



CAPHIRA®

Designed to consolidate the hair's integrity
Global natural protector of the hair follicle, fiber and scalp

Prevents hair loss

Increases follicle survival and stimulates the ferritin pathway



Stimulates follicle metabolism



Reinforces the hair fiber and protects it against dryness and chlorine stress



Restores and enhances hair shine



Improves scalp health

Provides soothing properties



PATENTED

Nowadays, a healthy-looking hair is a sign of good health with attractive appearance for women as well as men.

The hair market moves fast, constantly researching new components to improve hair looking.

Hair disorders have a dramatic impact on quality of life and emotional well-being. They are fundamentally caused by variations in hair follicle density, size and/or changes in the hair growth cycle as well as by hair loss (alopecia). Alopecia is a major concern in dermatology including different forms, the most common being the androgenetic alopecia, in both men (male pattern hair loss) and women (female pattern hair loss).

Therefore, such hair disorders must be taken into consideration.

Hair protects the scalp from sunburn and mechanical assaults, provides thermoregulation and social communication. It can be damaged by various environmental influences and chemical treatments leading to loss of quality, hair becoming dry with shine loss and possible scalp irritation.

GELYMA proposes CAPHIRA®, a smart natural patented combination of an extract of the red alga *Kappaphycus alvarezii* supplemented with seawater and vegetable organic glycerin.

This active offers a very interesting mineral composition due to its content in magnesium (1088 ppm), iron (22 ppm) and zinc (26 ppm). Such composition may help fighting mineral deficiencies known to cause problems to hair growth and scalp vitality.

CAPHIRA® is revealed as a powerful global protector of the three parts of hair: the follicle, the fiber and the scalp to consolidate the hair's integrity.

- **At the follicle level**, CAPHIRA® prevents hair loss by increasing follicle survival and stimulates the ferritin gene known to be linked to alopecia in women having an iron deficiency. It also boosts follicle metabolism through the increase of the expression of genes linked to cell cycle regulation and cell signaling.
- **At the hair fiber level**, CAPHIRA® reinforces the fiber. It increases the expression of major keratins genes to provide resistance against environmental and mechanical attacks. It protects the cuticle of dry hair and repairs damage caused by chemical stress. It restores and enhances shine.
- **At the scalp level**, CAPHIRA® ameliorates the general comfort for a healthier state, decreasing erythema and Inflammation of volunteers presenting scalp redness or visible irritation.

As a result, the hair feels revitalized with improved aesthetic qualities. It looks shiny and better protected against damage from dryness.

Effectiveness has been demonstrated on the hair follicle by gene expression analysis and *ex vivo* study (collaboration BIOALTERNATIVES-FRANCE) and on the hair fiber by scanning electron microscope observations. Other studies concerned hair shine (*ex vivo* on tresses) and the scalp status (*in vivo*) versus placebo (collaboration INOVAPOTEK-PORTUGAL).

CAPHIRA® is suitable in numerous hair care compositions combining protection and comfort.

It is COSMOS approved and China compliant.

Patent FR 2000877.

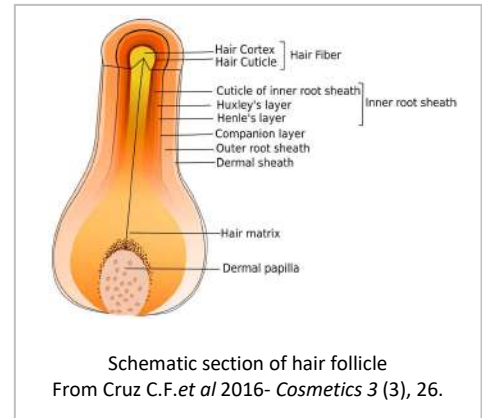
ACTION ON THE HAIR FOLLICLE

The follicle is the live part of hair from which the hair grows and where the hair fiber is generated.

This structure includes multiple compartments (*cf.* figure in front) clearly distinguishable by their morphology and type of differentiation.

It represents a unique, highly regenerative system that undergoes different phases of development and differentiation controlled by a network of signalling pathways.

It may have significant positive and negative influence on hair health.



CAPHIRA® is able to influence the hair follicle by two ways:

- prevention of hair loss and
- modulation of key biomarkers of the follicle metabolism.

CAPHIRA® prevents hair loss

Hair loss (also called alopecia) is a common problem that affects over 75% of men and 25% of women in developed countries with three major disorders named alopecia areata (AA), androgenetic alopecia (AGA), and telogen effluvium (TE). Causes are diverse, inducing in each case great emotional impact.

Increase of the hair follicle survival

Ex vivo study

Hair loss is characterized by abnormal hair cycles with reduced size and survival of most of the follicles.

Methods

Hair follicles are micro dissected from a human skin fragment (face lift, female donor, 66 years old). They are cultured in 24-well plates (2 follicles/well) in a culture medium for 20 days. Their survival is estimated by morphological observations of the hair bulbs and by counting the number of apoptotic bulbs versus the total number of bulbs at D13, D15, D17 and D20.

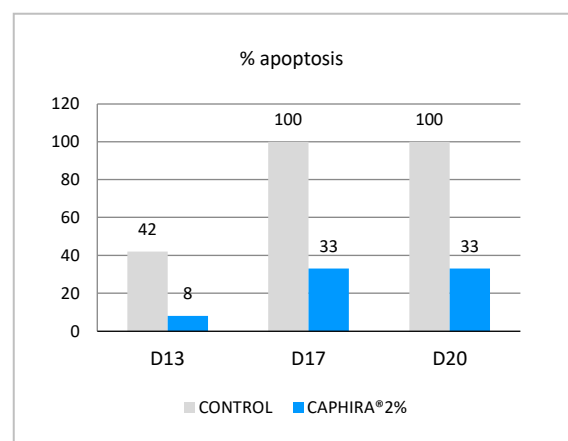
Results after only 20 days

In the control conditions, hair follicles start to undergo apoptosis from D13, with 42% of apoptotic hair bulbs. This phenomenon increases progressively at D15 (+75% apoptosis) and D17 and D20 (100% apoptosis).

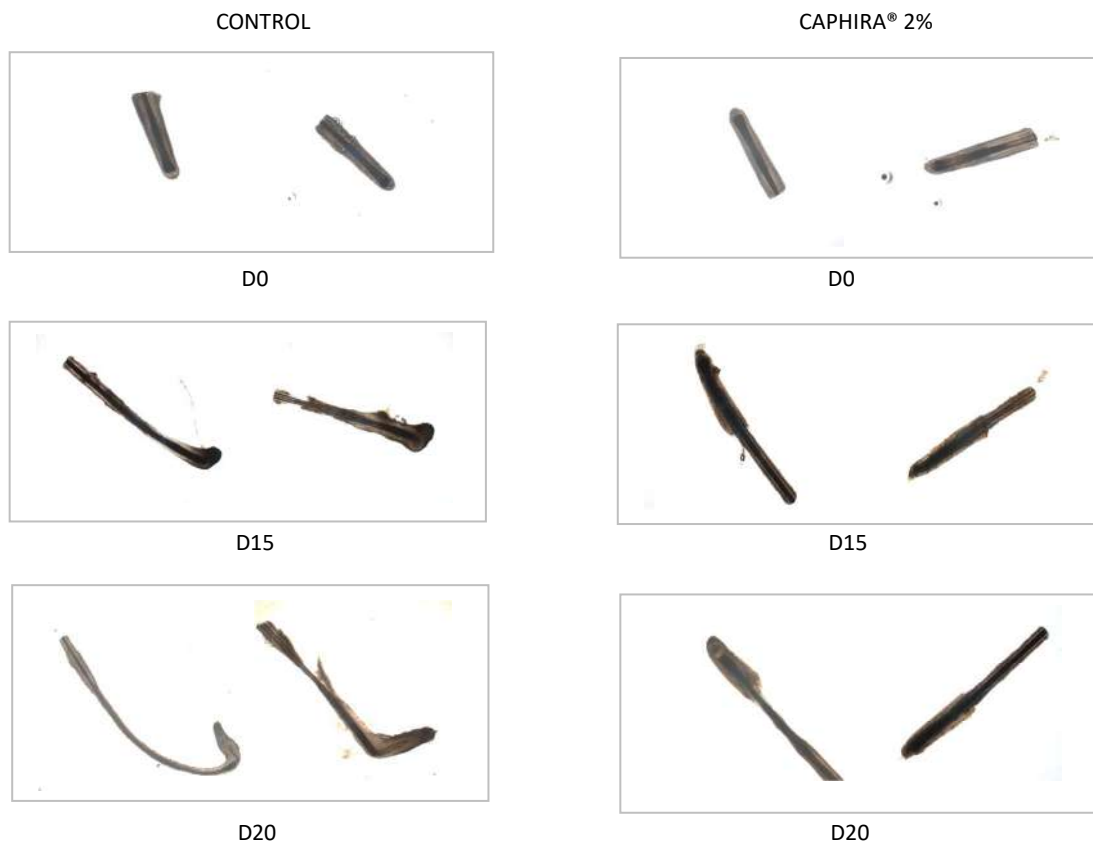
In response to a 2% CAPHIRA® treatment, the entry of the follicles into apoptosis is delayed.

At D13, just one follicle is apoptotic.

At D17 and D20, only 4 bulbs are apoptotic that represent 33% of the control.



Results are illustrated here after. Note the great deterioration of control bulbs at D15 and D20 compared to CAPHIRA® 2%.



CAPHIRA® at 2% clearly induces a beneficial effect on hair follicle survival. Therefore CAPHIRA® offers a protective effect leading to slow down apoptosis and prevent hair loss.

Stimulation of the ferritin pathway

Gene expression

Iron deficiency is known as a major cause of hair loss in women, rarely in men. It perturbs hair cycle in all alopecia forms. It disrupts hair synthesis and seems linked to hair thinning and premature graying.

Hair loss linked to iron stores related to the ferritin level would be present in 72% of women showing diffuse hair loss.

Ferritin is a ubiquitous iron-storage protein present with a concentration correlated to the amount of iron stores. It is regulated by iron-dependent genes that may be affected by iron deficiency.

So, appreciating the importance of ferritin as a factor in hair loss appears to be important for cosmetic hair treatment.

Methods

The expression of genes is analyzed using RT-q PCR method on total RNA extracted from the hair follicles in culture of each experimental conditions in duplicate (n=2). 32 genes are selected for their importance in hair follicle physiology.

Results

CAPHIRA® is able to over-express by 503% compared to control the ferritin gene FTH1 (*Ferritin, heavy polypeptide 1*) that encodes the heavy subunit of ferritin, the major intracellular iron storage protein.

Therefore, CAPHIRA® could help to prevent different forms of alopecia linked to ferritin pathways and especially for women alopecia. It could also contribute to fight hair thinning and premature graying.

CAPHIRA® stimulates follicle metabolism

Gene expression

The hair follicle metabolism is regulated by numerous signaling pathways involving numerous cytokines, growth factors neurotransmitters, transcription factors and enzymes acting in the different key compartments of the hair follicle.

CAPHIRA® modulates the expression of major biomarkers linked to the follicle metabolism.

Modulation of the transcription factors linked to cell cycle regulation

Hair follicle growth and apoptosis is accompanied by the activation of intrinsic apoptotic pathways through the expression of the apoptosis regulatory gene pair known as BCL-2 and BAX.

Results

Results show an over-expression compared to control of:

- ➔ +297% for BAX (*BCL2-associated X protein*)
- ➔ +103% for BCL2 (*B-cell CLL/lymphoma 2*).

CAPHIRA® could have a strong effect on the regulation of apoptosis mechanisms.

Modulation of the major growth factors linked to cell signalling

The dermal hair papilla, composed of specialized fibroblasts located at the base of the follicle, determines follicle growth characteristics. These cells secrete numerous cytokines and growth factors influencing growth in the various compartments of the follicle. In addition, some growth factors play important roles in the androgenic alopecia development.

Results

CAPHIRA® modulates the gene expressions of various growth factors known to be implicated in follicle development and hair alopecia.

BMP 4 gene (*Bone morphogenetic protein 4*) is a marker of hair shaft progenitors in the hair matrix.

- ➔ +119% compared to control.

EGFR gene (*Epidermal growth factor receptor*) is known for its effects on hair development and hair fiber differentiation

- ➔ +173% compared to control.

IGF 1R gene (*Insulin-like growth factor 1 receptor*) plays a key role in the regulation of hair growth and alopecia.

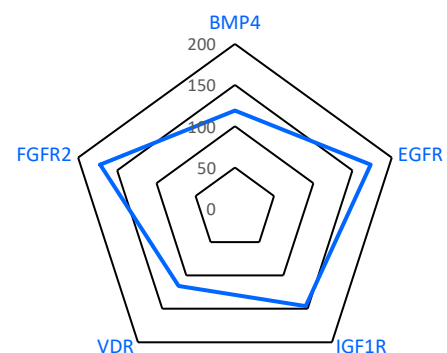
- ➔ +146% compared to control.

VDR gene (*Vitamin D (1,25-dihydroxyvitamin D3)*) is known to prevent alopecia when it is over-expressed.

- ➔ +116% compared to control.

FGFR2 gene (*Fibroblast growth factor receptor 2*) plays an essential role in the proliferation of epidermal cells. It is associated with hair thickness in Asian populations.

- ➔ +172% compared to control.



By over-expressing such major growth factors of the hair follicle, CAPHIRA® stimulates the follicle metabolism and could help to prevent alopecia.

ACTION ON THE HAIR FIBER

The hair fiber is composed of three layers: cuticle, cortex and medulla that can act separately or as a unit.

The cuticle with overlapping scales limits friction between hair fibers and provides sensory and shine characteristics. It encircles the cortex, the major part of the hair mass (75%), responsible for the mechanical strength and pigment of the hair. The central medulla contributes negligibly to the mechanical properties of hair fibers.

CAPHIRA® reinforces the hair fiber

Gene expression

The hair fiber is made up of 95% keratins that contribute to the physicochemical properties and ensure the strength, flexibility and protection of the hair.

Stimulation of hair keratins synthesis

The keratin gene family, made of 54 distinct functional genes in humans, includes two kinds of keratins: the epithelial cytokeratins or “soft” keratins and the hair keratins or “hard” keratins. Both kinds are divided into type I (acidic) and type II (basic to neutral) members.

Keratins act as highly dynamic structures with many functional roles managed by a complex pattern of keratin gene expression in the cuticle, the cortex and the medulla. Disturbances in these structures can result in hair diseases.

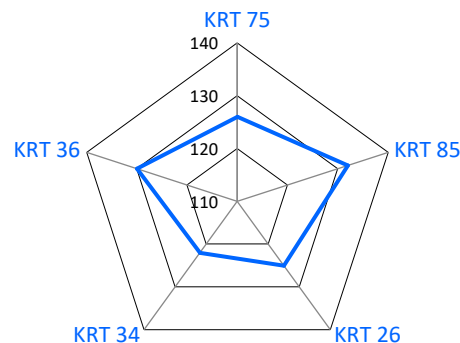
CAPHIRA® increases the gene expression of major hair keratins acting as the building components of fibers.

Results

The table here after groups the results.

| Genes | | | | % control |
|--------|-----------|-------------------|----------------|-----------|
| KRT 75 | (K6hf) | <i>Keratin 75</i> | <i>type II</i> | 129 |
| KRT 85 | (Hb5) | <i>Keratin 85</i> | <i>type II</i> | 132 |
| KRT 26 | (K2Sirs2) | <i>Keratin 26</i> | <i>type I</i> | 125 |
| KRT 34 | (Ha4) | <i>Keratin 34</i> | <i>type I</i> | 122 |
| KRT 36 | (Ha6) | <i>Keratin 36</i> | <i>type I</i> | 130 |

Keratins are known with two different nomenclature, the older name is in parenthesis.



CAPHIRA® modulates both types of keratins, necessary for the formation of intermediate filament keratin.

KRT 85 and KRT 36 are expressed in the hair cortex whereas KRT 75 and KRT 34 are in the medulla and KRT 26 in the cuticle. KRT 75 is specially expressed in the companion layer of the hair follicle and in the hair medulla. The mutation of some keratins, especially KRT 75 and KRT 85 can induce important hair disorders.

By over-expressing key keratins genes, CAPHIRA® stimulates keratinization, restores the integrity of fibers to reinforce the hair. Therefore, it provides resistance to environmental attacks to built stronger hair.

CAPHIRA® protects the hair fiber against dryness and chlorine stress

Ex vivo study

Both women and men of any age can have dry hair.

This situation becomes a common problem highly undesirable because it reflects troubles of hair health. Indeed, it can exist endogenous causes (e.g. deflection in sebum production influenced by hormones or changes in keratinization due dietary deficiencies in proteins, vitamins and minerals) or else exogenous causes brought about cosmetic hair treatments (e.g. applications of hair dyes, highlighting, straightening) or environmental factors (e.g. excessive exposure to sun, cold temperatures, salt water, pool chlorine, atmospheric pollution). In addition, when we age, hair tends to become increasingly drier.

Therefore, hair dryness affects the look and the shine and can lead to alopecia. It needs extra care.

In healthy hair, the scales of the cuticle lie flat, protecting the inner layers and helping hair to retain moisture. Smooth cuticle reflects light, inducing shiny appearance. Hair feels soft and silky to touch.

In damaged hair, the cuticle becomes lifted off. Hair becomes porous because it lost its ability to hold moisture. As a result, it looks dull with breakage and split ends.

Dry hair does not have enough moisture. It has lost its shine. Its cuticle became weathered and porous.

The cuticle acts as a hair's protective shield against aggressive situations, specially dryness. It is responsible for the hair structure.



CAPHIRA® is able to

- 1-preserve fiber integrity of dry hair and
- 2-repair damage caused by chemical stress (chlorine stress)

in order to restore healthy appearance.



Methods

The cuticle of dry hair is observed by scanning electron microscopy (SEM).

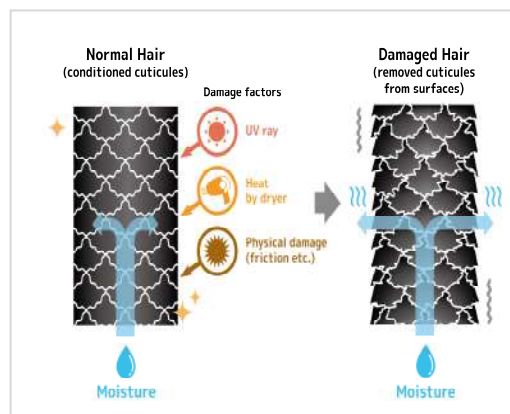
For the second experiment, dry hair is soaked in a solution of chlorine (0.03% Cl) for 1 minute, dried, then treated with 2% CAPHIRA® in water. The observations by SEM are done 24h after experiment.

Results

The observations of the hair cuticle by scanning electron microscopy are presented on next page.

They concern

- dry hair
- dry hair treated with a chlorine solution.



Protection of the cuticle of dry hair

Untreated control

CAPHIRA® treatment (2%)

The hair scales of dry hair appear broken and opened increasing the porosity and inducing hair loss.



The treatment with CAPHIRA® shows sealed scales with protected edges.

The fiber appears more protected.

CAPHIRA® at 2% protects the cuticle of dry hair fiber, defying dryness and preserving fiber integrity . The treatment with CAPHIRA® avoids water loss and limits friction between hair fibers.

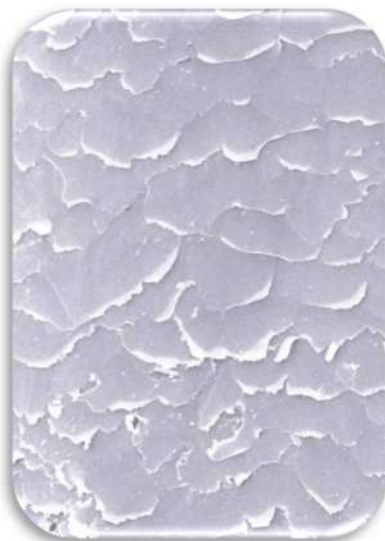
Protection of the cuticle of dry hair submitted to chlorine stress

Chlorinated water is known to cause significant damage to hair. It can induce a green tint to light hair as well as dryness and color loss.

Untreated control

CAPHIRA® treatment (2%)

The scales of the hair treated with chlorine solution are lifted up. In some areas, scales appear damaged and disintegrated.



CAPHIRA® clearly minimizes cuticle damage.

The cuticle is sheathed and its scales smoothed. Fissures and

CAPHIRA® at 2% restores dry hair chemically damaged by chlorine treatment. It regains integrity to the fiber working as a protective shield, repairing hair fibers damage from chemical and therefore facilitating hair dressing.

CAPHIRA® restores and enhances hair shine

In vivo efficacy

Shine is one of the most important and desired cosmetic attributes of the hair. Damages on cuticle as well as dust particles deposits reduce hair shine.

CAPHIRA® avoids hair shine loss and helps to restore healthy appearance.



Methods

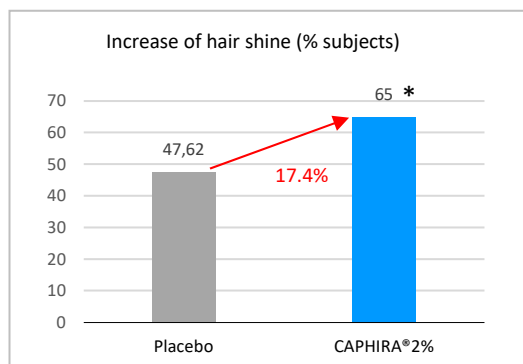
The hair shine efficacy is evaluated on two groups of 21 female/male volunteers. After a 14 days washout period using a neutral shampoo, a treatment is applied with a basic gel serum containing 2% CAPHIRA® versus placebo with a gentle massage once a day during 28 days.

Hair shine is evaluated by using an equipment Glossymeter® GL 200 (Courage + Khazaka electronic GmbH, Germany) conducted in triplicate at D0 and D28.

Results

The results are presented here after.

For the placebo at day 28, shine increased for 47.62% of subjects whereas for CAPHIRA® 2% in a basic gel, the shine increased for 65.00% of the subjects.



Macrophotographs of the scalp of volunteers illustrates results before and after 28 days of product application.



With the placebo gel, hair fibers look dull, without any lustrous.

With 2% CAPHIRA®, hair shine is restored after 28 days treatment. Hair looks healthy and shiny.

CAPHIRA® restores and visibly enhances shine for an improved healthy appearance.

ACTION ON THE HAIR SCALP

In vivo efficacy

The scalp, known to be a thin barrier, is the third most common area for sensitive skin after the face and the hands.

Sensitive scalp represents a frequent daily problem for dermatologists. Around 60% women and 40% of men present sensitive scalp.

Scalp health is essential to the vitality and density of hair.

CAPHIRA® improves scalp health

Affected scalp reveals the presence of various symptoms including itching, redness and inflammation linked to numerous causes e.g. dermatitis, lupus, acne, hair loss, perifollicular inflammation, irritation due to environmental factors such as pollution, UV radiation or to cosmetic hair treatments e.g. use of wrong shampoo, frequent change of hair color and mechanical injury from hair styling technic each day.

CAPHIRA® is able to take care of sensitive scalp presenting erythema and inflammation.

Methods

This clinical study is performed on two groups of 22 female/male volunteers, using once a day a basic gel serum containing 2% CAPHIRA® or a placebo serum during 28 days. The goal is to evaluate, in vivo, the scalp soothing efficacy by:

- (1) checking the reduction of the a^* parameter with the equipment Colorimeter® CL400 comparatively to baseline and to placebo and
- (2) evaluating the scalp area through clinical score assessment. This is performed by an expert comparatively to baseline and to placebo-

Soothing efficacy against scalp erythema

Colour evaluation

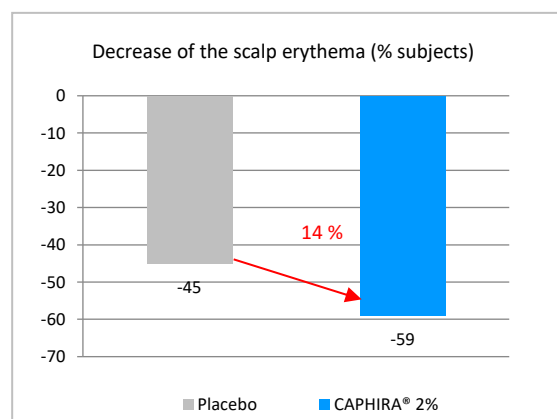
Results

The “a” parameter represents the chromaticity of the red (+100) to green (-100) axis. A lower a^* value means a less red skin and consequently a decrease on the scalp erythema.

The results obtained before and 28 days after the application of CAPHIRA® at 2% in a basic gel versus placebo are presented in front.

For the placebo at day 28, the a^* parameter decreased for 45.00% of the subjects (with a mean increase of 21.23% and maximum decrease of -55.43%).

For CAPHIRA® at 2% in a basic gel, at day 28, the a^* parameter decreased for 59.00% of the subjects (with a mean and maximum decrease of 11.53% and 88.65%, respectively).

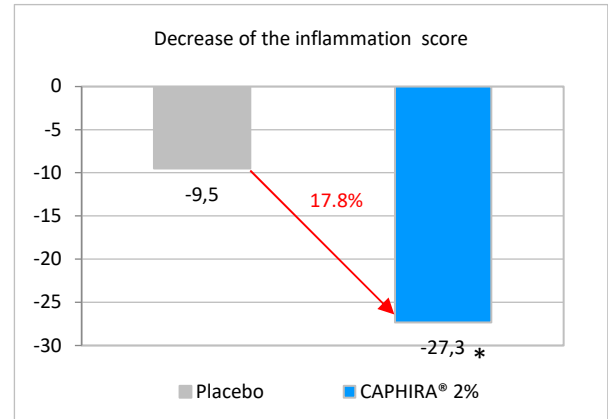
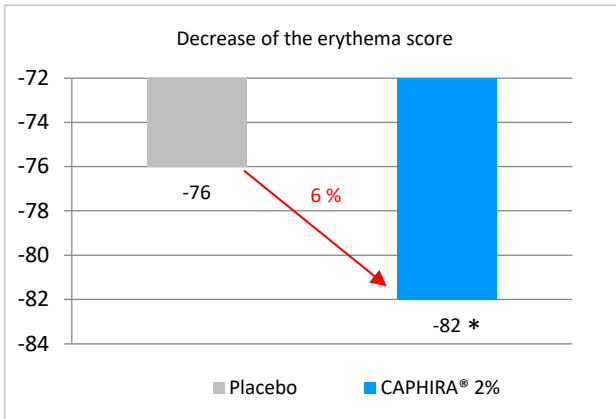


The treatment with 2% CAPHIRA® decreases significantly the scalp erythema condition to offer soothing effect.

Soothing efficacy against scalp erythema and inflammation
Clinical score assessment

Results

The total score results to the clinical assessment of the scalp by an expert, obtained before and 28 days after the application of CAPHIRA at 2% in a basic serum *versus* placebo. It concerns erythema and inflammation. A decrease of the score of each parameter is related with a positive scalp soothing effect (Wilcoxon Signed Ranks test).



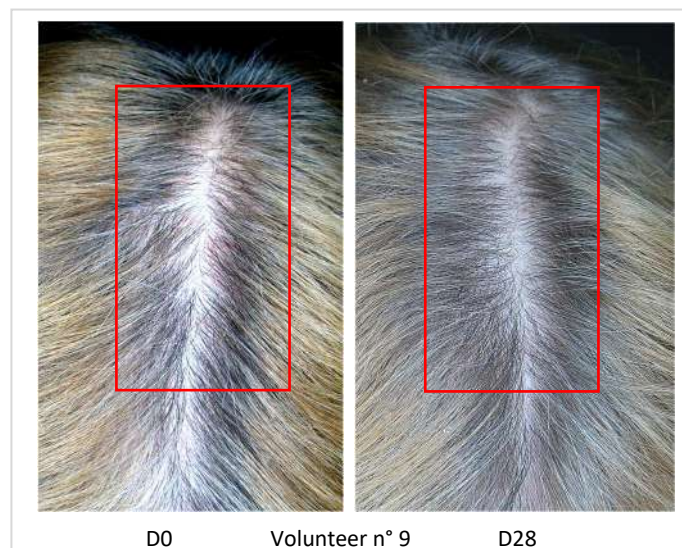
The treatment with 2% CAPHIRA® decreases significantly the score of erythema and inflammation.



PLACEBO

This volunteer shows red scalp which is typically sign of irritation.

The application of placebo does not improve the scalp redness after 28 days of treatment.



CAPHIRA® 2%

The scalp of this volunteer shows at D0 reddish irritated areas which have disappeared after 28 days of treatment.

The application, once a day, of a basic serum including 2% of CAPHIRA® during 28 days reduces scalp irritation and inflammation. It visibly induces an improvement of scalp health.

CONCLUSION & COSMETIC BENEFITS

CAPHIRA® combines an extract of the red alga *Kappaphycus alvarezii* supplemented with seawater and vegetable organic glycerin. It contains important minerals playing major roles for scalp and hair growth, specially magnesium, iron and zinc.

CAPHIRA® offers a natural patented global protection to provide beauty and comfort to hair and scalp.

CAPHIRA® works on the three parts of hair: the follicle, the fiber and the scalp.

► **At the follicle level,**

- ✓ CAPHIRA® prevents hair loss.
 - ♦ It increases the follicle survival, therefore slows down apoptosis.
 - ♦ It stimulates the ferritin pathway known to be linked to alopecia in women presenting iron deficiency (FTH1 ferritin gene +503%).
- ✓ CAPHIRA® boosts follicle metabolism.
 - ♦ it modulates the gene expression of growth factors known to be related to alopecia (IGF1R gene +146% - EGFR gene +172%)
 - ♦ It stimulates FGFR2 gene linked to Asian hair thickness + 172%.

► **At the hair fiber level,**

- ✓ CAPHIRA® reinforces and protects the fiber.
 - ♦ It increases the expression of major keratins genes to provide resistance against environmental and mechanical attacks.
 - ♦ It protects dry hair and repairs damage caused by chlorine stress.
 - ♦ It restores and enhances shine.

► **At the scalp level,**

- ✓ CAPHIRA® ameliorates the general comfort for a healthier state.
 - ♦ It decreases the scalp erythema and inflammation of volunteers presenting scalp redness or visible irritation.



As a result, hair feels full of vitality and shine and the scalp regains comfort and health. Hair youthfulness is improved.

COSMETIC APPLICATIONS

CAPHIRA® is suitable in numerous daily hair care products, in particular hair tonic, hair restorer, conditioner, balancing serums, treatment or styling gels as well as in sensitive scalp care formulations.

Recommended use level: 2%



| INCI names | CAS n° | EINECS n° | China listed | |
|-------------------------------|--------------------|-----------|--------------|-----------------------------------|
| glycerin | 56-81-5 | 200-289-5 | 02421 | 甘油 |
| water | 7732-18-5 | 231-791-2 | 06260 | 水 |
| Kappaphycus alvarezii extract | - | - | 08518 | 长心卡帕藻 (KAPPAPHYCUS ALVAREZII) 提取物 |
| Sea water | | | 02733 | 海水 |
| Preservative/ additive | <i>as required</i> | | | |

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