



Grow Factor #2

ANTIAGING MULTIACTION:

Radiant complexion, fresh, protected and rested skin.

GF 2 ANTI-AGE consists of a mixture of vitamins and amino acids rich in adenosine, which helps to form ATP improving the energy obtaining by the cell, and improving the blood flow, thus obtaining a homogeneous and visibly younger complexion.

Contains Scelleye, a growth factor similar to Plant-IGF-1, obtained from *N. Benthamiana*. Scelleye is especially suited for extremely delicate eye skin care. IGF-1 is a polypeptide essential for the formation and development of the skin. Very abundant in the basal layer of young skin.

Contains REVITALIN PF, a mitochondrial and cytoplasmic purified fraction from yeast with amino acids. It stimulates cellular respiratory activity and cell renewal, revitalizes skin's metabolism and strengthens its mechanisms of self-protection. It offers real benefits by increasing the oxygen content and its consumption by the skin to help provide energized and revitalized skin that looks and feels good.

The amino acid mixture is particularly rich in adenosine, which helps to form ATP and improves blood flow, thereby obtaining a homogeneous complexion.

This mixture of amino acids and vitamins work synergistically, giving the skin everything necessary to regenerate and defend itself against the adversities of the environment.

Contains stabilized vitamin C, which gives the product antioxidant and whitening activity, together with the Glutathione and Sophora Flavescens extract, makes the product to act on three levels:

1. Surface level:

- Antioxidant activity
- Anti-inflammatory effect

2. Level of epidermis:

- Exfoliating activity
- Promotes anti-tyrosinase activity
- Melanogenesis inhibition

3. Level of dermis:

- Inhibition of the enzymatic activity of MMP.
- Increased anti-glycation activity.

It incorporates **biomimetic peptides identical to the growth factors involved in cell renewal, resulting in younger skin.**

It provides **epigenetic activity**: Epigenetics is the new scientific discipline that allows influencing the behavior of genes to achieve optimal performance.

Today we know that the environment, our lifestyle, emotions ... in definitive, the history of the skin, generates epigenetic factors that influence decisively in our way of aging, more than the genetic inheritance itself.

The key? **COBIOGENOL**, an active ingredient from marine origin that acts like a chemical switch activating the genes "off" by certain epigenetic factors. Normalizing the generation of proteins necessary for the rejuvenation and regeneration of the skin, neutralizing oxidative stress generated by exposure to light and blue light, and re-structuring the stratum corneum, the outermost layer of skin, key in maintaining its Barrier and protective function.

All properties claimed for this product have been clinically demonstrated:

- Antioxidant activity
- Anti-inflammatory effect
- Exfoliating activity
- Anti-tyrosinase activity
- Inhibiting activity of melanogenesis.
- Epigenetic activity
- Protection against Electromagnetic radiation and Blue-Light

Introduction:

There are several different parameters that influence the aspect and attractiveness of skin in an important way, such as moisturization, firmness or wrinkles. However, one of the concepts that has most influenced the different standards for beauty throughout history is skin pigmentation, or tone.

A radiant complexion is associated with beauty. The pigment distribution, melanin, and skin texture vary according to health status and age. An irregular coloration is an indicator of the age of the skin, since the aging is associated with the presence of dark spots.

The difference in skin color is mainly due to the presence of melanin, a pigment that protects from external aggressions, such as UV rays.

When the body generates too much melanin to protect itself from this aggressions, or simply because of aging, accumulations can be created causing blemishes or changes in skin tone. **This disorder is called hyperpigmentation and can affect all skin types.**

Hyperpigmentation is the third major cosmetic concern, as it is one of the obvious signs of the decline of youth. For this reason, the cosmetic goal is to reduce blemishes and age spots, and to improve the skin tone.

Notably illuminates the skin while fully respecting its natural and health characteristics. **In vitro tests showed that the synergistic combination of ingredients contained in Grow Factor #2 ANTIAGING MULTIACTION: inhibits 90% melanin synthesis.**

Contains a **combination of active ingredients** that bring **luminosity and vitality to the skin, giving it immediate, radiant and healthy appearance** and protects it from external aggressions: **Radiación Electromagnética y Blue-Light.**

- ✓ It allows to recover the luminosity and light lost as a result of the chronological aging, or an undue exposure to the UV rays (photo-aging), as well as numerous aggressions to which our skin is exposed daily (pollution, cold, tobacco, poor diet, lack of sleep, stress, ...).
- ✓ With a continuous use, it manages to homogenize skin tone and reduce unwanted pigmentation.

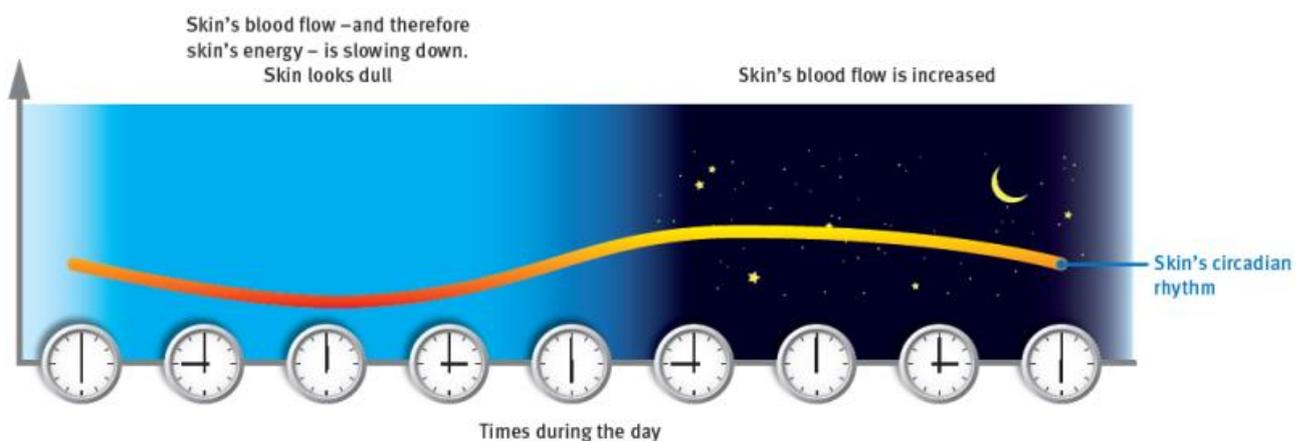
-
- ✓ Contributes to reduce wrinkles and lines of expression through the synthesis of collagen and elastin.
 - ✓ It increases skin's the face lack of firmness, smooth and elasticity by stimulating the synthesis of collagen which contributes to regenerate the tissue support dermal matrix.

BIOACTIVE INGREDIENTS IN GF#2 ANTIAGING:

REVITALIN PF: Improves circadian rhythms to get a young and radiant complexion

It is a mitochondrial and cytoplasmic purified fraction from yeast rich in amino acids. It stimulates cellular respiratory activity and cell renewal, revitalizes its metabolism and strengthens the mechanisms of self-protection of the skin. It offers real benefits by increasing the oxygen content and its consumption by the skin to help provide energized and revitalized skin that looks and feels good. The amino acid mixture is particularly rich in adenosine, which helps to form ATP and improves blood flow, thereby obtaining a homogeneous complexion.

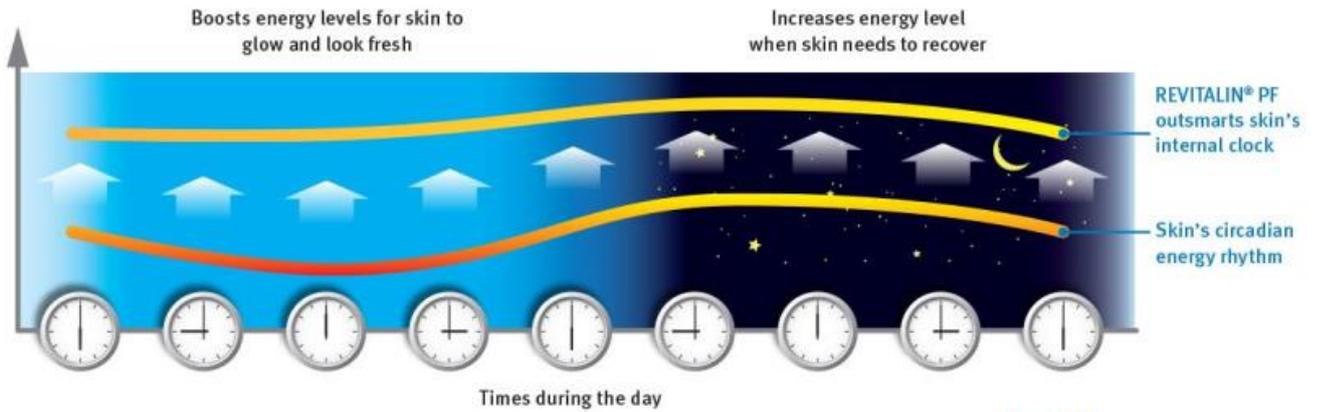
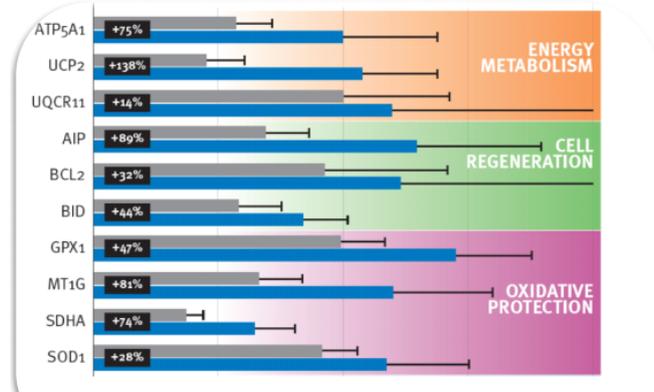
This mixture of amino acids and vitamins work synergistically, giving the skin everything necessary to regenerate and defend itself against the adversities of the environment.



Biological effect of REVITALIN® PF on mitochondria:

REVITALIN® PF stimulates the expression of key genes related to mitochondrial activity and protection.

Gene expression was measured in keratinocytes with UVB after 4 h of pretreatment with REVITALIN® PF



0.5%)

How to create cellular energy?

Without oxygen,
Mitochondria uses
GLYCOLYSIS



Mide GLICOLISIS
via
Tasa de Acidificación
Extra Celular
(ECAR)



Source: Picture from Seahorse Bioscience

With oxygen,
Mitochondria uses
RESPIRATION



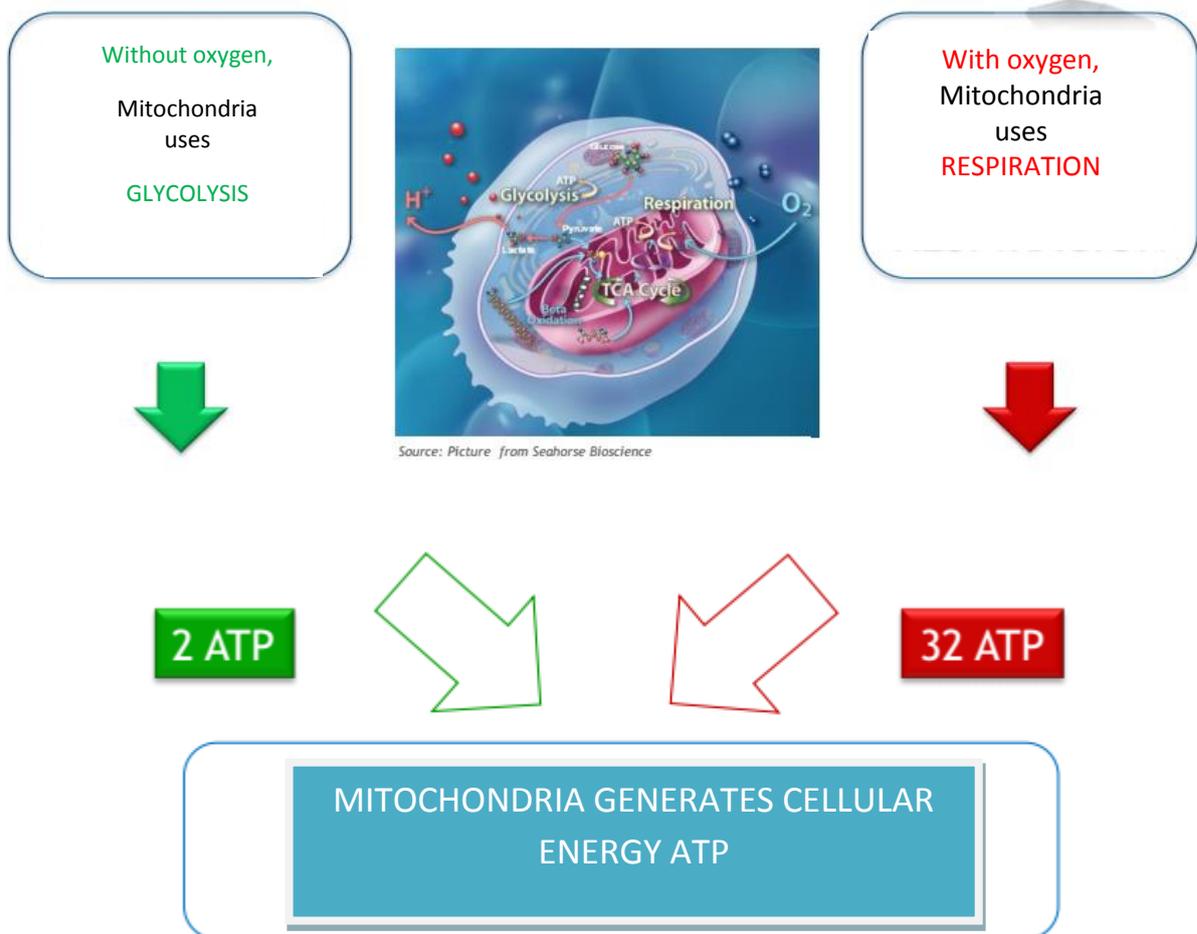
Mide RESPIRACION de la
MITOCONDRIA
via
Tasa de consumo de oxígeno
(OCR)



Measures RESPIRATION of
MITOCHONDRIA via
Oxygen consumption rate (OCR)

How to measure cellular energy?

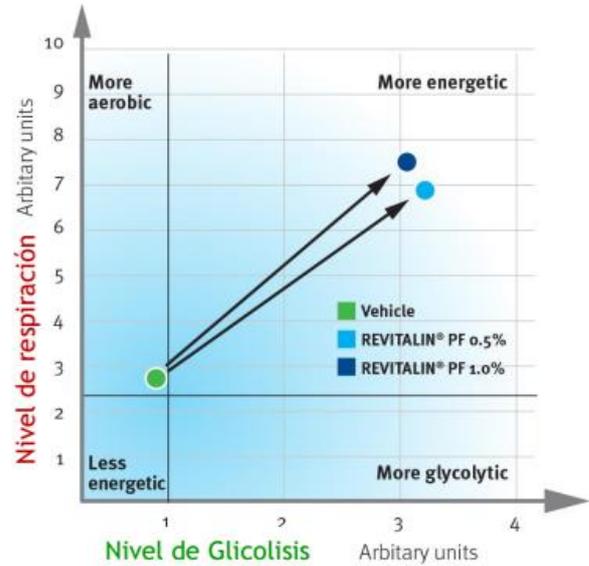
By means of an Extracellular Flow Analyzer, the level of respiration / cellular glycolysis can



REVITALIN® PF Recharges the cellular energy during the night.

During the night, the cells are not stressed and are in the process of renewal. REVITALIN® PF gives you the energy you need to recharge and recover!

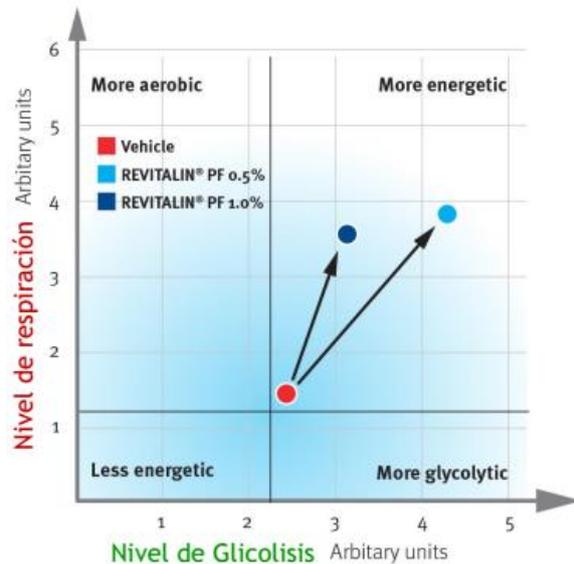
En keratinocitos humanos sin estresar



REVITALIN® PF Increases cellular energy during the day

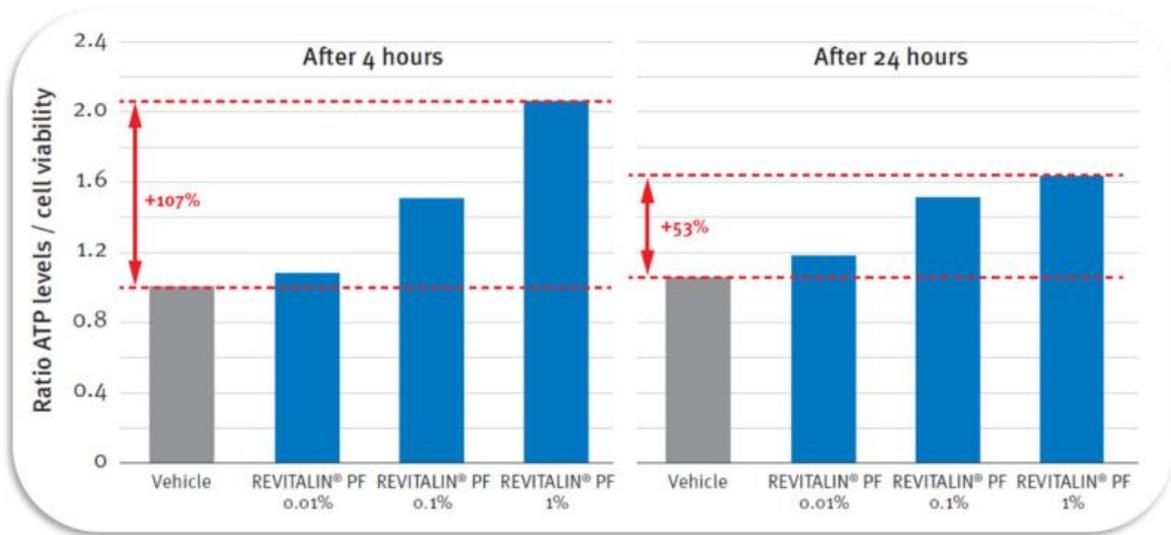
During the day, the cells are stressed and the energy level is lower than at night. REVITALIN® PF gives them the energy to defend themselves against the environment around them.

En keratinocitos humanos estresados



Maintains a high level of energy for 24 hours

REVITALIN® PF dose-dependently increases ATP levels above 110% at 4 h and above 53% at 24 h. ATP levels were measured in human keratinocytes after 4 and 24 hours of treatment with REVITALIN® PF (0.01%, 0.1%, 1%).



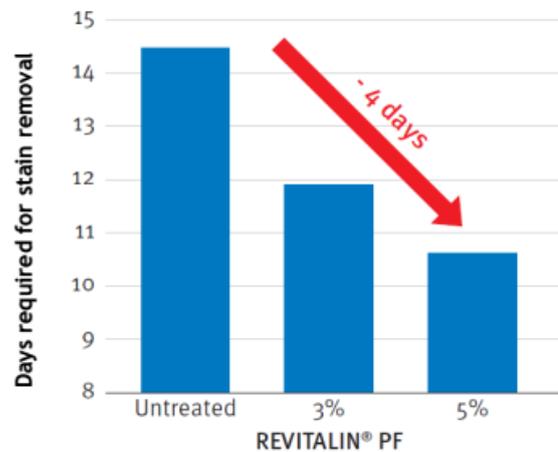
Clinical study In vivo: fresh and radiant aspect of the skin



A radiant and fresh-looking skin is evaluated by measuring the cell renewal using the dansyl chloride technique.

40 Volunteers (ages between 30 and 55 years) were treated with 3% or 5% REVITALIN® PF twice a day for one period of 20 days. Removal of dansyl chloride staining was evaluated.

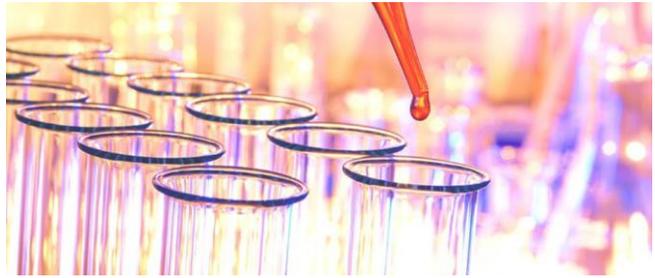
REVITALIN® PF helps to accelerate the renewal of the cells of the surface of the skin up to 4 days and produces a more radiant complexion.



SCELLEYE: BIO-MIMETICAL PEPTIDE. Plant Growth Factor

What are growth factors?

Growth factors are proteins that bind to their own receptors on the cell surface with the primary result of activating cell proliferation and / or differentiation.



Growth factors regulate the expression of the constituent proteins of the extracellular matrix: collagen, elastin, laminin, etc.

What are bio-mimetic peptides?

They are synthetic agonists (which have the same function) as natural growth factors and completely mimic their action, providing the same clinical benefits.



Scelleye is a growth factor similar to Plant-IGF-1, obtained from *N. Benthamiana*. Scelleye is especially suited for extremely sensitive eye care of the eyes, helping to restore the activity of the epidermal basal layers, as well as activating the proteasome and decreasing

carbonylation, for effective purification of damaged proteins.

In addition, it diminishes the crow's feet and the circles under the eyes.

IGF-1 is a polypeptide essential for the formation and development of the skin. Very abundant in the basal layer of young skin. During UV exposure, it prevents tissue damage. Aging skin has low levels of IGF-1.

Scelleye contains plant-derived IGF-1 from wild plants and protects the delicate skin from the eye's. In addition, it diminishes the crow's feet and the circles under a complete care of the outline of the eyes.

IGF-1 is a polypeptide essential for the formation and development of the skin. Very abundant in the basal layer of young skin. During UV exposure, it prevents tissue damage. Aging skin has low levels of IGF-1.

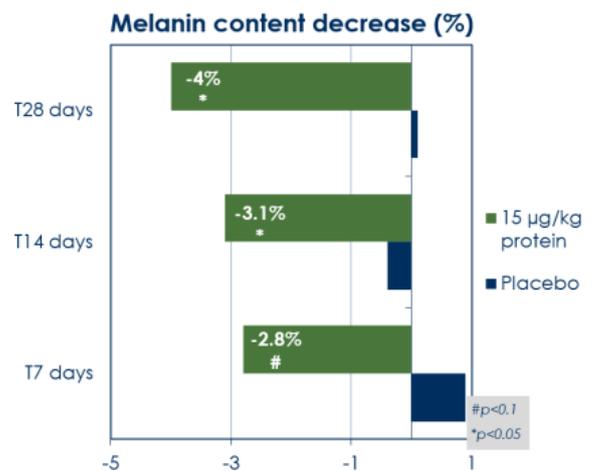
Scelleye Contains plant-IGF-1 from wild plant biofactories to help you design your true beauty covering multiple eye care concerns such as UV, pollutants, wrinkles and dark circles.

In vivo efficacy: double blind assessment of eye care efficacy

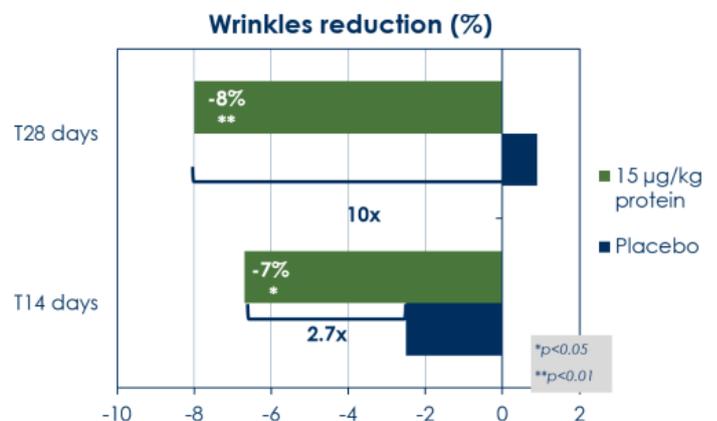
Caucasian women (51 ± 6 years old) showing dark circles, applied a gel cream with 15 µg/kg (0.015 ppm) protein around one eye, twice daily for 28 days. Placebo was applied around the other eye

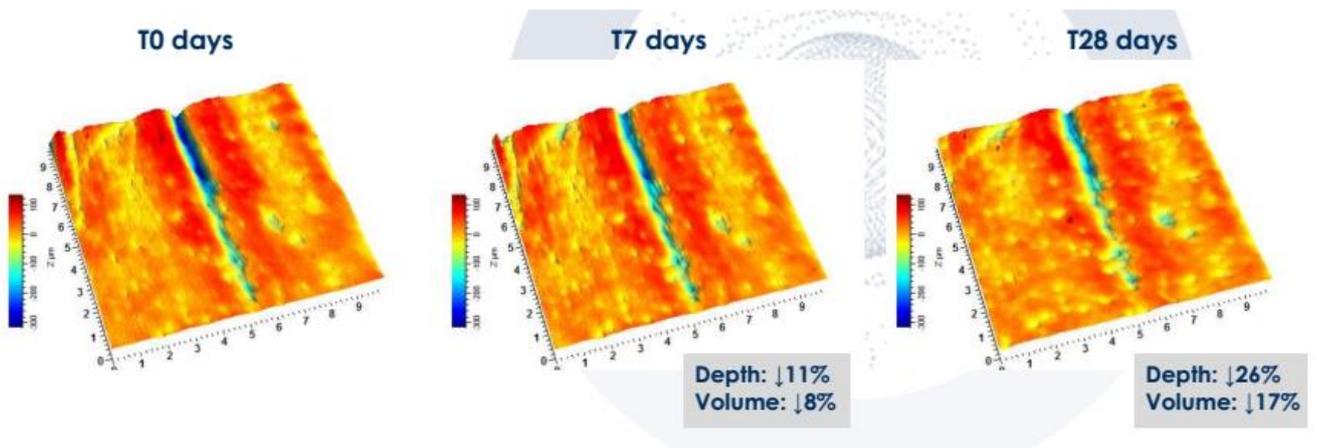
Evaluation of: Melanin (Siascope), Crow's feet replicas (Visia®), Skin replicas (FOITS)

- 3% significant reduction of melanin content under the eyes after 7 days with Scelleye™
- 4% improvement after 28 days, indicating a dark circles soothing.



- 7% and 8% significant reduction of crow's feet after 14 and 28 days with Scelleye™
- 10-fold less wrinkles than placebo after 28 days.





COBIOGENOL: Electromagnetic protection, protection against Blue-Light. Epigenetic Science



First active ingredient focused on reducing the biological disorders produced by exposure to **Electromagnetic Radiation**.

Electromagnetic waves are a form of energy consisting in vibrations of electric and magnetic

fields. We live in a sea of invisible electronic pollution, which is becoming toxic to our health.

We do not see or perceive them but are increasingly present in our domestic environment. Wherever we might be, non-ionizing radiation is all around us. We are constantly exposed to magnetic fields generated by appliances and domestic electrical installations: mobile phones, WIFIs, microwaves, television, radio, computers, etc.

As technology advances and the use of these devices increase, both at the workplace or private areas, our exposure to non-ionizing radiation is likely to intensify further.

▪ Oxidative Stress



The “digitization” of our world means that our cells are exposed to a continuously increased level of non-ionizing radiation, for which they have not adapted. In the last decade, EMR (Electromagnetic Radiation) levels have increased dramatically, and we are starting to realize its negative consequences. EMR is an environmental stress factor for human health, and skin as a physiological barrier is the first

objective of this radiation.

This exogenous stress leads to oxidative cellular stress, the formation of excessive reactive oxygen and nitrogen species and reaction products. It leads to a mitochondrial metabolic dysfunction: ROS causes a disruption of Mitochondrial function and cellular ATP Levels.

The massive oxidative cell stress leads to chronic inflammation. Several studies [1][1][3] have shown that skin exposure to cell radiation suffers several biological parameter alterations:

- ✓ Massive increase in free radical production (ROS)
- ✓ Massive Increase of pro-inflammatory cytokines
- ✓ Decrease in cell regeneration
- ✓ Reduction in structural proteins: key molecules involved in the stratification of the epidermis
- ✓ Lost in cohesion between keratinocytes
- ✓ TEWL increase: dehydration, the skin becomes more vulnerable and sensitive
- ✓ Stratum corneum weakening
- ✓ Disturbed skin refraction: lost in brightness, becoming dry and uncomfortable

COBIOGENOL, is a functional ingredient proved to reduce the skin biological alterations, resulted from the exposure to EMR.

It helps at the restoration process of the skin, being a specific anti-stress agent. It is a **concentrated solution of purified marine glycogen**, ready to use at cosmetic skin care preparations.



Glucose is the most important sugar at the cellular level. It plays a very important role in the energetic metabolism of the cells. Its energy is used at the restoration process of the skin.

CLINICAL EFFICACY TESTS:

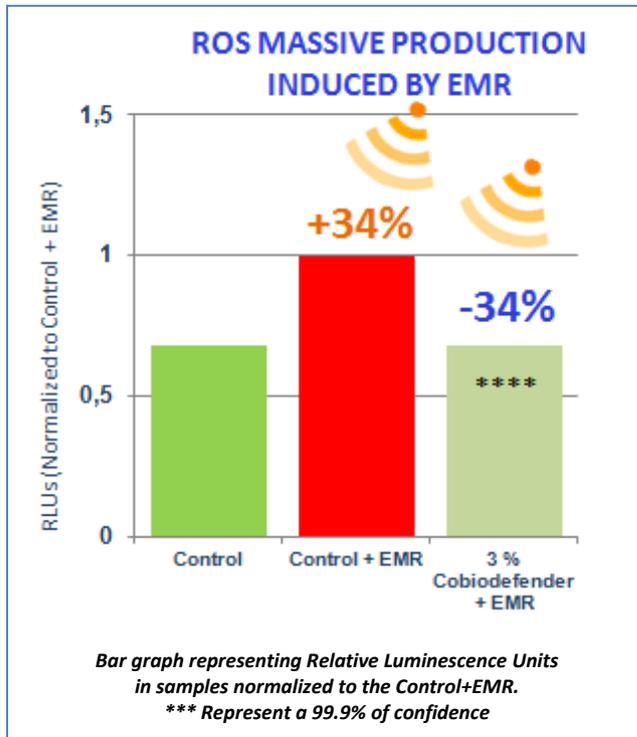
- **Effects of COBIOGENOL Preventing and protecting from Electromagnetic radiation-induced oxidative stress:**
-

Several exogenous stimuli such as ionizing radiation, EMR, UV light, smoke, inflammatory processes and some human diseases trigger off free radicals production, causing severe damage in the mitochondrial membranes provoking the massive release of free radicals (ROS).



The goal of this study was to evaluate the capacity of COBIOGENOL in protecting cells from the damage caused by induced electromagnetic radiation (EMR), by reducing oxidative stress (ROS).

To this end, Human keratinocyte cells were exposed to 6 hours of EMR generated by a mobile phone to assess the response of skin cells to the induced oxidative stress and test the potential of COBIODEFENDER EMR to prevent EMR-induced ROS.



After 6 hours exposition, EMR induced ROS accumulation $34,26 \pm 3,13\%$ and treatment with COBIODEFENDER EMR **reduced EMR-induced ROS production $34,82 \pm 3,12\%$** indicating a protective effect.

▪ **Cellular epigenetic rejuvenation**

Epigenetics is a new paradigm in the Science of Anti-Aging.

It is the study of the mechanisms involved in the regulation of gene activity: the biological mechanisms that will switch genes on and off without altering their sequence.

Epigenetic change happens regular and naturally but can also be influenced by several factors including age, the environment (UV radiation, pollution...), lifestyle, emotions and diseases and much more that are yet to be discovered.

These factors discussed above, have the ability to "turn" or "turn off" certain genes, whose effects will be observed physically or physiologically.

The "on" or "off" effect of genes can be accomplished by three mechanisms:

- 1) **MicroRNAs**
- 2) Histone modification
- 3) DNA mutilation

What are miRNAs?

MicroRNAs (or “miRNAs”) are chemical “switches”. They are small fragments of RNA responsible for protein synthesis. These control mechanisms are key elements of epigenetic regulation. Its production is constantly modified by the environment and living conditions, including our emotions. MicroRNAs turn on and off numerous biological processes such as cell survival, skin repair, processes, hair growth...

Epigenetics and the future of skin care

We can regulate microRNA expression to rejuvenate. miRNAs are involved in regulation processes such as cell cycles, DNA repair systems, reactions to oxidative stress, apoptosis.



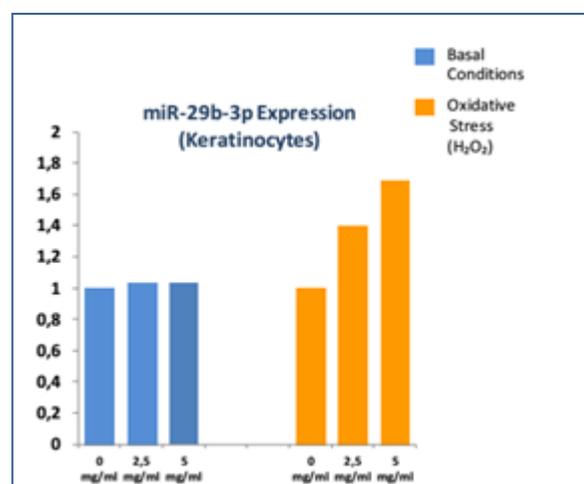
During aging and other external aggressions, chromatin (the genetic material in the nucleus of our cells) becomes senescent and disorganized contributing to premature aging.

COBIOGENOL is a natural epigenetic active ingredient that can regulate microRNA expression. This means that it has the ability to act on the expression of miRNAs and "**switch on**" or "**switch off**" certain genes.

- By **in vitro assays in human keratinocytes** (skin cells), COBIOGENOL has been shown to have the ability to **rejuvenate cellular chromatin, making aging cells acquire characteristics of young cells.**

COBIOGENOL increases the expression of miR-29b-3p, a miRNA that "**switch on**", or "activates" the synthesis of protein P53: **Protein guardian of genetic material, which has a potent antioxidant, anti-stress and anti-aging activity.**

- Under conditions of cellular stress induced by photo-oxidation (photo-aging) and



oxidative stress, (by hydrogen peroxide), COBIODEFENDER EMR reduced the levels of **H3K79me3**, a miRNA considered as an **aging clock, inducing a cellular rejuvenation**.

Summary of COBIOGENOL activity:

- ✓ Protection of oxidative stress caused by electromagnetic radiation
- ✓ DNA protection and rejuvenation
- ✓ Anti-aging activity
- ✓ Aged cells acquire characteristics of young cells

CORUM 9515: New generation of stable vitamin C



CORUM 9515 is a new generation of stable vitamin C derivative that provides superb whitening effects, serves to promote collage synthesis and protects DNA damage.

- ✓ **Effective and stable skin lightening agent**
- ✓ **Balance the skin tone**
- ✓ **Reduce dark spot**
- ✓ **Prevent photoaging**
- ✓ **Increase collagen synthesis**
- ✓ **Excellent anti-oxidation properties**
- ✓ **Scavenge radical**
- ✓ **DNA protection**

Vitamin C, or L-ascorbic acid, acts as a cofactor for collagen synthesis. It has a high regenerating ability, by its collagen synthesis stimulating activity.

Vitamin C is essential for the proline hydroxylation, therefore in the development and maintenance of collagen integrity. In addition, vitamin C inhibits the synthesis of Extracellular Matrix Metalloproteinase enzymes of, enzymes which stimulates collagen degradation in the dermis.

Vitamin C's collagen stimulating properties provides it with wound healing properties, caused by trauma, cuts, burns, or surgery. It is also suitable for the formation of new tissues.

Vitamin C belongs to the group of water soluble vitamins, and like most of them, it is not stored in the body for a long period of time, but in small quantities which are eliminated

through urine. For this reason, Vitamin C daily administration is important in order to provide sufficient antioxidant protection.

Its chemical structure is similar to that of glucose (in many mammals and plants, this vitamin is synthesized from glucose and galactose). All compounds which possess the biological activity of ascorbic acid are known as Vitamin C. We should note that the only active form of Vitamin C is L-Ascorbic Acid.

As Vitamin C is a water-soluble substance, it is rapidly eliminated from the organism. Our body tends to protect vital organs, so any vitamin deficiency is felt primarily in the skin (less vital organ), which explains the importance of its topical application.

Pure Vitamin C is very unstable and sensitive to oxidation. Vitamin C contained is stabilized by an ethyl group and its effectiveness has been tested clinically:

Clinical Efficacy Studies

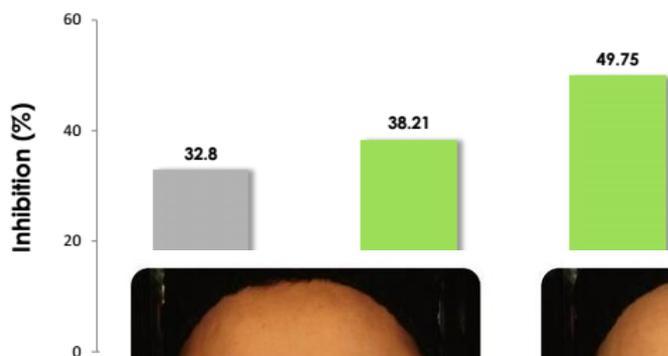
1- In-vitro whitening activity study - melanin assessment on human melanocytes:

An in-vitro evaluation of the Ethyl Ascorbic Acid anti-pigment ability was performed (Ethyl Ascorbic Acid is the Vitamin C form contained in VITAMIN C BRIGHTNESS SPRAY).

Theophylline was incubated with melanocytes in order to increase melanin production. Subsequently, Ethyl Ascorbic Acid was added at concentrations of 15 mg / ml and 20 mg / ml respectively, and comparing with kojic acid, a known anti-pigment ingredient.

At both concentrations of Ethyl Ascorbic Acid clear depigmentation effect was observed, obtaining 49.75% whitening effect with 20mg/ml Ethyl Ascorbic Acid:

Whitening effect (%)



2- In-vivo whitening efficacy

A study on the in-vivo whitening capacity of Vitamin C (as Ethyl



Ascorbic Acid) for 28 days in 20 healthy Asian women aged 25 to 40 years old with skin type III was performed.

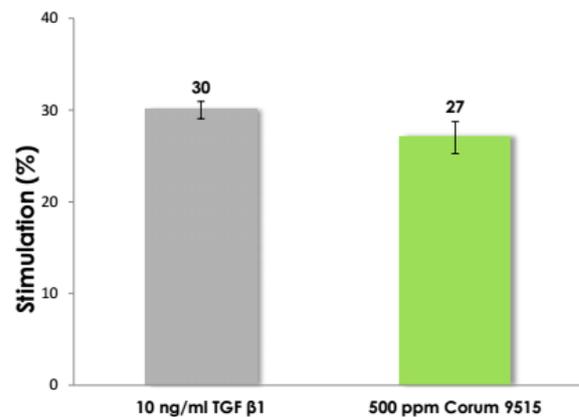
A significant improvement in the skin lightening measured by chromatography observed:

3- Stimulation of natural collagen synthesis:

The Stimulation of natural collagen synthesis activity was evaluated on human fibroblast culture.

After 24 hours of culture, the collagen was quantified using a Sircol Quantification Kit. Vitamin C had a similar effect on collagen synthesis that of TGF β 1 (growth factor which stimulates collagen synthesis):

Stimulation of natural collagen synthesis:



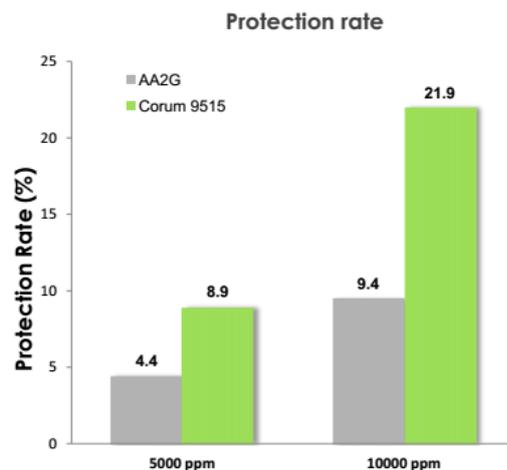
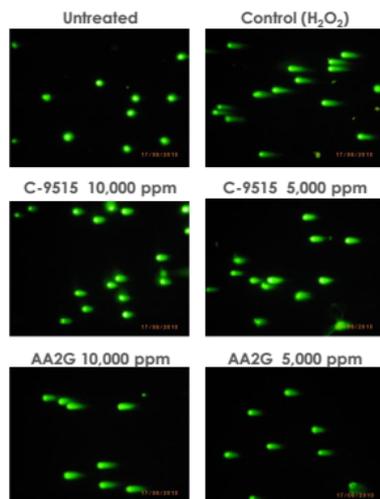
4- DNA protection by Comet assay in human fibroblasts:

The comet assay is a technique used to detect DNA damage and cell repair capacity. It is based on the DNA labile alkaline lysis at sites where damage has occurred.

When DNA is in good condition, it has a highly organized association with matrix proteins in the cell nucleus. When damaged, this organization is interrupted. The single DNA strands losing their compact structure and relaxes, expanding out.

Human fibroblasts were treated with Vitamin C (Ethyl Ascorbic Acid) for 24 hours, and then exposed to 100 mM H₂O₂. It was shown that Vitamin C at concentrations of 5000 ppm and 10,000

was able to protect



ppm, able

DNA:

Vitamin C Mechanisms of action:



Vitamin C anti-aging action is exerted through several ways:

1. Synthesis and repair of dermal collagen

Deficiency of ascorbic acid (AA) produces significant alterations in connective tissue, since Vitamin C is essential for collagen synthesis.

Vitamin C is essential for the transformation of proline in hydroxyproline and lysine in hydroxylysine (essential constituents of collagen). Consequently Vitamin C offers stability to the extracellular matrix.

Vitamin C is essential for the transformation of proline in hydroxyproline

The local increase of vitamin C means therefore significantly promote collagen production; therefore improved skin elasticity and greater resistance in wall capillaries are assessed.

2. Antioxidant activity

Vitamin C protects cells from free radicals. From all the scientific publications regarding Vitamin C, the most interesting are those related to the photoprotective effect of ascorbic acid when topically applied.

In mouse and pig it showed that when ascorbic acid is applied before UV radiation exposure, the negative consequences it causes in the skin (erythema, histological changes, "burned cells", wrinkles ...) decreased significantly .

A study published by the Journal of Investigative Dermatology in May 1996, describes how topical application of vitamin C, vitamin E and Selenium protects rats skin cells from damage caused by exposure to UVB rays.

In parallel, the British Journal of Dermatology some years before, evidenced this protective effect of vitamin C, when used topically, on pig skin damaged by ultraviolet radiation.

The Spanish Journal of Physiology published a study showing how direct application of vitamin C protects, and thus prevents the aging in human skin cells in culture subjected to a strong oxidation stimulus with hydrogen peroxide.

One might think that its photoprotective effect was physical, that is to say, topical vitamin C behaves as a sunscreen, and however, its absorption spectrum has nothing to do with the

emission of UV radiation. Later it was found that UV radiation produced a significant decrease in the levels of ascorbic acid in the skin.

All this goes to show that the UV light, after exhausting all the vitamin C present in the skin, cause an increase in free radicals, making manifest the neutralizing action of vitamin C.

3. Anti-inflammatory action

Vitamin C inhibits NFκB, which is responsible for the activation of a number of pro-inflammatory cytokines. Therefore, Vitamin C has a potential anti-inflammatory activity and can be used in conditions like acne vulgaris and rosacea. It can promote wound healing and prevent post-inflammatory hyperpigmentation.

4. Vitamin C as a whitening agent

When choosing a whitening agent, it is important to differentiate between substances that are toxic to the melanocyte and substances that interrupt the key steps of melanogenesis. Vitamin C falls into the latter category of depigmenting agents. Vitamin C interacts with copper ions at the tyrosinase-active site and inhibits action of the enzyme tyrosinase, thereby decreasing the melanin formation.