



# MEADOW GLOW

Brightening Effect  
of Elegance



## ProlCell® MeadowGlow Technical Data Sheet

### Lightening Effect of Elegance Skin Brightening and Anti-Fatigue Active

#### Origin

Developed from *Spiraea ulmaria* (Meadowsweet) stem cells using ProlCell® Technology. ProlCell® Technology enables to benefit the effects of plant stem cells and small RNA's in their vesicles.

#### Effects

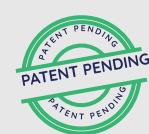
- It suppresses hyperpigmentation, ensuring the skin appears bright.
- It prevents glycation by inhibiting lipid peroxidation and reduces the appearance of aging.
- It reduces skin wrinkles by increasing collagen and elastin synthesis.
- It prevents the tired and aged appearance of the skin by balancing the levels of misfolded proteins.

ProlCell® MeadowGlow DW (Disperses in water)

INCI Name: Glycerin, *Spiraea ulmaria* Extract, Xanthan Gum

ProlCell® MeadowGlow WS (Water-Soluble)

INCI Name: Glycerin, *Spiraea ulmaria* Extract, Sodium benzoate, Potassium sorbate



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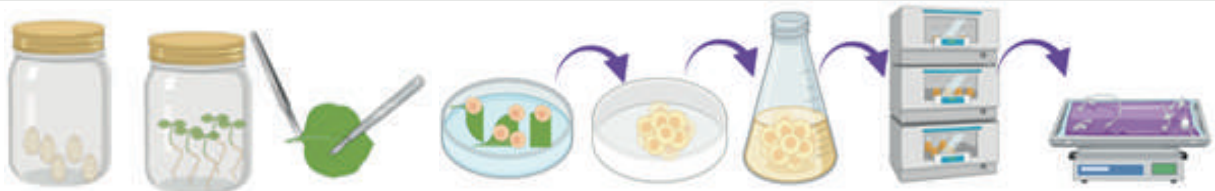
# ProlCell® Technology

ProlCell® Technology has two different mechanisms of action. The first is the use of the plant stem cells and their components, and second is the use of small RNAs-enriched EVs (Extracellular vesicles), or exosomes, secreted from plant stem cells. Exosomes are small vesicles with a lipid structure that contain molecules such as peptides, lipids, secondary metabolites, mRNA, and small RNAs, and serve as important signaling molecules in intercellular communication. Small RNAs, which are found inside cells and are also encapsulated within exosomes, are short RNA molecules that play a crucial role in gene regulation. It has been shown in recent scientific studies that plant-derived small RNAs not only regulate plant cell functions but also influence gene expression in human cells.

Based on these studies, ProlCell® technology, which has a patent application, enables the synthesis of exosomes with enriched small RNA content from plant stem cells. Products developed using this technology contain plant stem cell components and exosomes enriched with small RNA secreted from stem cells. Plant stem cell-derived exosomes not only have cell renewal activity specific to stem cells, but also, due to the small RNAs they contain, exhibit regulatory effects on gene expression in human skin cells.

## 1. Actives from Plant Stem Cells

Plant stem cell technology is based on the principle of controlled propagation of dedifferentiated plant cells (plant stem cells) under sterile laboratory conditions and obtaining plant components specific to stem (dedifferentiated) cells. When plant tissues are mechanically damaged, they form cell clusters called callus to repair the damage. Callus cells have totipotent properties, meaning they have the ability to transform into all cell types and organs of the plant, and even to regenerate a whole new plant. For this reason, they are referred to as stem cells. Due to their totipotent nature, plant stem cells possess cell renewal and cell regeneration activity. Their ability to stimulate cell renewal is not limited to plants but is also observed in human skin cells. These properties make plant stem cells an effective cosmetic active ingredient. transform into all cells and organs of the plant and even to form a new plant. For this reason, they are called stem cells. Plant stem cells have new cell generation and cell renewal activity due to their totipotent properties. Plant stem cells show their cell renewal stimulating activity not only on plants but also on human skin cells. These properties enable plant stem cells to be an effective cosmetic active ingredient.



## 2. small RNAs from Supernatant

To obtain small RNA-enriched exosomes from plant stem cells, the cells are subjected to specific elicitor applications. Once the incubation with elicitors is complete, the cells are harvested and separated from the nutrient medium. The collected cells are kept under optimized conditions for a specific period until the next step is completed. A small sample is taken from the filtered nutrient medium, and exosomes are isolated from the medium using an ultrafiltration method.

Subsequently, small RNAs in the exosomes are isolated using RNA extraction methodologies. After the isolation step, the quantity and quality of small RNAs are measured, and the required amount of small RNA for production is optimized.

For each ProlCell product, optimization R&D studies are conducted to obtain small RNA-enriched exosomes. Once the optimization step is completed, small RNA-enriched exosomes and plant stem cells are combined to prepare ProlCell® products.





# ProlCell® Technology

## ProlCell® Production Process Flow:

- In vitro seedlings are obtained from seeds.
- A few leaf or stem fragments of the in vitro seedlings are mechanically injured to induce callus formation.
- The callus is transferred into a liquid culture to establish cell cultures.
- Plant stem cells are produced on a large scale in bioreactor systems under optimal growth conditions specific to each cell type.
- Through elicitor application, the synthesis yield of target small RNAs in plant cells is enhanced.
- After the incubation stage is completed, the cells are collected and separated from the culture medium.
- Exosomes are isolated from the culture medium.
- The small RNA content of the exosomes is measured.
- Exosomes (containing the target small RNAs) and plant stem cells are combined to prepare ProlCell® products.
- Finally, they are transformed into cosmetic active ingredients in both water-dispersible and water-soluble forms.

## Advantages of ProlCell® Technology:

- COSMOS approved certified
- Vegan certified
- Halal certified
- All production stages of ProlCell® Technology are 100% plant-based and derived from plant-origin materials. It contains no animal-derived ingredients or by-products and is not tested on animals.
- Eco-friendly. Only a few plant tissue fragments are needed to obtain plant cell cultures. This prevents excessive plant consumption, helping to conserve nature while saving labor and resources (soil and water).
- Allows the cultivation of even rare or endangered plant species.
- The plant materials used are free from environmental pollutants, herbicides, and pesticides.
- Production can be carried out independently of external factors such as soil composition, climate, and season.
- Target small RNA-containing exosomes are utilized through plant cell-specific elicitor stimulations.

## ● ProlCell® MeadowGlow (queen of the meadow)

*Spiraea ulmaria*, known as the Queen of the Meadow, is a perennial flowering plant belonging to the Rosaceae family, commonly found in damp meadows. Its pure white flowers, with their sweet, and almond-like scent, are considered one of nature's most elegant adornments.

Blooming in summer, these flowers resemble a queen's crown illuminated by the sun's rays, which is how the plant earned its regal name.

Queen of the Meadow is synonymous with nature's grace and healing properties. Its story extends from its botanical characteristics to its historical and mythological significance. In Celtic mythology, this plant symbolized love and loyalty. It was commonly used in bridal crowns and bouquets at weddings, as it was believed to strengthen the bond between two hearts.

Meadowsweet, frequently referenced in Shakespeare's works, symbolized elegance and beauty. For this reason, it has also been called the "Flower of Queens. During the Elizabethan era in England, it was especially cultivated in palace gardens for its aesthetic and aromatic appeal.

With ProlCell technology, we developed MeadowGlow using the stem cells of *Spiraea ulmaria*, nature's elegant plant, and exosomes enriched with small RNAs.

## ● ProlCell® MeadowGlow Production Process and Mechanism of Effect

Meadowsweet plant stem cells are incubated with elicitors during optimal growth phases to synthesize exosomes enriched with targeted small RNAs. Exosomes containing enriched small RNAs are combined with plant stem cells to obtain ProlCell® MeadowGlow.

Small RNAs, which are also carried by undifferentiated plant cells, play a role in communication between different cells, tissues, and even organisms when packaged into exosomes. The intercellular communication effect of exosomes with ProlCell MeadowGlow is used in regulating the activity of human skin cells.

ProlCell® MeadowGlow, enriched target small RNAs found in the plant stem cell components and exosomes of the meadow queen, stimulates the expression of genes associated with brightening, anti-wrinkle and anti-fatigue activity by affecting the expression of relevant genes in human skin cells.

ACTV Biotechnology has developed ProlCell® MeadowGlow as a skin brightening, anti-wrinkle and anti-fatigue active ingredient by combining ProlCell® Technology with the stem cells of the elegant and impressive plant *Spiraea ulmaria* and exosomes enriched with small RNA content.

### **ProlCell® MeadowGlow**

- **ProlCell® MeadowGlow makes the skin appear brighter**

Skin blemishes, also known as hyperpigmentation, are caused by an increase in the melanin pigment produced by melanocyte cells, which give color to the skin, eyes and hair. The main causes of hyperpigmentation are UV rays and genetic predisposition, while hormonal changes, acne, pregnancy, and birth control pills are among other factors.

UV rays, one of the main triggers of melanocytes irregularities that lead to hyperpigmentation, not only cause spots by increasing melanin synthesis but also stimulate further melanin production, leading to the darkening and expansion of existing spots.

ProlCell® MeadowGlow suppresses excessive melanin synthesis in the skin, promoting an even skin tone and a brighter appearance.

- **ProlCell® MeadowGlow suppresses lipid peroxidation and protects against glycation**

Highly reactive radicals, such as the hydroxyl radical, attack polyunsaturated fatty acids, causing the detachment of a hydrogen atom from the methylene (—CH<sub>2</sub>—) group, thereby initiating lipid peroxidation. Lipid peroxidation can lead to disruption of the cell membrane integrity and a decrease in membrane potential, increased permeability to H<sup>+</sup> and other ions, and the disruption of organelle integrity.

Lipid peroxidation, the oxidation of unsaturated fatty acids by free radicals, also leads to the formation of MDA (malondialdehyde) products. MDA products also react with proteins, contributing to the formation of advanced glycation end-products (AGEs). The accumulation of AGEs causes cross-linking with the skin's fundamental structural proteins, such as elastin and collagen, leading to their dysfunction. As a result, the skin's firmness and elasticity decrease, and the formation of wrinkles begins.

ProlCell® MeadowGlow exhibits an anti-glycation effect by suppressing lipid peroxidation and prevents the formation of wrinkles, skin damage, and aging on the skin.

- **ProlCell® MeadowGlow reduces the appearance of insomnia and fatigue, providing a fresh look to the skin**

The endoplasmic reticulum (ER) is an organelle that synthesizes, folds, and responds to cellular stress by producing secreted proteins, while also maintaining calcium balance. Calnexin type 1 integral is an ER transmembrane chaperone that temporarily retains newly synthesized and misfolded glycoproteins. During the process of protein synthesis and folding, the cell either generates an unfolded protein response (UPR) or an ER stress response. In cases of insomnia, fatigue, and stress, the ER does not produce an unfolded protein response.

As a result, the accumulation or degradation of misfolded proteins causes the appearance of aging on the skin.

The decrease in collagen and elastin proteins significantly contributes to the increased appearance of aging. Collagen is a protein synthesized by fibroblast cells located in the dermis layer of the skin, providing structural integrity, elasticity, and durability. COL1A1 is a protein encoded by the collagen Type I Alpha gene, which is necessary for the production of Type I collagen. Type I collagen is the most common type of collagen found in the body and is present in structural tissues such as skin, bone, tendon, connective tissue, and cartilage. COL1A1 provides the structural integrity, strength, and durability of the skin, while also playing an important role in anti-aging by resisting the decrease in skin elasticity. COL3A1 is found in the skin along with COL1A1 and plays an important role in the elasticity of the skin. COL1A1 is the most abundant collagen in the dermis layer of the skin, constituting approximately 80-90% of it. COL3A1 is the second most common type of collagen found in the skin and typically constitutes about 10-15%.

ELN (Elastin) is an extracellular matrix protein synthesized by fibroblast cells, which imparts elasticity to the skin. The decrease in elastin in the skin due to fatigue and the consequent loss of skin elasticity, along with the loss of collagen, leads to wrinkles and sagging.

ProlCell® MeadowGlow reduces the appearance of aging, wrinkles, and fatigue on the skin by promoting the degradation of non-foldable proteins and stimulating collagen and elastin synthesis.

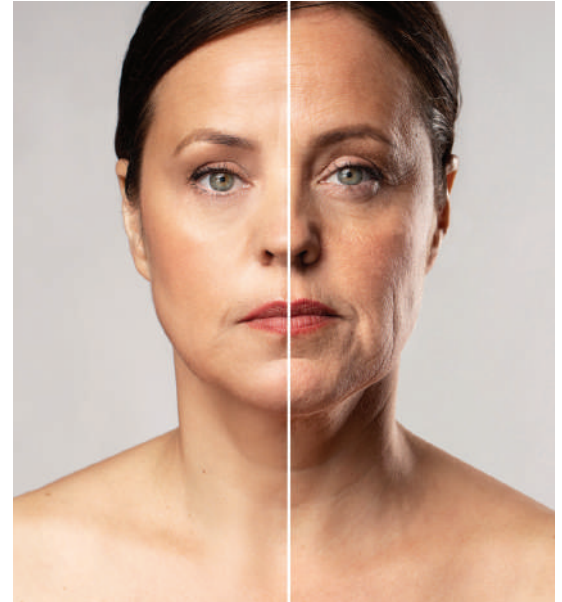
# Efficacy Tests

## In vitro Tests

**Cell line:** Mouse melanoma cells, Human normal fibroblast cells, Keratinocyte cells

**Test ingredient:** 250 and 500 µg/mL ProliCell® MeadowGlow Bioactive (It is a composition of exosomes containing dissolved plant stem cells and enriched small RNAs in the cell culture medium)

**Parameter:** Determination of melanin content by in vitro melanin content assay, Determination of anti-glycation effect using the MDA method, Analysis of expression of COL1A1, COL3A1,



## The evaluation of the effect of small RNA-enriched EVs

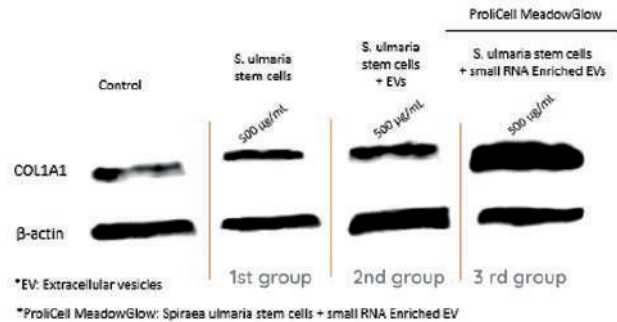
The in vitro efficacy of MeadowGlow containing *S. ulmaria* stem cells and small RNA-enriched EVs (3th group, ProliCell MeadowGlow) was compared with the group treated with only *S. ulmaria* stem cells (1st group) and the group treated with *S. ulmaria* stem cells and EVs (2nd group).

ProliCell MeadowGlow was determined to be the most effective group among the groups.

## Determination of COL1A1 Protein by Western Blot Assay

It was observed that compared to fibroblast cells treated with only *S. ulmaria* stem cells (1st group), the group treated with both *S. ulmaria* stem cells and EVs (2nd group) showed a higher expression of Type 1 Collagen-C. Furthermore, the highest expression was found in cells treated with *S. ulmaria* stem cells and small RNA-enriched EVs (3th group), in other words, ProliCell MeadowGlow.

ProliCell® MeadowGlow exhibits anti-aging activity, stimulating collagen synthesis.



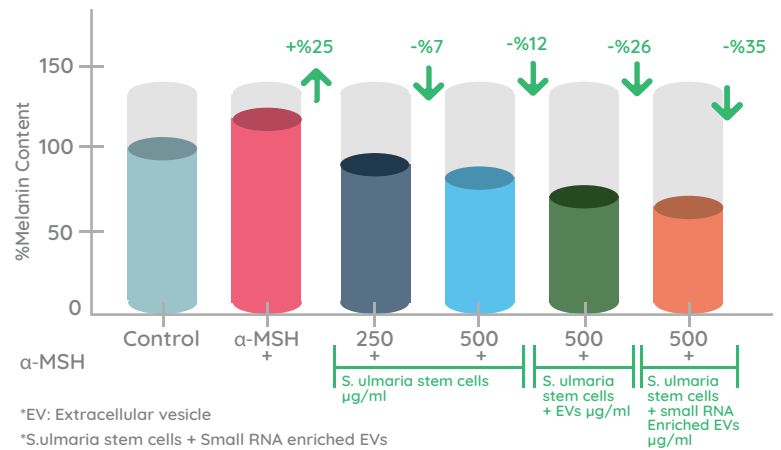
## Effect on Melanin Synthesis

Excessive and irregular secretion of melanin pigment causes dark spots and an uneven skin tone. To eliminate the unevenness in skin tone and reduce the appearance of dark spots, it is necessary to suppress the excessive synthesis of melanin.

ProliCell® MeadowGlow's melanin synthesis suppression activity was determined through a melanin content assay.

MeadowGlow, showing the highest reduction. ProliCell MeadowGlow brightens the skin and helps balance skin tone by suppressing melanin synthesis in melanocytes.

## Effect on Melanin Synthesis



## Efficacy Tests

Melanocyte cells were treated with 200  $\mu\text{M}$   $\alpha$ -MSH to promote melanin formation in order to measure the amount of melanin present. Following  $\alpha$ -MSH treatment, the cells were cultured with *S. ulmaria* stem cells, EVs, and ProliCell MeadowGlow concentrations. When the outcomes of the melanin synthesis experiment's were assessed in relation to the cells that received  $\alpha$ -MSH treatment;

*S. ulmaria* stem cells reduced melanin content by 7% at a concentration of 250  $\mu\text{M}$  and by 12% at 500  $\mu\text{M}$ , while the addition of EV to *S. ulmaria* stem cells at a concentration of 500  $\mu\text{g}/\text{mL}$  suppressed melanin synthesis by 26%, and ProliCell MeadowGlow at 500  $\mu\text{g}/\text{mL}$  suppressed melanin synthesis by 35%. ProliCell<sup>®</sup> MeadowGlow helps brighten the skin and balance the skin tone by suppressing hyperpigmentation.

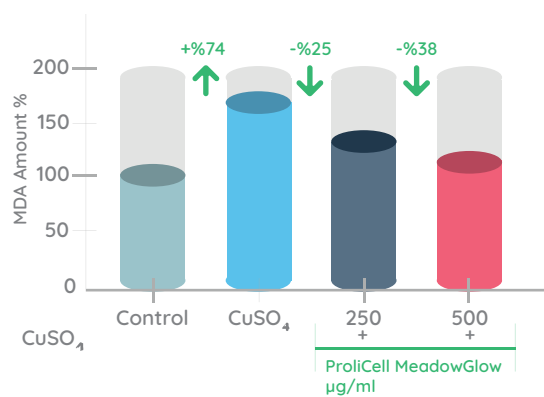
### Determination of Anti-Glycation Effect Using the MDA Method

Lipid peroxidation occurs as a result of the oxidation of fat molecules in cells, and this process leads to the degradation of cell membranes. Lipid peroxidation can lead to a decrease in membrane fluidity and membrane potential, an increase in permeability to  $\text{H}^+$  and other ions, and the disruption of organelle or cell integrity. When cell integrity is compromised, a rough appearance, wrinkles, skin damage, and aging occur on the skin.

Malondialdehyde (MDA) is a compound associated with cellular damage, oxidative stress, lipid peroxidation, and aging, and it appears as a byproduct in the body due to oxidative stress, where free radicals and reactive oxygen species (ROS) oxidize and damage cellular structures.

The amount of MDA can be determined in vitro using the Thiobarbituric Acid Reactive Substances (TBARS) test. With this test, the red-pink color formed by the reaction of MDA and thiobarbituric acid (TBA) in the MDA-TBA complex is measured at a wavelength of 532 nm.

#### Anti-Glycation Effect with the MDA Method



ProliCell MeadowGlow provides a protective effect against cellular aging through its anti-glycation activity by reducing MDA formation.

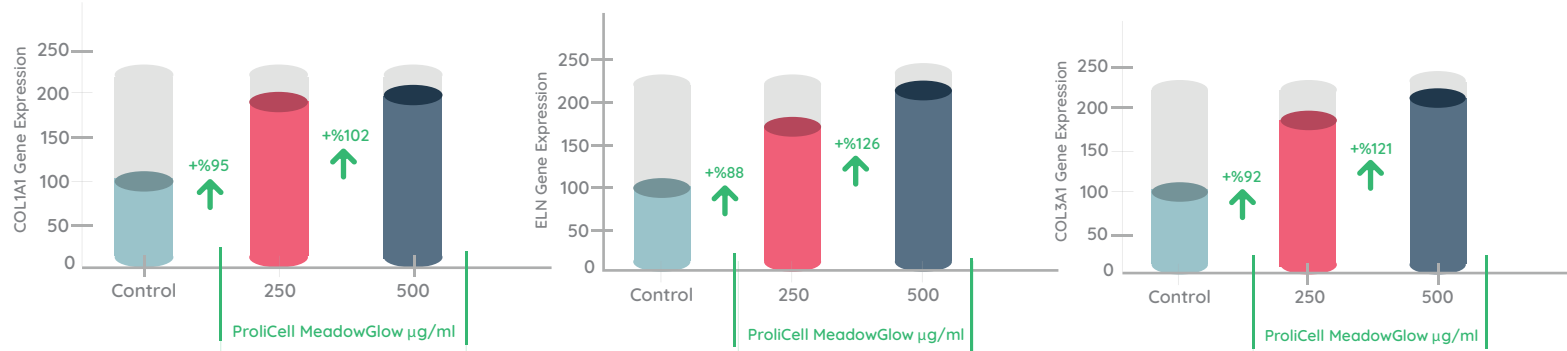
For lipid peroxidation analysis, keratinocytes were incubated with 0.3 mM  $\text{CuSO}_4$  to induce MDA levels, and then incubated with ProliCell MeadowGlow concentrations. The cells in the group treated with  $\text{CuSO}_4$  showed a 74% increase in MDA (malondialdehyde) levels compared to the control group.

Compared to the group treated only with  $\text{CuSO}_4$ , the cells treated with ProliCell MeadowGlow showed a 25% reduction in MDA levels at a concentration of 250  $\mu\text{g}/\text{mL}$  and a 38% reduction at a concentration of 500  $\mu\text{g}/\text{mL}$ .

## Expression Analysis of Genes Associated with Wrinkle Appearance

The effect of ProlCell® MeadowGlow on the expression of COL1A1 (collagen type 1), COL3A1 (collagen type 3), and ELN (Elastin) genes, which are associated with collagen synthesis and elastin synthesis in fibroblast cells, was analyzed using the RT-qPCR method.

### Expression Analysis of Genes Associated with Wrinkle Appearance



ProlCell MeadowGlow reduces the appearance of wrinkles by increasing the expression of COL1A1, ELASTIN and COL3A1 genes.

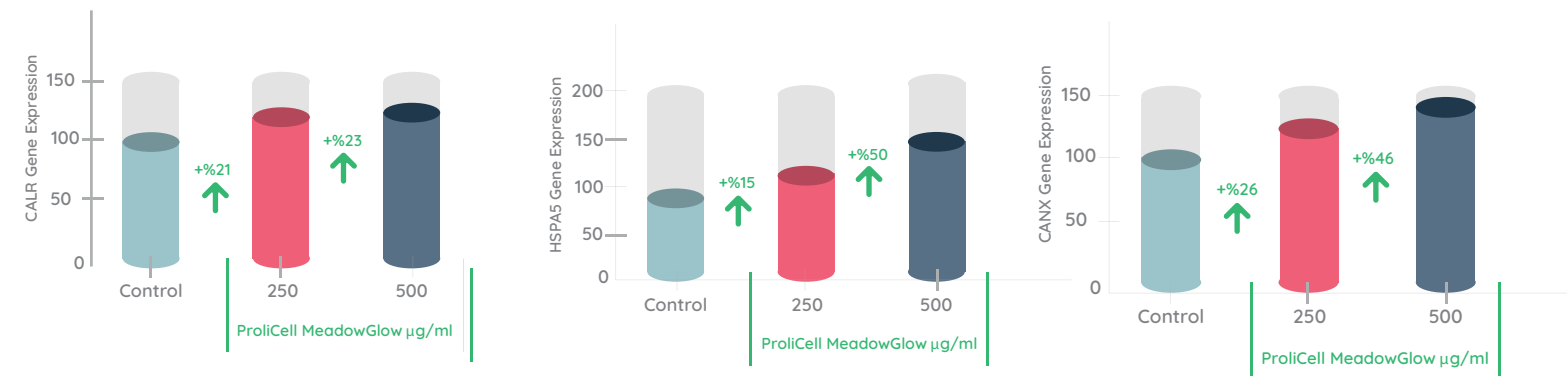
Fibroblast cells were incubated with ProlCell® MeadowGlow at concentrations of 250 and 500 µg/mL for 24 hours, and gene expressions were determined by RT-qPCR. In the analyses conducted, compared to the control group, the following results were observed in the cells treated with ProlCell® MeadowGlow; The expression of the COL1A1 gene at 250 µg/mL was 95%, and at 500 µg/mL, it was 102%. The expression of the ELN gene at 250 µg/mL was 88%, and at 500 µg/mL was 126%. The expression of the COL3A1 gene increased by 92% at 250 µg/mL and by 121% at 500 µg/mL. ProlCell® MeadowGlow reduces the appearance of wrinkles by increasing the expression of COL1A1, COL3A1, and ELN genes.

## Expression Analysis of Genes Associated with Fatigue Appearance

As a result of the unfolded protein response and endoplasmic reticulum stress, chaperone proteins such as Calreticulin (CALR), Calnexin (CANX), and Binding Immunoglobulin Protein (BIP-HSPA5) are involved in the temporary retention of unfolded glycoproteins.

The effect of ProlCell® MeadowGlow on the expression of CALR, CANX, and HSPA5 genes was determined by RT-qPCR analysis.

### Expression Analysis of Genes Associated with Fatigue Appearance



ProlCell MeadowGlow reduces the appearance of fatigue and wrinkles caused by insomnia by increasing the expression of CALR, CANX and HSPA5 genes.

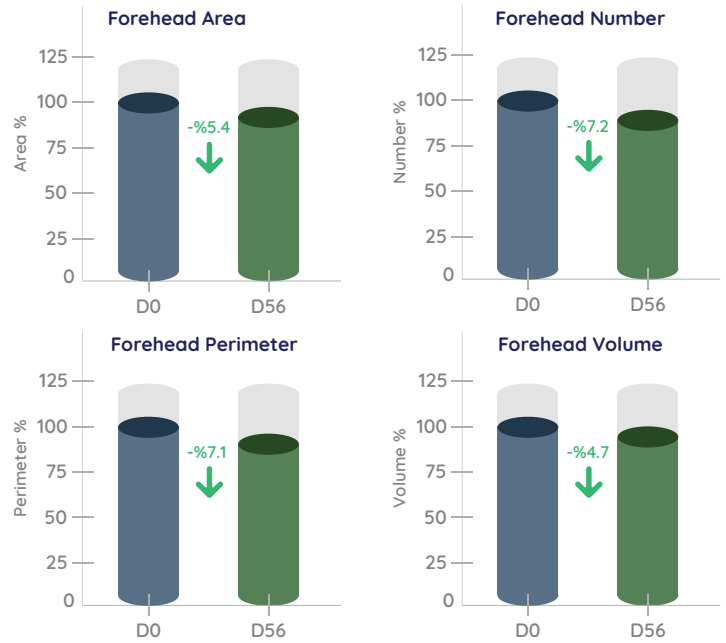
Fibroblast cells were incubated with ProlCell® MeadowGlow at concentrations of 250 and 500 µg/mL for 24 hours, and gene expressions were determined by RT-qPCR. In the analyses conducted, compared to the control group, the following results were observed in the cells treated with ProlCell® MeadowGlow; The expression of the CALR gene was at 21% at 250 µg/mL and at 23% at 500 µg/mL. The expression of the HSPA5 gene was at 15% at 250 µg/mL and 50% at 500 µg/mL. The expression of the CANX gene increased by 26% at 250 µg/mL and by 46% at 500 µg/mL. ProlCell® MeadowGlow increases the expression of CALR, CANX, and HSPA5 genes, facilitating the removal of misfolded proteins, thereby reducing the appearance of aging caused by insomnia and fatigue.

# In Vivo Efficacy Tests

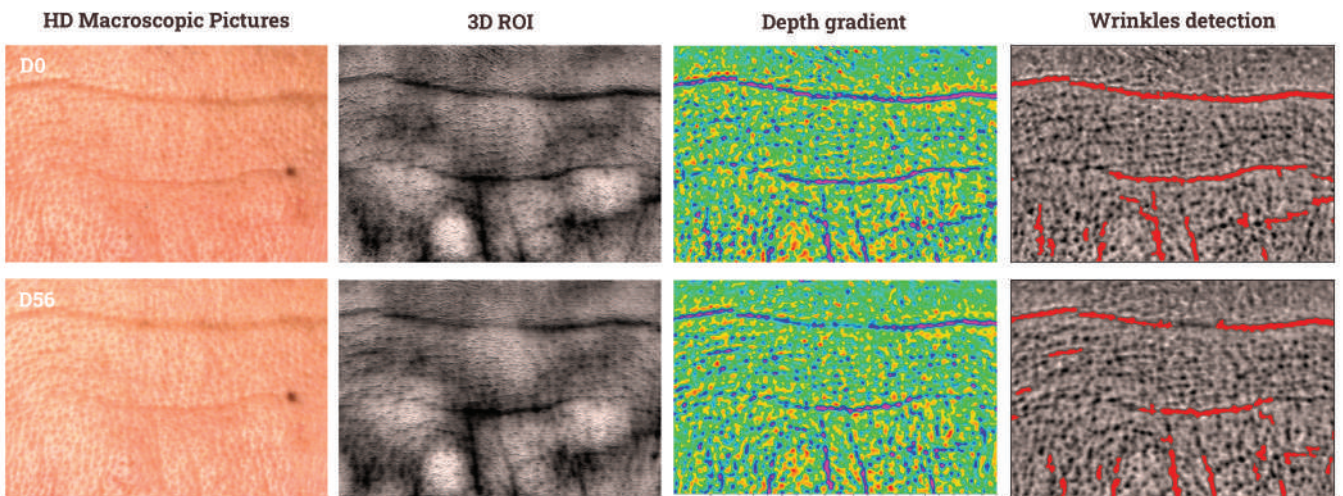
## Skin Brightening and Anti-aging Activity

- A clinical evaluation with the test treatment was initially carried out on 22 volunteers, aged from 41 to 65 years (mean  $52.8 \pm 6.3$ ).
- Volunteers were female between the ages of 35 and 65, presenting mild to severe signs of ageing
- Serum (containing 2% ProliCell MeadowGlow) was applied to the volunteers' face area twice a day for 56 days.
- Measurements were recorded before starting treatment (D0) and after 8 weeks of treatment (D56).

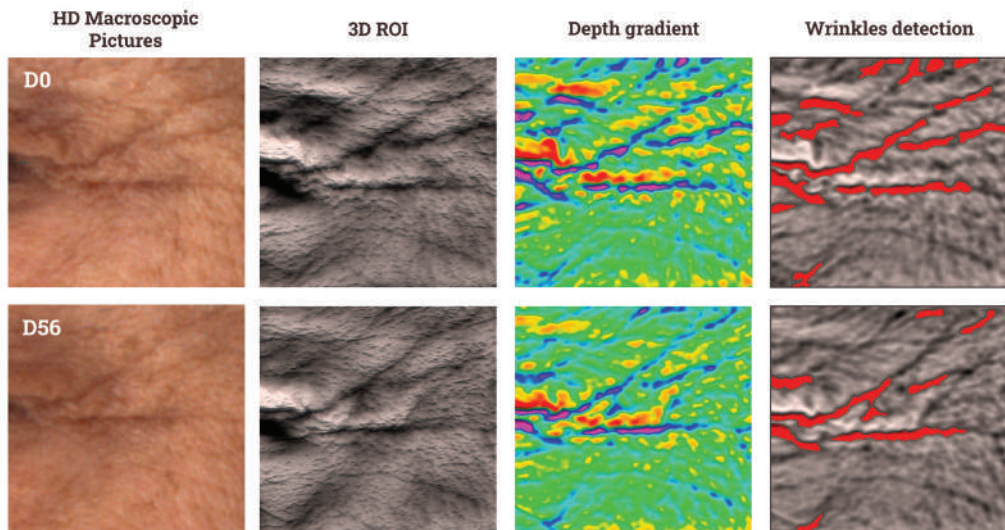
## Effect on forehead wrinkles for volunteers



Change in of the area, number, perimeter and volume forehead in volunteers

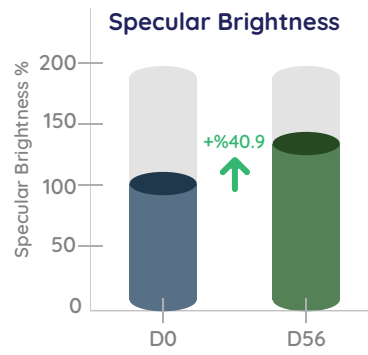
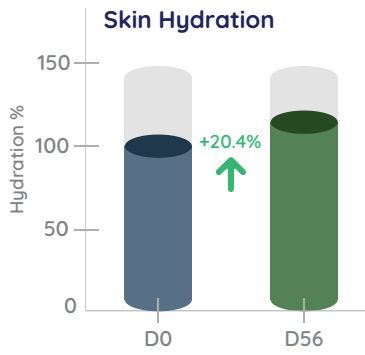


## Effect on forehead wrinkles for volunteers



## Effect on Crow's feet wrinkles for volunteers

# In Vivo Efficacy Tests



Change in specular brightness in volunteers





# ProliCell® MeadowGlow Technical Data Sheet

## Lightening Effect of Elegance Skin Brightening and Anti-Fatigue Active

### Effect Mechanisms

- Balances melanin synthesis
- Protects cell integrity
- Improves the appearance of stress and fatigue
- Brightening effect

### Cosmetic Uses

- Skin brightening in skincare products
- Anti-aging skincare products
- Anti fatigue in skincare products.

### Features

Origin: **Herbal**  
Appearance: **Viscous cell lysate suspension**  
Color: **Brown**  
Odor: **Characteristic**  
Usage: **Add below 40°C in cold-hot processes.**  
Usage rate: **2-5%**  
pH: **5-7**



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