal layer. The epidermal basal layer is enhanced with Epidermal Stem Cells (ESCs). In effect, cells in this layer give rise to all epidermal structures, including a stratified epidermis (also called the interfollicular epidermis) and epidermal appendages, such as hair follicles, sebaceous glands, and sweat glands. The underlying dermis is derived primarily from the mesoderm under the ectoderm. The mesoderm is the primary source of mesenchymal stem cells that give rise to collagen-producing fibroblasts, subcutaneous adipocytes, and immune cells in the skin [Sc1].
Basal cells express several distinctive markers, including keratins and transcription factors. Periodically, these cells withdraw from the cell cycle, commit to differentiate terminally, move outward, and are

eventually shed from the skin surface. This architecture allows the epidermis to generate a self-perpetuating barrier that keeps harmful microorganisms out and essential body fluids in.
Stem cells are undifferentiated cells with a young genotype capable of self-renewal and differentiating to produce an organ or tissue, such as the skin. At this point, they are identified as multipotent cells. Since 50% of the progeny of the stem cell population remains undifferentiated, stem cells help to preserve homeostasis and ensure the renewal of damaged or senescent differentiated cells.
Still, epidermal stem cells are frequently affected by the environment. Oxidative stress, such as pollution or ultraviolet radiation, causes damage to stem skin cell DNA. This damage alters their capacity for self-renewal and differentiation, leading to a decrease in the pool of stem cells and ultimately to the aging of the skin.

### REFERENCE

[Sc1] Panich U., Ultraviolet Radiation-Induced Skin Aging: the role of DNA Damage and Oxidative Stress in Epidermal Stem Cell Damage Mediated Skin Aging, Stem cells International, 7370642, 2016.

## DKK1 DKK3

### BACKGROUND & BIBLIOGRAPHY

The implication of interactions between melanocytes and fibroblasts in the regulation of melanogenesis is well-known and widely studied. Although these interactions are not yet fully understood, they are at the origin of the whiteness of the palm-plantar areas. They are now used in cosmetics for the development of depigmenting products.
Yamaguchi et al. [Do1] demonstrated that a soluble messenger produced by the fibroblasts of the palmoplantar areas could modify the differentiation program of the melanocytes in these areas, leading to a decrease in the production of melanin. The Yamaguchi team identified this messenger as Dikkopf-1 (DKK-1) protein.
The signaling pathways used by DKK-1 to produce these results are well-identified today. Through its antagonistic action on the Wnt receptor, DKK-1 is indeed able to shunt the intracellular signaling pathways activated by β-catenin, generally responsible for the regulation of genes involved in cell differentiation.
Yamaguchi et al. [Do1] also demonstrated that DKK-3, a molecule like DKK-1 but without effect on the Wnt receptor, could play a regulatory role in the impact of DKK-1. The greater the quantity of DKK-3 in the vicinity of this receptor to Wnt, the weaker the interactions between DKK-1 and this receptor. An increase in DKK3 reduces the inhibitory effects of DKK-1 on cell differentiation.
The work of Yamaguchi et al. [Do1] suggests that the identification of agents influencing the DKK1 / DKK3 ratio in cultures of normal human dermal fibroblasts of non-palmoplantar origin would make it possible to control the production of melanin from normal non-palmoplantar human melanocytes, and more generally genes involved in cell differentiation.

### REFERENCE

[Do1] Yamaguchi Y. et al., Mesenchymal-Epithelial Interactions in the Skin: Increased Expression of Dickkopf by Palmoplantar Fibroblasts Inhibits Melanocyte Growth and Differentiation, J. Cell Biol. 165 2, pp. 275-285, 2004.

## ZAG

### BACKGROUND & BIBLIOGRAPHY

Zinc alpha-2-glycoprotein (ZAG) is a plasma glycoprotein that derives its name from its electrophoretic mobility and from its ability to be precipitated by Zn salts [Za1]. ZAG is part of the immunoglobulin gene superfamily and has a three-dimensional structure that is highly homologous to major histocompatibility

complex (MHC) class I and II molecules [Za2].
To further investigate the biological properties of ZAG, stable transfectants of recombinant human (rh)ZAG were created in the B16F10 murine melanoma cell line. The effect of ZAG transfection on melanin production was confirmed in vitro and in vivo. So were the impact of exogenous ZAG on melanin production by parent B16 cells and melan-A primary melanocytes and the effect of ZAG on tyrosinase expression and activity. These studies show that ZAG inhibits melanin production in both normal and malignant melanocytes. The mechanisms include post-transcriptional effects on tyrosinase protein, with the potential for additional indirect effects. These studies resulted in the identification of a previously unknown biologic function of ZAG and have confirmed a method of modulating melanin production, thereby preventing or decreasing pigmentation of skin and hair due to increased melanin production [Za3] [Za4].

### REFERENCES

[Za1] BURGI W. Preparation and Properties of Znα2-glycoprotein of Normal Human Plasma, J. Biol. Chem. 236, p. 1066-1074, 1961.
[Za2] Sanchez M.L et al., Structure of Human ZAG, a Fat-Depleting Factor Related to MHC Molecules, Science 283, pp. 1914-1919, 1999.
[Za3] Hale L., Method of Modulating Melanin Production, United States Patent No. US 7,803,750 B2, 2010.
[Za4] Ghada F. M. et al., Highlights in Pathogenesis of Vitiligo, World J. Clin. Cases 16 3 3, pp. 221-230, 2015.

## Melanogenesis

### BACKGROUND & LITERATURE

Skin pigmentation is a complex process that, in the epidermis as in the hair follicles, begins with the synthesis of melanin in the melanosomes within the melanocytes, followed by the transfer of the melanosomes to the surrounding keratinocytes, which will, in turn, carry the pigment and possibly degrade it.

In humans, the entire melanocyte population is found in the hair follicles and the basal layer of the epidermis. Whatever their location in the skin, melanocytes have a common embryological origin, the neural crest from which they derive in the form of melanoblasts (non-pigmented cells).

There are two types of melanin in epidermal cells, eumelanin, a brown-black pigment, and pheomelanin, a yellow-red pigment. In melanocytes, eumelanosomes and pheomelanosomes coexist. Tyrosinase is the key enzyme that regulates the first steps in the synthesis of pheomelanin and eumelanin: the conversion of L-tyrosine to L-3,4-dihydroxyphenylalanine (L-DOPA) and the oxidation of this compound into dopaquinone. From dopaquinone, the synthetic routes differ for eumelanin and pheomelanin.

Melanin's primary role is to protect the skin from the harmful effects of UV rays, thus preventing the development of skin cancer [M1].

### REFERENCES

[M1] Brenner M. et al., The Protective Role of Melanin Against UV damage in human skin, Photochem. Photobiol. 84 3, p. 539-549, 2008.

## Bleomycin hydrolase

### BACKGROUND & BIBLIOGRAPHY

Bleomycin hydrolase (BH) has an essential physiological role in localizing the stratum corneum (SC) in mammalian skin and generating free amino acids from citrullinated peptides in the last step of the filaggrin degradation pathway [Bl1].

Keratin fibers in the epidermal granular layer aggregate by binding into a filaggrin protein during keratinization, creating a specific form known as a keratin pattern. However, a precursor of filaggrin, profilaggrin (comprising 10 to 12 tandemly repeated filaggrin units), is present in large amounts in the keratohyalin granules of granule cells. During keratinization, keratin fibers are aggregated by dephosphorylation, together with the formation of filaggrin monomers. Once the aggregated fibers are deiminated by the action of an enzyme known as peptidyl arginine deiminase (PAD) and released from keratin, they are degraded into amino acids in the upper horny layer. These amino acids are natural moisturizing factors (NMF) and play an essential role in retaining moisture in the horny layer and absorbing ultraviolet rays [Bl1].

Amino acids serve as the main component of NMF and originate in filaggrin. The correlation between dry skin and filaggrin has been established. In recent years, amino acids have been determined to decrease in dry skin with senile xerosis and other atopic diseases [Bl2].

### REFERENCES

[Bl1] Hibino T. et al., Bleomycin Hydrolase Production Promoter, United States Patent US 2014/0010901 A1.
[Bl2] Horii I. et al., Stratum Corneum Hydration and Amino Acid Content in Xerotic Skin, Br. J. Dermatol. 121 5, pp. 587-592, 1989.

## Endothelins

### BACKGROUND & BIBLIOGRAPHY

Endothelin (ET) is the strongest vasoconstrictor known in the human body. Paradoxically, a decrease in endothelin is also known to create a vasodilator effect [En1] [En2].

Endothelin is a bioactive factor that continually contracts smooth vascular and non-vascular muscles via direct and indirect actions. An increase in endothelin activity is thought to provide continuous vasoconstriction to blood vessels in peripheral sites, kidneys, and the brain. In animals, including humans, three types of endothelin family peptides (ET-1, ET-2, and ET-3) with similar structures are present. All these peptides have vasoconstriction and vasodilation actions [En3].

In recent years, the role of endothelin in various cells other than smooth vascular muscle cells has been evidenced. Scientific publications, for instance, have reported that generation of ET-1 and other factors are increased in keratinocytes when the skin is exposed to UV irradiation and have suggested ET-1 to be associated with melanogenesis in melanocytes exposed to UV irradiation.

Accordingly, suppression of the expression of endothelin is thought to be helpful in the prevention or amelioration of skin pigmentation [En4] [En5] [En6].

### REFERENCES

[En1] Hirata, Y. et al., Cellular mechanism of action by a novel vasoconstrictor endothelin in cultured rat vascular smooth muscle cells, Biochem. Biophys. Res. Commun. 154 3, p. 868-875, 1988.
[En2] Shalinkumar P et al., H2S Mediates the Vasodilator Effect of Endothelin-1 in the Cerebral Circulation. Am. J. Physiol. heart circ. Physiol. 315, pp. 1759-1764, 2018.
[En3] Hashimoto H. et al., Patent PCT/JP2017/039319.
[En4] Imokawa G. et al., Endothelin-1 as a New Melanogen: Coordinated Expression of its Gene and the Tyrosinase Gene in UVB-Exposed Human Epidermis, J. Invest. Dermatol. 105 1, pp. 32-37, 1995.
[En5] Imokawa G. et al., Endothelins Secreted from Keratinocytes are Intrinsic Mitogens for Human Melanocytes, J. Biol. Chem. 267, pp. 24675-24680, 1992.
Gilchrest B. et al., Mechanisms of Ultraviolet Light-Induced Pigmentation, Photochem. Photobiol. 63, pp. 1-10, 1996.

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