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LIPOREDUCTYL®

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NO TRACE FROM CELLULITE



**EFFICIENT PREVENTION,
POTENT LIPOLYSIS,
LIPOXIDATION BY-PRODUCT CAPTURE
AND MICROCIRCULATION ACTIVATION
IN ONE PRODUCT!**

GENERAL DESCRIPTION

Cellulite is primarily a condition of poor microcirculation that causes damage to the fat tissue under the skin.

Aesthetically, cellulite is a problem consisting in the visual presentation of weakened, damaged fatty tissue and fibrous connective tissue in the shape of lumps and dimples, commonly known as “orange skin”.

Cellulite is usually found on the thighs and butt, specially in women. It affects about 80 to 95% of women, regardless of whether they are overweight, average weight or thin, while it only affects 5% of men due to differences in fat levels and hormonal system. It is a complex process which has several causes of diverse nature: dietetic, vascular, endocrine, lifestyle, etc.

Females have their subcutaneous fat structured in small chambers separated by vertical walls of tissue. The whole framework is irrigated by a complex vascular system of arterioles and capillaries responsible for circulation and drainage.

The failure of this microcirculation system results in leakage of liquid into the surrounding tissue. This liquid retention in the interstitial spaces also affects adipocytes, which start to produce excess triglycerides and grow in size, becoming trapped in the connective network. This tissue congestion causes swelling, prevents nutrients such as oxygen of being carried to the tissue, and hinders the drainage of toxins. A negative cycle starts where enlarged adipocytes pressurize the microcirculation system causing more liquid to leak and more adipocytes to grow.

Connective tissue, including collagen and elastin, becomes increasingly damaged; eventually becoming so severely compromised that they scar, causing stretch marks.

The cosmetic result is an uneven distribution of fat and damaged tissue which modifies the appearance of the skin, provoking the well-known lumpy “orange skin” dimples.

A cosmetic treatment against cellulite must act in two different ways: on the fat (lipolytic effect) and on the circulation (venotonic effect).

LIPOREDUCTYL[®] contains multivesicular liposomes of classical anti-cellulite ingredients combined with the synergistic effect of a GHK tripeptide. These liposomes favour effective penetration through the skin, so the transport of the actives to the deepest layers of the epidermis allows effective action on both the lipolytic and venotonic fronts. LIPOREDUCTYL[®] contains the following actives:

- **CAFFEINE** presents a lipolytic effect: it blocks enzymes responsible for the destruction of AMPc, which is involved in triglyceride breakage. It also possesses vasodilator properties, increasing blood flow. Therefore, it contributes to both the lipolytic and venotonic effect.

- BUTCHERBROOM (RUSCUS ACULEATUS) EXTRACT acts mainly on the microcirculation, decreasing capillary permeability due to its content in a flavonoid called Rutin.
- IODINE compounds such as TEA-HYDROIODIDE have effective lipolytic properties by stimulating lipases.
- IVY (HEDERA HELIX) EXTRACT contains Hederine, an active saponin responsible for blood vessel protection and permeability decrease. Ivy helps to reabsorb the oedemas present in the initial stages of cellulite.
- CARNITINE is well-known for enhancing triglyceride mobility and accelerating their breakdown.
- ESCIN is a venotonic and anti-oedematous ingredient.
- GLYCYL-HISTIDYL-LYSINE acts as a specific scavenger for certain by-products of lipidic peroxidation such as unsaturated aldehydes. The capture of these by-products increases the effectiveness of the anti-cellulite components.

The combination of all these actives and a special liposomal delivery system capable of penetrating to the lowest levels of the epidermis ensures an effective treatment against cellulite.

In vitro studies show that LIPOREDUCTYL® has a very specific effect on adipocyte differentiation, since it is a strong inhibitor of the maturation process. LIPOREDUCTYL® acts on the metabolic pathways that lead to the accumulation of lipid droplets inside healthy adipocytes, which means it helps to prevent cellulite, rather than only burning fat once cellulite has already developed.

PROPERTIES AND APPLICATIONS

Four specific cellulite-fighting actions:

1. Revolutionary cellulite prevention due to action on the maturation process of adipocytes.
2. Traditional lipolytic activity provided by classic anti-cellulite ingredients.
3. Activation of microcirculation due to the powerful venotonic profile of several actives.
4. The GHK peptide acts as an efficient scavenger for by-products of lipidic peroxidation.

These properties translate into visual effects:

- Enhanced microcirculation improves the skin's complexion
- Improved skin hydration and skin elasticity
- Reduction in thigh and buttock circumference
- Reduction in extracellular water and body fat mass

LIPOREDUCTYL[®] can be included in creams, lotion, gels, sera, etc, especially in products intended for a preventive anti-cellulite treatment.

TECHNICAL INFORMATION

PRODUCT SPECIFICATIONS

LIPOREDUCTYL®	
INCI name of the active ingredient	Caffeine, Butcherbroom (Ruscus Aculeatus) Root Extract, Tea-Hydroiodide, Carnitine, Escin, Ivy (Hedera Helix) Extract, Tripeptide-1.

Note: small, needle-shaped, white particles may appear due to precipitation of caffeine. These particles do not affect the quality of the product.

PRESENTATION

LIPOREDUCTYL® CPK	
Code	P02-ES600
Preservatives	Potassium Sorbate, Phenoxyethanol.
Appearance	Paste

PROCESSING

LIPOREDUCTYL® CPK can be added in the aqueous phase once the emulsion is formed. It should be provided that the temperature is below 40°C.

LIPOREDUCTYL® CPK is stable at a pH range between 4.0 and 7.0.

INCOMPATIBILITIES

Ionic surfactants and strong oxidants.

SOLUBILITY

Soluble in water.

DOSAGE

A dosage of 5-10% is recommended in final cosmetic formulations (emulsions, gels, sera...).

EFFICACY TESTS

In vitro tests

CELLULITE PREVENTION: Inhibition of adipocyte maturation and effect on lipid droplet size

A test was carried out on human adipocytes in order to assess LIPOREDUCTYL[®]'s power as a preventive treatment for cellulite. An *in vitro* cell culture model of human preadipocytes was used, and they were stimulated to differentiate to adipocytes. This was accomplished by using a potent mixture of differentiation agents which induces a strong accumulation of fat inside the lipid droplets contained in the preadipocytes. The lipid droplets were visualised by phase contrast microscopy and quantified by image analysis.

During image analysis, the following parameters were quantified (average \pm SD of duplicate experiments): number of cells per area, number of differentiated adipocytes per area, number of lipid droplets per adipocyte and size of lipid droplets. The results are shown in the following graphs:

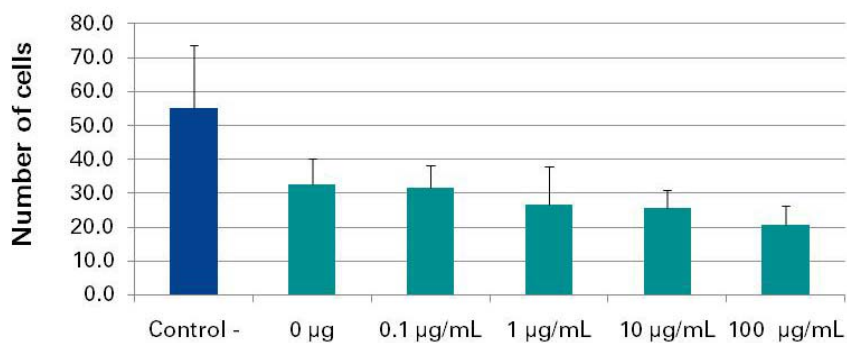


Figure 1. Effects of LIPOREDUCTYL[®] on the number of cells per area

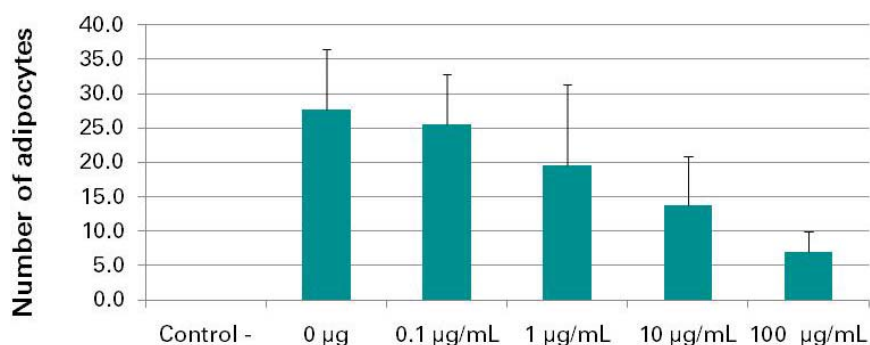


Fig. 2. Effects of LIPOREDUCTYL[®] on the number of adipocytes per area

Conclusions: the number of adipocytes decreases whilst the number of total cells is not affected which means LIPOREDUCTYL[®] targets specifically adipocyte maturation and is not cytotoxic.

Note: the number of cells in the negative control (non-differentiated adipocytes) is higher than in the differentiated cells (either treated with LIPOREDUCTYL[®] or not) due to the differentiation process which stops proliferation. For the negative control there are no adipocytes, indicating no spontaneous differentiation of preadipocytes.

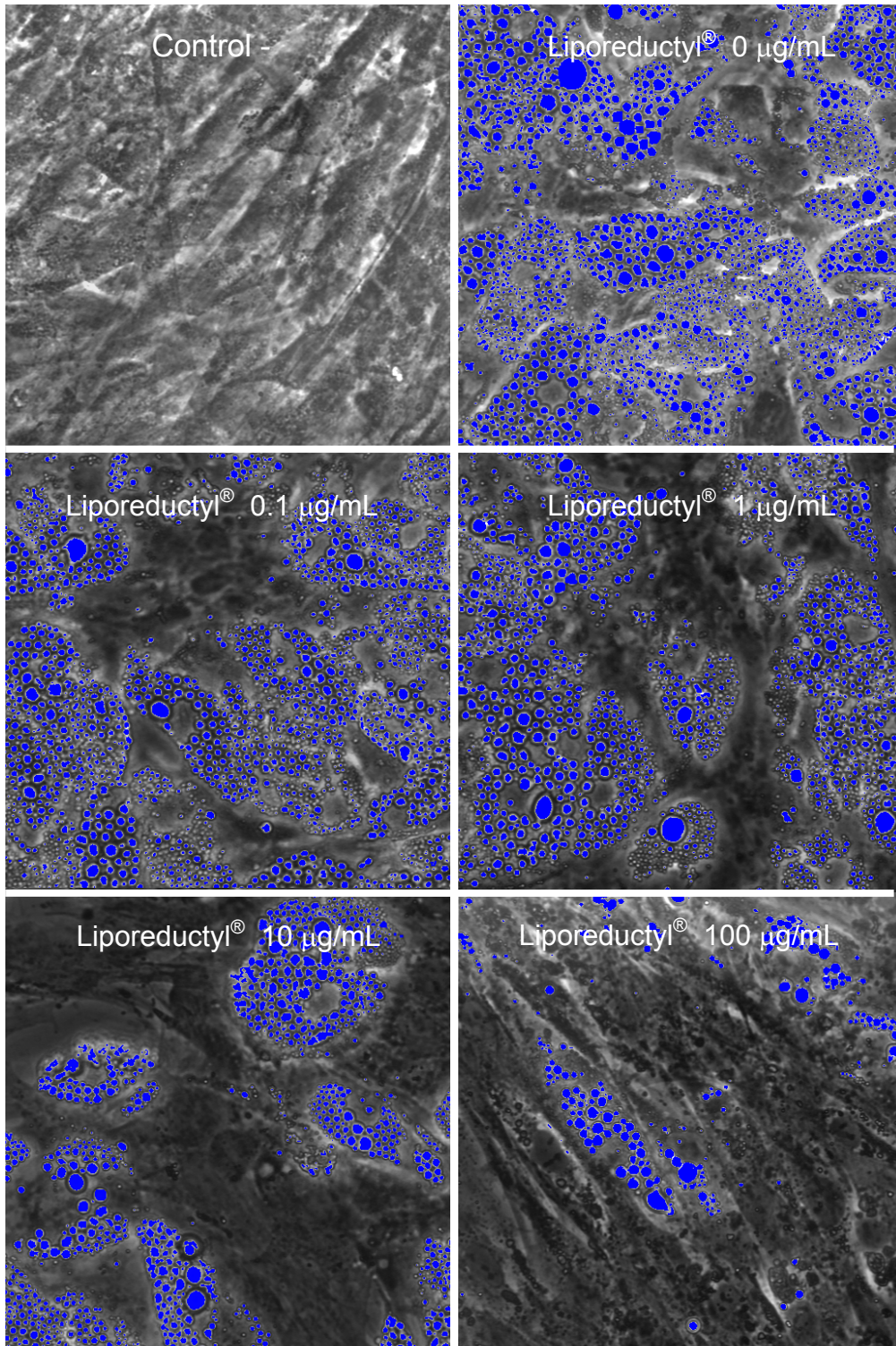


Fig. 3. Lipid droplets (in blue) inside adipocytes

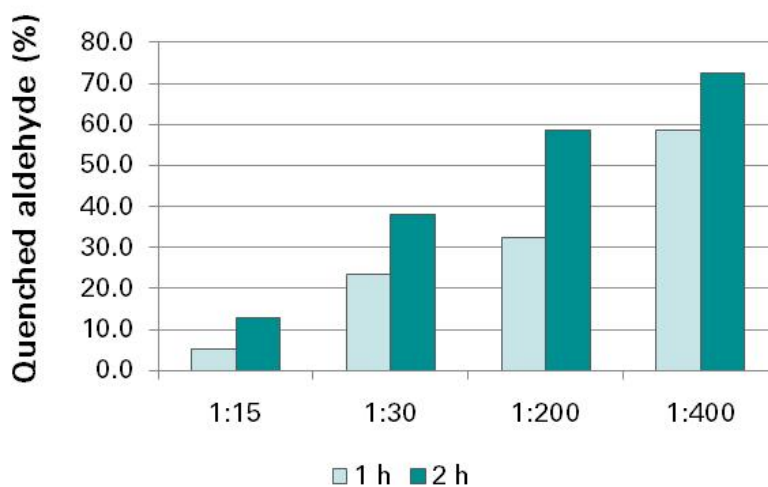
The images show the reduction in adipocytes and consequently in lipid droplets. The decrease is dose dependent. This test confirms the effectiveness of LIPOREDUCTYL® for preventive anti-cellulite treatments.

SEQUESTERING ACTION: the GHK Tripeptide effectively captures lipid peroxidation by-products

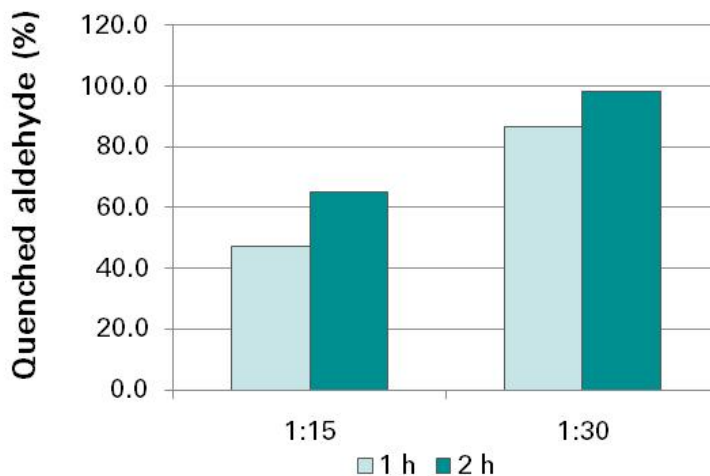
Skin aging is accelerated by processes such as lipid peroxidation. Tissues affected by skin aging contain elevated levels of reactive α,β -unsaturated aldehydes, such as 4-Hydroxy-2-nonenal (HNE), Malondialdehyde (MDA) and Acrolein, all of which are well known by-products of lipid peroxidation.

The tripeptide GHK is a potent aldehyde-sequestering agent.

Quenching activity GHK vs HNE



Quenching activity GHK vs Acrolein

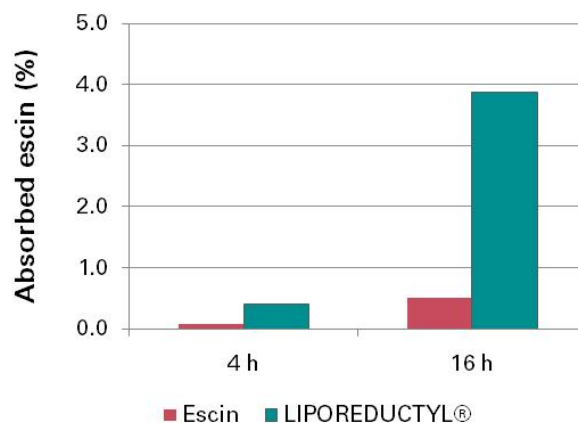
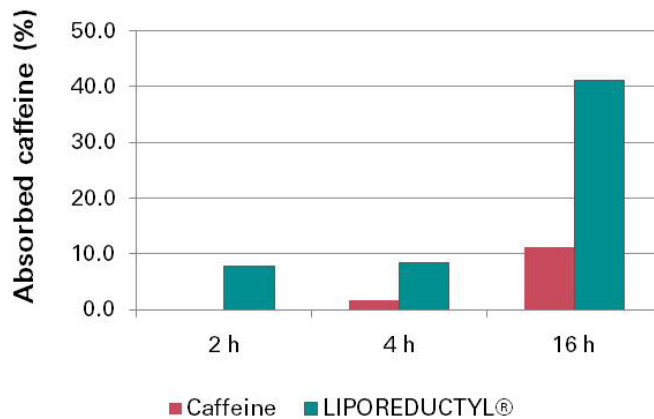


PERCUTANEOUS ABSORPTION STUDIES

A 3D *in vitro* skin model was used, consisting of pluristratified human keratinocytes, showing morphology and functionality close to that of *in vivo* human skin. Under the artificial epidermis there is a semipermeable membrane in communication with the underlying compartment which contains the culture medium (undernatant). The skin model is Skinethic[®] (Skinethic Laboratories, Nice).

LIPOREDUCTYL[®] (200 mg) was added to each epidermal unit, the quantities of caffeine and escin in the formula having been previously determined. Pure caffeine was diluted to 20 ppm in the culture medium and 200 µL were placed in contact with the skin model. Pure escin was diluted to 50 ppm in the culture medium and 200 µL were placed in contact with the skin model.

After 2, 4 and 16 h an amount of 200 µL of undernatant was collected from each well to evaluate caffeine and escin absorption. The samples were weighed and analysed by HPLC.



Conclusions: LIPOREDUCTYL[®]'s **liposomal formulation** favours **epidermal penetration**, as demonstrated by the fact that caffeine penetration is increased almost 5 fold compared to pure caffeine and escin penetration is increased up to almost 8 fold. The encapsulation of the actives in liposomes also enables a **slow release**, as proved by determinations at 16 hours, where caffeine is absorbed 3 times more than pure caffeine and escin reaches its maximum absorption of almost 4% (7.7 times more than pure escin).

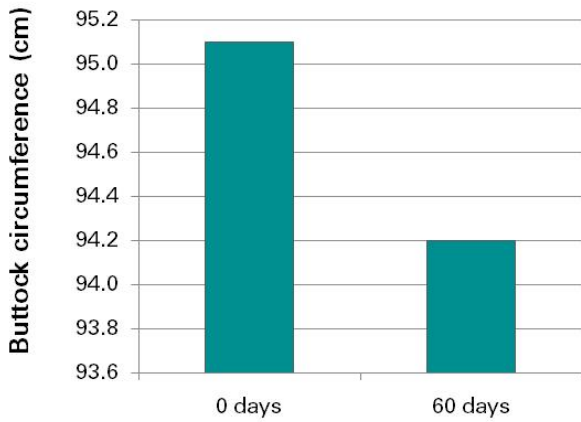
In vivo tests

Evaluation of the anti-cellulite effects on the skin of LIPOREDUCTYL®.

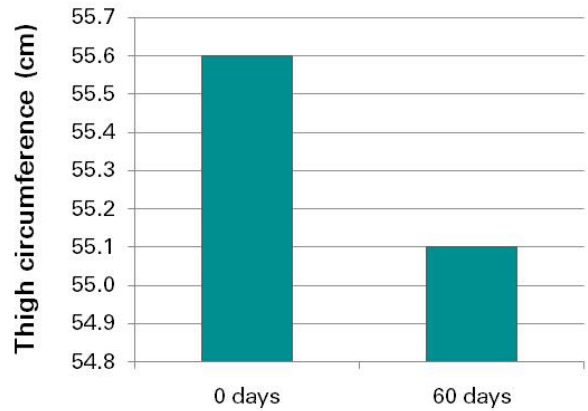
The global action of LIPOREDUCTYL® as an effective anti-cellulite was evaluated in a study performed on 20 females with cellulite imperfections, aged between 18 and 70. A gel containing 7% of LIPOREDUCTYL® was applied daily for 60 days on specific body areas (Glute SX, Glute DX, Femoris Post SX, Femoris Post DX, Femoris Ant SX, Femoris Ant DX) and the following parameters were studied:

Instrumental measurement	<ul style="list-style-type: none"> ▪ circumference of buttocks and thighs ▪ body fat mass* ▪ extracellular water* ▪ skin moisture** ▪ elasticity***
	<p>Measurement performed by:</p> <ul style="list-style-type: none"> • STA/BIA instrument* • Corneometer** • Cutometer*** <p>All instruments are authorised according to EU regulations.</p>
Subjective evaluation (by dermatologist)	<ul style="list-style-type: none"> ▪ microcirculation ▪ orange skin ▪ presence of nodules ▪ skin smoothness ▪ skin compactness ▪ complexion
	<p>A score between 1 – 4 is given to the dermatologist's evaluation. A Frideman test is used for the statistical analysis of non parametric data (Cosmetic News, 130, 30 – 32).</p>
Video Capillaroscopy	<p>Images of the skin were taken, before and after the test, using Video-Capillaroscopy which achieves 200 X magnifications of cellulite imperfections allowing the study of microcirculation, etc. This technique makes it possible to study:</p> <ul style="list-style-type: none"> -Fracture of the polygonal net -Capillary splitting -Apical microaneurysms of ansae

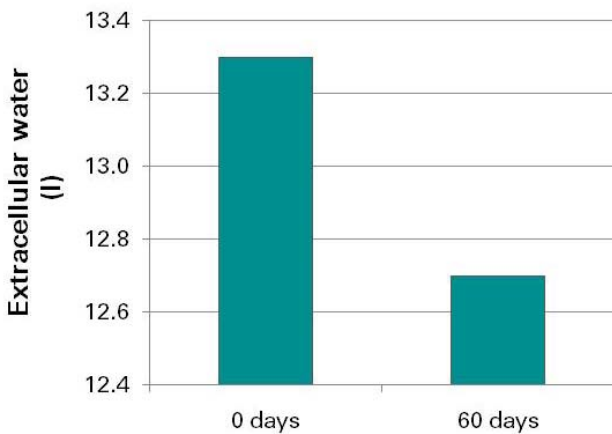
Instrumental measurements



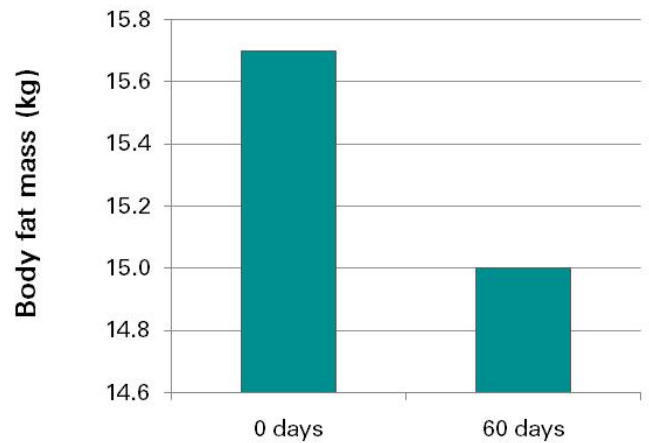
15% of volunteers showed a very significant decrease of 2.0 to 3.0 cms while 60% showed a significant decrease of 0.5 to 1.0 cms.



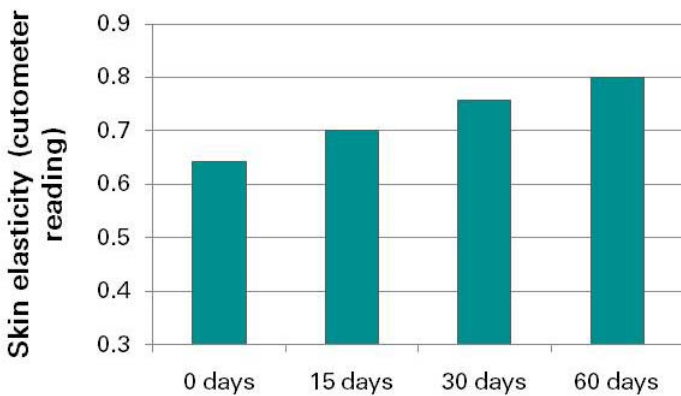
85% of volunteers presented a significant decrease of 0.5 to 1.0 cms.



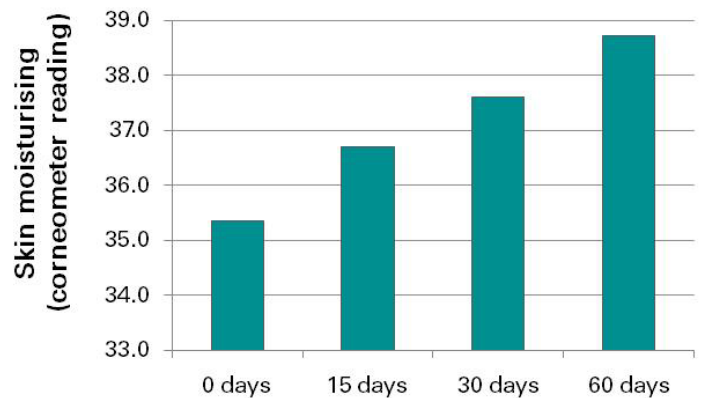
60% of volunteers show a very significant decrease of 0.5 to 1.6 litres



50% of the volunteers show a significant decrease of 0.6 to 1.4 kgs

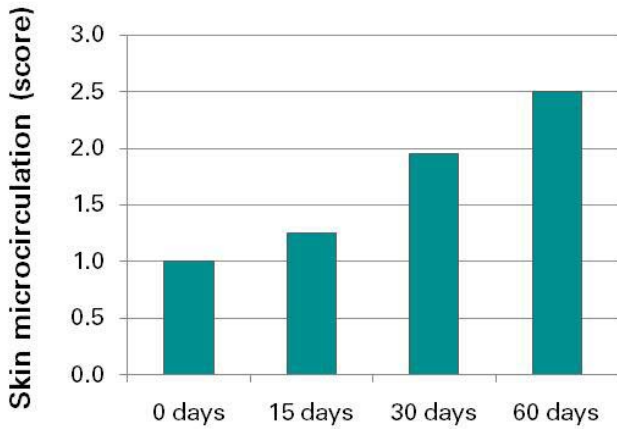


After 30 days, the increase was of 17.5% and after 60 days it was of 24.4%.

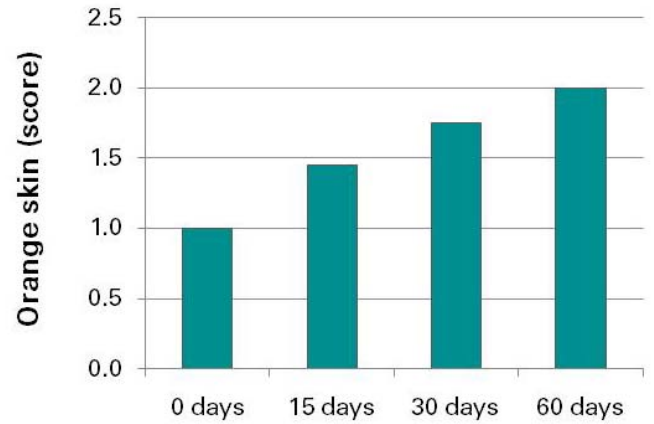


After the treatment, the moisturising index had increased by 9.5%.

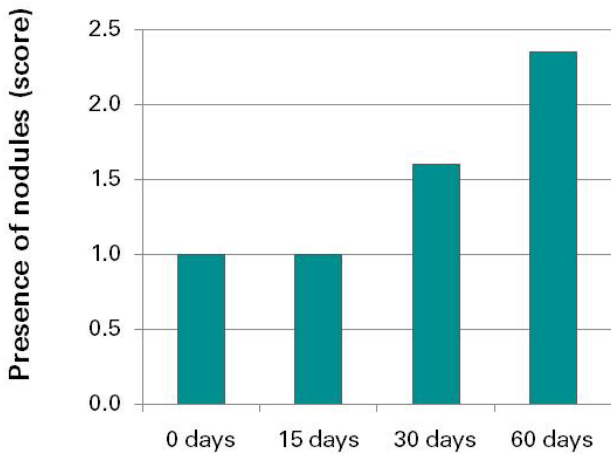
Dermatological evaluation



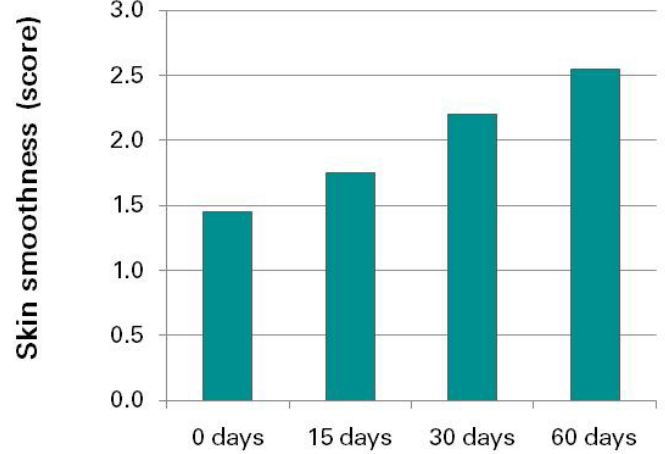
The polygonal net is more regular in 60% of volunteers after the test. Another 35% had a slight improvement.



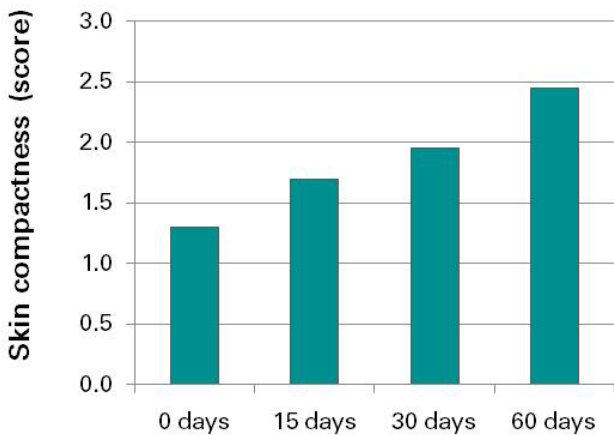
75% of volunteers presented an improvement in orange skin, one third of those presented a fairly good improvement.



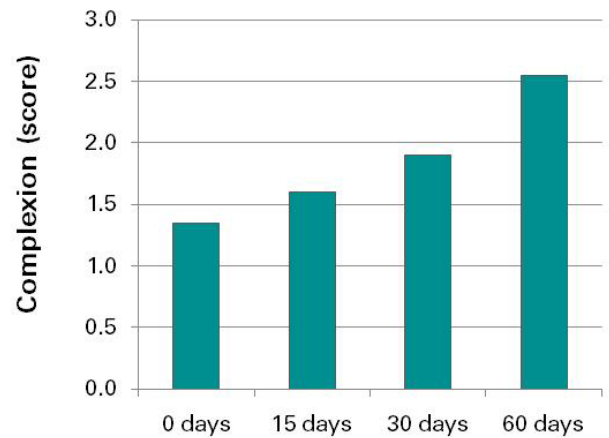
In 95% of volunteers nodules condition has improved, and both micronodules and macronodules seem less evident. 40% experienced a fairly good improvement.



65% of the volunteers finished the test with smooth skin



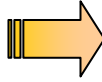
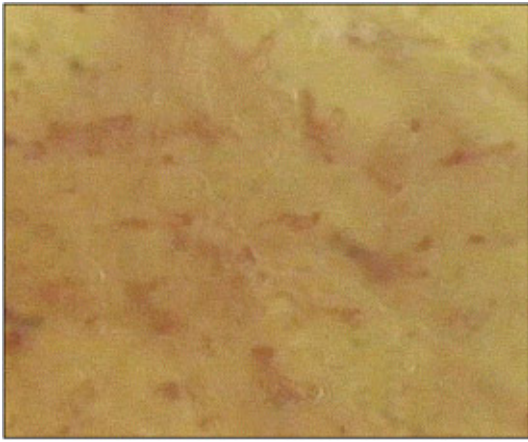
There is a significant variation of skin compactness from the 30th day of treatment which is an index of improved cutaneous trophism. After the treatment, 55% of volunteers show a compact and elastic skin.



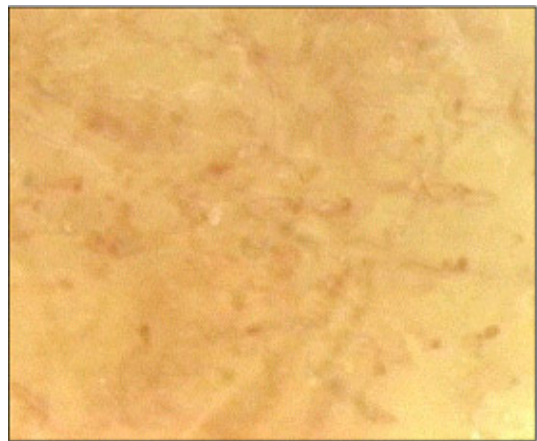
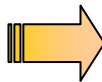
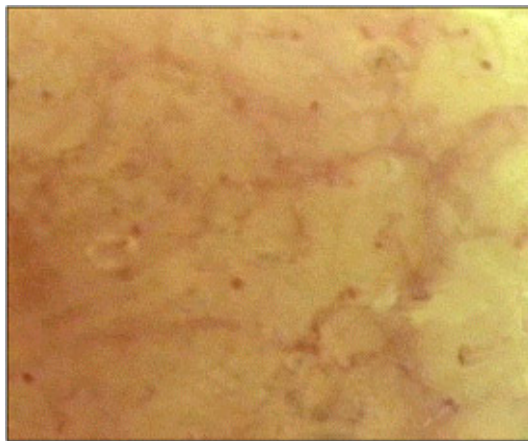
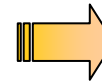
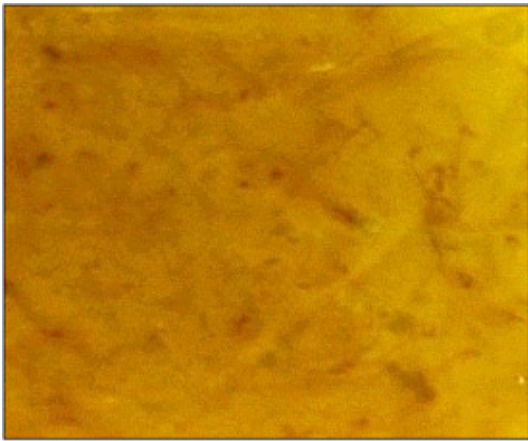
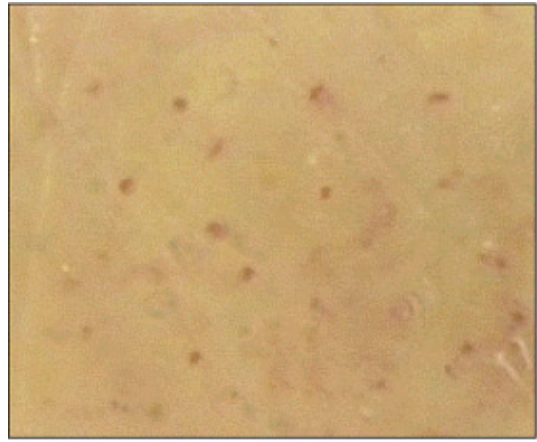
After the treatment, 65% of the volunteers show a rosy complexion which is a sign of improved microcirculation.

Video Capillaroscopy

0 days



60 days



CONCLUSIONS:

- ❑ All pictures show an improvement in the structure of microcapillaries and a decrease in microhaemorrhages.
- ❑ The macroscopic translation is a rosier complexion, less evident presence of nodules and an improvement in the degree of orange skin.

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