OKINACEA®

The anti-aging power behind

Green caviar / Sea grape

*

Improves skin functional integrity by reinforcing the DEJ

Increases skin firmness by increasing the dermal structure

Reduces skin roughness

Gelyma

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SUMMARY

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INTRODUCTION

Human skin consists of different layers.

The epidermis is the outer layer whose principal role is to protect the body. It gives the skin its impermeability and resistance. While different cell types co-exist in the epidermis, the keratinocytes constitute the main cell type (90%). Keratinocytes produce special fibrous and water-insoluble proteins named keratins. These keratins are constituents of the corneal layer of the epidermis which protects the skin against harmful external factors (heat, cold, dehydration).

The inner layer of the skin is the dermis, a conjunctive tissue containing cells (fibroblasts) dispersed in a complex medium called the extracellular matrix. There are various types of structural elements in the matrix showing different functions *e.g.* collagen gives the skin its strength, elastin fibers give the skin its elasticity and proteins called glycosaminoglycans give the skin its turgor.

The junction between the epidermis and the dermis is an important structure named the dermal-epidermal junction (DEJ).This structure provides adhesion of the dermis to the epidermis and has a mechanical support role which is partly responsible for skin tonicity. It is also responsible for the exchange of nutrients from the epidermis to the dermis, thanks to its rete-ridges that form the interlocking connection between the epidermis and the dermis and increases the surface area of the epidermis exposed to the needed nutrients

Skin, like the other organs, is subjected to ageing.

Skin ageing is a complex biological process resulting from both intrinsic or genetically programmed ageing that occurs with time and extrinsic ageing caused by environmental factors.

Intrinsic and extrinsic ageing of the skin follow different pathways but alone or in concert, these processes induce numerous external signs of skin ageing that happen at both epidermis and dermis levels. The amount of water held by the epidermis decreases, skin keratinocytes renewal rate slows down. In the dermis, the renewal of collagen fibers diminishes, glycosaminoglycans production decreases, the extracellular matrix becomes disorganized. All these events conduct to the apparition of wrinkles and fine lines, thinning of the skin, loss of firmness, elasticity and moisture.

The effects of ageing also affect the dermal-epidermal junction. The rete-ridges flatten out, making the skin more fragile and making it easier for the skin to shear. This process also decreases the amount of nutrients available to the epidermis by decreasing the surface area in contact with the dermis.

Many research approaches have been put forward to fight skin ageing for defying such manifestations, this being become a common wish of men and women. These ways include prevention against external environment (sun, pollution…), activation of cell regeneration and strengthening the extracellular matrix (collagen and elastin).

In order to limit the ageing signs, GELYMA has developed OKINACEA®, an extract of Sea Grape associated with hydrolyzed Rice proteins.

Sea Grape also known as “green caviar” or “umi-budo” (lit. sea grape) is one of the five algal delicacies eaten by Okinawans, the inhabitants of the Japanese island Okinawa renowned for their longevity.

OKINACEA® targets both the dermal-epidermal junction (DEJ) and the dermis.

OKINACEA® improves the skin status more specifically

- by strengthening the dermal-epidermal junction with
  - increase of laminin-5 synthesis and
  - increase of collagen IV synthesis

  thus reinforcing the integrity of the DEJ structure and regulating the exchange of molecules between keratinocytes and dermis,

- by stimulating the synthesis of the extracellular matrix compounds with
  - increase of glycosaminoglycans synthesis
  - increase of collagen production

  thus preventing wrinkle formation and increasing skin firmness by renewal and enrichment with matrix macromolecules.

This finally leads to a visible cosmetic benefit against ageing signs that has been proved thanks to clinical and consumer use tests.

ALGAL SOURCE

OKINACEA® is extracted from the green seaweed: *Caulerpa lentillifera*, also known as “sea grape “or “green caviar”.

➢ Classification

The species *Caulerpa lentillifera* belongs to:

Empire	*Eukaryota*
Kingdom	*Plantae*
Phylum	*Chlorophyta*
Class	*Ulvophycea*
Order	Caulerpales-Bryopsidales
Family	*Caulerpaceae*
Genus	*Caulerpa* J.V. Lamouroux 1809
Species	*lentillifera* J.Agardh 1837.

• Synonyms

Chauvinia lentillifera (J.Agardh) Kützing, 1849
Chauvinia microphysa Kützing, 1863
Caulerpa kilneri J.Agardh 1873.

• Common names

“lato” , “lato-bilog” , “ar-arosep” in the Philippines
“Rong Nho” in Vietnam
sea grapes, “umi-budo” in Okinawa (lit. Sea grape)
green caviar.
small sea grapes (FAO name).

The genus *Caulerpa* includes 75 marine species showing an important morphological variability, probably due to environmental factors.

From other genera of green algae, the genus *Caulerpa* is identifiable on the basis of distinctive anatomical, cytological and biochemical characters.

The thallus consists of a non septate siphonous structure differentiated into a creeping and densely branched stolon that produces tufts of colorless rhizoids downward and photosynthetic fronds upward.

These fronds show an extremely diverse morphology including thread-like, blade-like, pinnate, spongy and vesicular structures. Consequently the various species of *Caulerpa* are classified on the basis of their fronds, especially shape and structure.

➤ Morphology & Biology

The thallus of *Caulerpa lentillifera* (Fig. 1 a, b) consists of horizontal irregularly branched stolons bearing numerous erect fronds which are densely covered by subspherical short ramelli. Each ramulus consists of a short stalk and a globose tip, 1-3 mm in diameter. The distinct constriction between the tip of the stalk and the base of the globose tip is a characteristic of this species.

These stipitate ramelli are generally placed on 5-8 longitudinal rows. They resemble bunches of little grapes. Colours range from bright green to bluish and olive green. Erect branches may reach up to 15 cm in height.

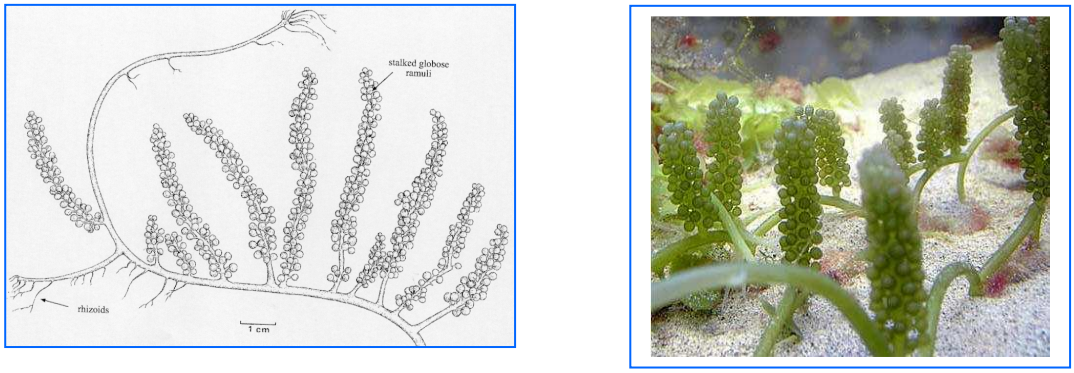


Fig. 1 – Morphology of *Caulerpa lentillifera*

a –drawing after Trono, 1986 – Philippine Seaweeds, 201-288. b – *in situ* as reef form

Caulerpa species are formed by one huge cell which is vulnerable to substantial plasma loss. They are equipped with efficient wound healing properties involving the formation of a "plug" of cell wall material and actin-mediated contraction.

The thalli used for OKINACEA® can reach 5cm long. The figures 2 (a – b) show the morphology of thalli chosen for the making of OKINACEA® and prove that the used species is well *lentillifera* (and not *racemosa*) by the presence of the constriction at the top of the stalk (b ↑).

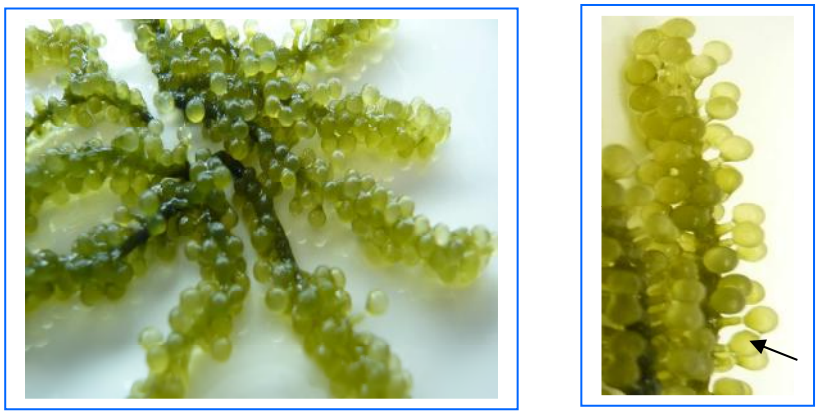


Fig. 2 – Morphology of *Caulerpa lentillifera* used for OKINACEA® (Photos GELYMA)

As the other *Caulerpa* species, *C.lentillifera* is heteroplastic with chloroplasts mixed with amyloplasts. Growth is apical and indeterminate. Reproduction is by fragmentation. Sexual reproduction is uncommon.

➤ Ecology & Geographical distribution

C. lentillifera is widely distributed in:

- ♦ Africa: Egypt, Ethiopia, Kenya, Madagascar, Mauritius, Somalia, South Africa, Tanzania
- ♦ Asia: Japan, Indonesia, Malaysia, Singapore, Thailand, Vietnam, India, Pakistan, Philippines, Sri Lanka,
- ♦ Pacific Islands: Federated States of Micronesia, Hawaiian islands, Marshall Islands, Solomon Islands, New Caledonia.
- ♦ Australia, New Zealand and Maldives.

C. lentillifera is commonly found on sandy or muddy sea bottoms in shallow protected areas.

➤ Chemical composition

Caulerpa species have distinctive biochemical characters:

- the photosynthetically active pigments are siphonaxanthin and siphonein. Siphonein is derived from siphonaxanthin by esterification of the primary OH group with lauric acid (H. Kleinig & K. Egger, 1967 – Phytochemistry , 6:1681-1686).

- the skeletal constituent of cell walls is not cellulose but xylan. In fact, different polysaccharides have been identified in *Caulerpa* species. A complex heteropolysaccharide contains β-1-3 xylooligosaccharides (T.Yamagaki *& al.,* 1996 – Bioscience, biotechnology and biochemistry 60 (8) : 1222-1228, M.Kiyahara *& al.,* 2006 – J.Biochem. 140 (3) : 369-373).

In *Caulerpa lentillifera*, the water-soluble fraction is a mixture of 1,4 α and 1,3 β-D glucans and proteins (N.M. Schevehenko *& al.,* 2009 – Chemistry of Natural Products).

Detailed studies of the chemical composition of *Caulerpa lentillifera* collected either in North Borneo or Vietnam have been published.

These compositions range as follows (in % DW) :

total protein content from	10.41 - 12.49
ash	24.21 - 37.15
crude fiber	1.91 - 3.17
carbohydrate	38.66 - 59.27
lipid	0.86 - 1.11

Among minerals, sodium, potassium magnesium and calcium are present in abundance. The major oligoelements are iron and zinc. Copper, selenium and iodine are also quoted.
Taurobetaine (N,N,N-trimethyltaurine) has been isolated from *C. lentillifera*. This constitutes the first report on the occurrence of such product in marine green algae (T. Higa, 1982 – Bull. Coll. Sci. Univ. Ryukyus, 33: 75-79).

The contents of fatty acids are as follows:

Mono-unsaturated		36.83 % total fatty acid,
Polyunsaturated		16.76
with	ω 6 :	8.04
	ω–3:	7.55
	ratio ω6 / ω3	1.07

Some *Caulerpa* species have been found to contain terpenoid metabolites, many of which possess the novel bis-enol acetate functionality, unique to green algae of the related families Caulerpaceae and Udoteaceae.

A major sesquiterpenoid metabolite caulerpenyne is a unique acetylenic sesquiterpenoid isolated from different *Caulerpa* species.

Caulerpicin is also present in *Caulerpa* species .It is a minor metabolite, a mixture of N-acylsphingosines or ceramides.

The bright yellow orange pigment caulerpin is found too in different species, but has not been isolated in *Caulerpa lentillifera* (*cf*. in K.C. Guven *& al.*, Mar.Drugs, 2010 – 8 : 269-284).

According different published studies on *Caulerpa* species*,* the presence of caulerpenyne and caulerpicin has not been quoted in *Caulerpa lentillifera*.

➤ Bioactivities

It is important to recall that caulerpin and caulerpicin have been described as toxic constituents in some of *Caulerpa* species but evidences in several studies indicate that they have no acute toxicity (*cf.* T. Higa & M. Kuniyoshi, 2000- 19: 119-137).

Their effects have been studied on marine animals (*cf*. K.D.Meyer & V.J.Paul, 1992 – Mar.Ecol. Prog. Series 82: 249-257). The conclusion was that caulerpenyne and caulerpin extracted from three different *Caulerpa* species (*C. racemosa, cupressoides* & *sertularioides*) did not act to deter feeding by herbivorous fishes, even at the highest natural concentrations.

Caulerpin shows a structure related to auxin and promotes plant growth.

The cytotoxic effects of caulerpenyne from *Caulerpa taxifolia* were studies in different *in vitro* models: skin cells, primary cultures of melanocytes and keratinocytes, keratinocytes lines and bone marrow cells. The risks of cutaneous and /or food intoxications to humans may be considered minimal (D. Parent-Massin, 1996 – J. Toxicology & Environmental Health, Part A, 47 (1) : 47-59).

The MeOH extract of *Caulerpa racemosa* contains caulerpin that shows interesting anti-inflammatory activity, probably due to the presence of the indole group (E.Tenorio de Souza *& al*., 2009 – Mar.Drugs 7: 689-704).

The caulerpin extracted from the acetone extract of *Caulerpa racemosa* does not show any activity on the growth of melanoma cells, compared to other seaweeds (F. Dutra-Rocha *& al*., 2006 – Phytopherapy Research , 21 (2):170-175).

The polysaccharides extracted from *Caulerpa brachypus* shows strong anti-Herpes simplex virus type-1 (HSV-1) activities and seems to be promising candidate of antiviral agents acting on different stages in the virus replication cycle (J-B. Lee *& al.*, 2004 – Planta Med. 70 : 813-817).

To our knowledge, few studies are relative to the bioactivities of *Caulerpa lentillifera.* Any of them quotes the slightest toxicity of extracts.

Caulerpa lentillifera would be used as medicine in Philippines in order to treat high blood pressure and rheumatism. It also shows antifungal properties (G.C. Trono, Jr – 1998 – The seaweed resources of the Philippine. In: Seaweed resources of the world, pp 47-61, Yokosuka, Japan).

➤ Utilizations

Caulerpa lentillifera is a highly favoured species for human consumption, due to its soft and succulent texture, in some places in Asia especially in Japan, the Philippines, Malaysia and Indonesia.

Caulerpa lentillifera is eaten raw as a snack or used as a kind of vegetable to make salad (Figs. 3 & 4). It is said to taste refreshing.

Fig. 3

In Okinawa, the Japanese island where inhabitants are renowned for their longevity, five native seaweeds are eaten for better health, especially *Caulerpa lentillifera*.

There, sea grape is known as a delicacy called “umi-budo” (lit. sea grape). Sea grape is pickled in salt and then soaked in water for use. It is delicious eaten with vinegar soy sauce (Fig.3).The popping sensation when the little grains are chewed is very popular.

Fig. 4

For that reason, this Okinawa speciality is also called “green caviar”: caviar-like seaweed pods that pop in the mouth just like the famous fish eggs.

Caulerpa lentillifera is well adapted to pond culture with a water temperature range between 25°C and 30°C and placed away from any freshwater sources.

The pond cultivation is very successful on Mactan Island, Cebu in the Central Philippines. Cuttings are planted by hand and harvested about two months later. About 400 ha of ponds are under cultivation, producing 12-15 tonnes of fresh seaweed per hectare per year. Then, sea grape is sold on the markets in Cebu and Manila (Fig.5) or exported towards Japan.

Fig. 5

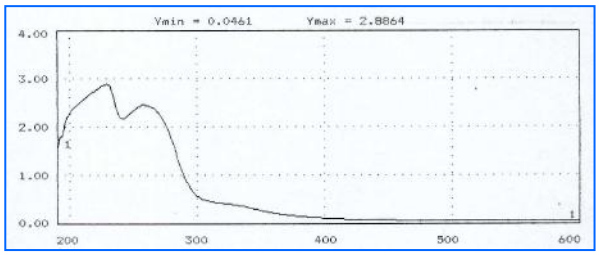
Culture experiments of sea grape occur in Vietnam and India too, this alga being considered in these countries as a suitable candidate for human food for the next 50 years.

THE ACTIVE INGREDIENT OKINACEA®

Specifications

on a control batch

- Appearance : liquid limpid
- color : amber
- odour : typical
- pH : 6.0 ± 1
- density : 1.020 ± 0.020
- dry residuals (%) : 3.9 ± 0.8
- solubility : insoluble in oils
- UV visible spectrum (5% in water):



- microbiology : bacteria : < 100 germs / ml.
  : yeasts, moulds : < 100 germs / ml.
  : pathogens : free.

Composition

Ingredients	Amounts %
water	65
Caulerpa lentillifera extract	31
Hydrolyzed Rice bran protein	4

Addition of preservative as required.

INCI names	water	CAS n° 7732-18-5	EINECS n° 231-791-2
	Caulerpa lentillifera extract		
	Hydrolyzed Rice Bran protein	CAS n° 94350-05-7	EINECS n° 305-224-5

As in all other body tissues, nutrition plays a vital role in skin maintenance and health. Nutrient deficiencies can cause poor wound healing and reduced tensile strength of the scar. It results in thin and fragile skin.

Mineral composition

on a control batch

Minerals act as structural components of skin cells. They assist in the formation of epidermal cells and cell membrane exchanges. They also serve as cofactors of metalloenzyme systems involved in numerous reactions.

➢ Macroelements (mg/kg)

Sodium	: 5122
Calcium	: 111
Magnesium	: 38
Potassium	: 30

➢ Trace elements (mg/kg)

Silicium	: 29
Zinc	: 1.3
Iron	: 1.1
Manganese	: 0.9
Copper	: < 0.5
Selenium	: < 0.5
Iode	: 0.52

➢ Heavy metals (mg/kg)

Cadmium	: < 0.05
Mercury	: < 0.05
Arsenic	: < 0.05
Lead	: < 0.05

➢ **Sodium** regulates cellular osmotic pressure.

➢ **Magnesium** is an important enzymatic cofactor. It is indispensable for activation of Zn-dependent metalloenzymes. It is involved in collagen synthesis.

➢ **Calcium** is greatly implicated in remineralization process of the skin.It plays an optimal role in cellular regulation and acts on all skin components.

➢ **Potassium** acts on cellular membrane permeability. It works closely with sodium to maintain the cells osmotic balance. It aids in energy metabolism.

➢ **Silicium** is an essential element in the maintenance of youth and vitality of the skin. It is known to be a bonding agent of the four macromolecules that make up the matrix of the skin. So it acts on the reorganisation of the dermis architecture and improves the elasticity of the skin. It fights free radicals.

➢ **Zinc** is also an essential element for healthy skin. It plays a primordial role in skin physiology. It produces a beneficial effect on the healing of wounds by modulating cutaneous inflammation and speeding up the re-epithelialization process. It stimulates the proliferation of keratinocytes and fibroblasts in wounds. It increases collagen synthesis. It is a vital component of many enzyme reactions.

➢ **Iron** is required for normal skin and during wound healing. It is absolutely necessary to oxygen transport towards tissues. By activation of enzymes (catalase and peroxydase), it is involved in cell metabolism. It acts in collagen synthesis as cofactor of prolyl- and lysyl-hydroxylases.

➢ **Manganese** contributes to the activity of Mn-SOD located into mitochondria of cutaneous cells. It is the cofactor of prolidase which performs in collagen degradation. It is involved in the synthesis of mucopolysaccharides and proteoglycans.

➢ OKINACEA® contains in significant quantities all minerals with mineralizing, balancing and ground correcting properties.

Amino acid composition

on a control batch

Amino-acids	g/100 g
aspartic acid	0.21
glutamic acid	0.41
glycine	0.10
cysteine	0.01
serine	0.12
threonine	0.07 mg / 100g
tyrosine	0.10
alanine	0.12
valine	0.10
leucine	0.14
isoleucine	0.07
proline	0.10
hydroxyproline	< 0.02
phenylalanine	0.10
methionine	0.03
lysine	0.08
arginine	0.18
histidine	0.05
tryptophane	< 0.02

➤ **Glutamic acid** and **aspartic acid** are the major amino acids present. They play important role in the Krebs cycle which brings indispensable energy to cells.

➤ **Arginine** has many functions. It is known to make nitric oxide which helps to relax the blood vessels. It also takes part in forming proteins and stimulates growth hormones.

➤ **Leucine** is an essential branched-chain amino acid that cannot be manufactured in the body. It is an extremely important amino acid and nutritional component because it controls our body's ability to process proteins, minerals and vitamins.

➤ **Isoleucine** is also an essential amino acid that helps in energy production as well as valine.

➤ **Alanine** plays a key role in glucose-alanine cycle between tissues and liver. It is involved in glycogenosynthesis.

➤ **Lysine** and **threonine** promote the formation of collagen.

➤ OKINACEA® contains all essential amino-acids (in red on the table).

➤ All amino-acids indispensable for improving skin integrity and vitality are present

➤ Thanks to its richness in minerals and amino acids, OKINACEA® facilitates cells diet and thus revitalizes their metabolism.

Remarks

➤ Presence of xylose and xylooligosaccharide

OKINACEA® contains a small quantity of xylose and xylooligosaccharide that can contribute to effectiveness of active. It is proved that xylose derivatives improve the status of aged skin by increasing GAGs synthesis (N. Pineau *et al.*, 2008- Eur J. Dermatol. 18 :36-40) and restoring the DEJ integrity (J. Sok *et al.*, 2008 – Eur. J. Dermatol., 18 : 297-302).

➤ Absence of caulerpin and caulerpenyne

OKINACEA® is performed from an aqueous extraction. So, it cannot contain caulerpin and caulerpenyne. Both compounds have been isolated from lipoid extracts of *Caulerpa* species and their eventual cytotoxicity studied *in vitro*.

The cytotoxic effects of OKINACEA® have been performed *in vitro* on normal human fibroblasts cultured in the presence of different concentrations of active (from 0.5% to 8%) and evaluated by using the XTT method (study at SEPhRA, France).

	Control	0.5%	1%	2%	4%	6%	8%
Absorbance at 450 nm	0.2309 ± 0.0081	0.2231 ± 0.0062	0.2285 ± 0.0113	0.2376 ± 0.0034	0.2133 ± 0.104	0.2381 ± 0.005	0.2381 ± 0.0049
% viability	100	97	99	103	92	103	106
p (Student test)		0.0906	0.3723	0.0999	0.0198	0.0947	0.0217

This study proves the non-cytotoxicity of OKINACEA®.

Storage

OKINACEA® should be stored in the original sealed containers in a clean and dry place, at a temperature between 15°C and 25°C. If stored under the advised conditions, OKINACEA® remains stable for at least 18 months.

Pack size: 2 Kg - 5 Kg - 10 Kg.

Safety

No animal experimentation

Standard safety testing has proved that OKINACEA® is safe for cosmetic use.

Patch assay on 10 healthy adult volunteers during 48h has shown that at 100% OKINACEA® can be considered as very lightly irritant regarding its primary skin tolerance.

Het Cam method has shown that at 10 % OKINACEA® can be considered as slightly irritant regarding its ocular primary tolerance.

The bacterial reverse mutation test (AMES test) has proved that OKINACEA® is considered to be non mutagenic / non pro-mutagenic.

The assessment of sensitizing potential on 105 volunteers has proved that OKINACEA® can be considered as hypoallergenic.

cf. annex pp. 27-30.

EFFECTIVENESS EVALUATION

OKINACEA®

Sea grape extract associated with Hydrolyzed Rice Proteins

Strengthening of the dermal-epidermal junction

Stimulation of collagen IV	Overexpression of collagen IV Immunohistochemical study on human skin biopsies
Stimulation of Laminin 5	Overexpression of Laminin -5 Immunohistochemical study on human skin biopsies

Renewal & enrichment of the dermal extracellular matrix

Stimulation of GAGs synthesis	Overexpression of GAGs Immunohistochemical study on human skin biopsies
Stimulation of collagen I synthesis	Overexpression of collagen I Immunohistochemical study on human skin biopsies
	Increase of the production of pro-collagen I ELISA testing on human fibroblasts

Anti-ageing effect

Reduction of skin roughness	Clinical study on crows' foot areas 25 volunteers
Improvement of skin appearance	Consumer test

Your defense against skin ageing by targeting both the DEJ & the dermis

Strengthening of the dermal-epidermal junction

The junction between the epidermis and the dermis is an important and complex structure called the dermal-epidermal junction (DEJ) or the epidermal basement membrane.

Ultrastructurally, the DEJ is composed of four component areas (R.A. Briggaman & C.E. Wheeler, 1975 – J. Invest. Dermatol. 65: 71-84): (1) the basal cell plasma membrane with hemidesmosomes that are specialized attachment devices
(2) an electron-lucent area : the lamina lucida, (3) the basal lamina and (4) sub basal lamina that include anchoring fibrils, dermal microfibril bundles and collagen fibers.

These structures derive their origin from the epidermis and dermis. The basal lamina is primarily of epidermal origin, the anchoring fibrils of dermal origin.

The DEJ serves various functions *e.g.* epidermal-dermal adherence, mechanical support for the epidermis. It also controls proliferation and differentiation of basal cells in the epidermis. It maintains the polarity of the epidermis (A. Satoshi, 2001 – J. SCJ 35:1-7). It assures the cohesion and exchanges between the two major skin compartments.

The basal lamina is rich in collagen IV and laminin, molecules that play a role in providing a structural network and bioadhesive properties for cell attachment.

The dermal-epidermal junction interlocks forming finger-like projections called rete-ridges. These ridges increase the surface area of the epidermis that is exposed to these blood vessels and the needed nutrients.

The ageing of the skin comes with significant physiological changes to the skin, especially at the DEJ with possible disruption and reduplication.

According a study of abdominal skin, the surface area of the DEJ decreases from 2.64 mm² in subjects aged 21 to 40 years and to 1.90 mm² in subjects aged 61 to 80 years (A.A. Katzberg, 1958 – Annat. Rec. 131: 717).

This loss of DEJ surface area may lead to the increased fragility of skin. This process also decreases the amount of nutrients available to the epidermis by decreasing the surface area in contact with the dermis, also interfering with the skin's normal repair process. It might lead to the formation of wrinkles and sagging.

Therefore, early epidermal basement membrane care appears to be an effective approach to prevent skin ageing, to keeping efficient nutrient exchanges and the rete-ridges as wavy as possible.

Overexpression of collagen IV

Collagen IV, also called Type IV collagen, is found exclusively in basement membranes where it constitutes a major constituent.

Collagen IV is involved especially in maintaining a functional interface between the epidermis and the dermis by providing a framework for other molecules. It is also important in the maintenance of mechanical stability.

In sun-exposed skin, it has been proved a significant diminution of collagen IV in the bottom of wrinkles compared to the flanks of wrinkles. This loss of collagen IV may affect the mechanical stability of the DEJ and contribute to wrinkle formation (J.L. Contet-Audonneau *& al.,* 1999- Br. J. Dermatol. 140 : 1038).

Therefore to maintain or restore an optimum physiological state of the dermal-epidermal junction, it is imperative to have a means of increasing the amount of collagen IV therein.

Method

All *ex vivo* studies included in this report have been performed at Laboratory BIO-EC (Longjumeau – France).

24 skin explants were obtained from an abdominal plastic surgery of a healthy Caucasian woman (53 years old). They are cultured in a specific survival explants medium : BEM (BIO-EC's Explants Medium).

2 mg of a formulation (Carbopol gel) containing 2% of DERMOCEA® were applied on the skin stripes at the following times: Day 0, Day 2, Day 5 and Day 7. The results are compared with untreated explants.

Explants were taken off at D0 and D9. Each explant was cut into two parts : one half was fixed in ordinary Bouin solution for previous morphological analysis while the other half was frozen at -75°C for immunostaining.

Optical observations have been performed by using a microscope Leica type DMLB equipped with a camera Olympus DP 72.

Specific immunomarking of collagen IV is performed on frozen cryostat cut tissues thanks to monoclonal antibodies anti-collagen FV (SBA) and revealed by FITC.

Cells nuclei are then stained with propodium iodide.

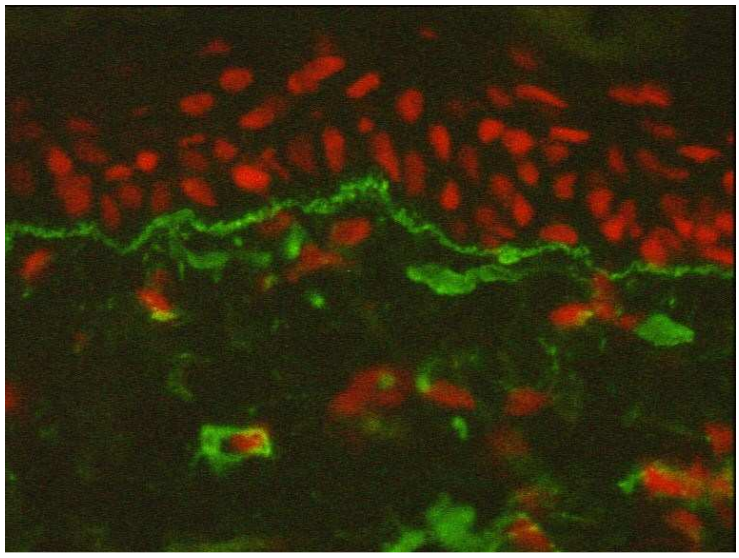
Collagen IV can then be observed in the dermal-epidermal junction area and in the upper papillary dermis due to fluorescent marking.

Results

Results are illustrated next page.

Control explants
without treatment

The labelling is seen variously regular along the DEJ. It is less visible in the papillary dermis but it is clearly distinct on the basal membranes around appendages.



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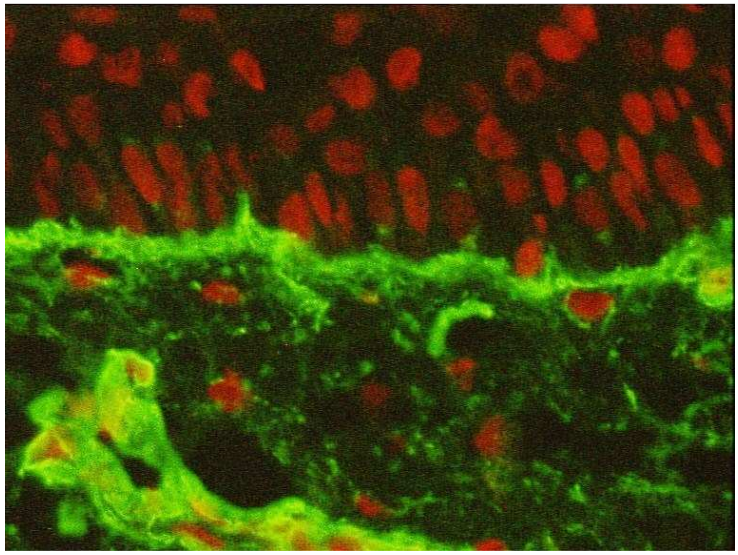
Treated explants
with 2% OKINACEA®

The marking is relatively strong, regular along the DEJ. It is moderated in the basal keratinocytes and strong on the basal membranes around appendages.



➤ OKINACEA® increases the expression of collagen IV and therefore helps to maintain an optimal physiological state at the interface between the dermis and the epidermis.

➤ OKINACEA® is capable of stimulating the collagen IV synthesis thus insuring the stability of the DEJ.

Overexpression of laminin-5

The major adhesive component of the dermal-epidermal junction is laminin-5: a complex glycoprotein. It is localized mainly to the lamina densa and partially to the lower lamina lucida. It is also associated predominantly with hemidesmosomes (T. Massunaga *& al*., 1996 – J. Histochemistry & Cytochemistry 44 (11) : 1223-1230).

Laminin-5 is an essential protein for binding epidermis to dermis. It mediates stable adhesion of basal keratinocytes through hemidesmosomes (L. Borradori. & A. Sonenberg, 1999- J. Invest. Dermatol. 112: 411-418).

Laminin-5 is known to promote the formation of the epidermal basement membrane (M. Tsunenaga *& al.,* 1998 – Matrix Biology 17: 603). It has been also demonstrated (D. Frank & W.G. Carter, 2004- J. Cell Science 117: 1351-1363) that the deposition of laminin-5 regulates keratinocyte polarization and persistent migration.

So, laminin-5 plays a key role together with the basement membrane in cell communication, adhesion and skin regeneration.

Laminin-5 synthesis has been proven to decrease in aged skin (F.Vasquez *& al*., 1996 – Maturitas 25 (3) 209-215 ; B. Le Varlet *& al.,* 1998 – J. Invest.. Dermatol. Symp. Proc . 3 (2) : 172-179). This causes a loss of contact between dermis and epidermis and results in the skin losing elasticity and becoming saggy.

Therefore, the dermal-epidermal junction is also enhanced by substances that stimulate laminin-5 synthesis.

Method

This *ex vivo* study has been performed at Laboratory BIO-EC (Longjumeau-France)

Specific immunostaining of laminin-5 is performed thanks to monoclonal antibody anti-laminin-5 (clone P3E4, Santa Cruz Biotech) and revealed by FITC (fluorescein isothiocyanate).

Laminin-5 can then be observed in the dermal-epidermal junction area due to fluorescent labelling.

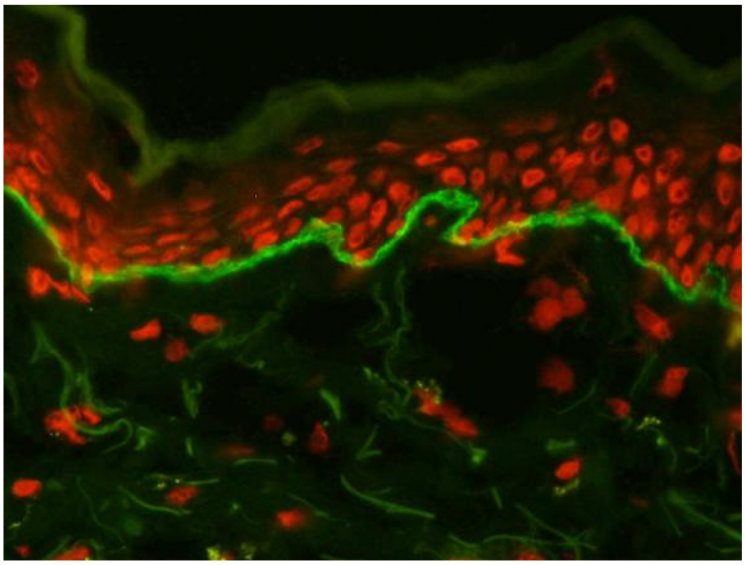
Results

None labelling has been observed when the saline buffer solution PBS can be used in substitute for the antibody.

➤ OKINACEA® is able to promote the synthesis of laminin-5 and therefore fortifies the cell adhesion and reinforces the epidermal basement membrane.

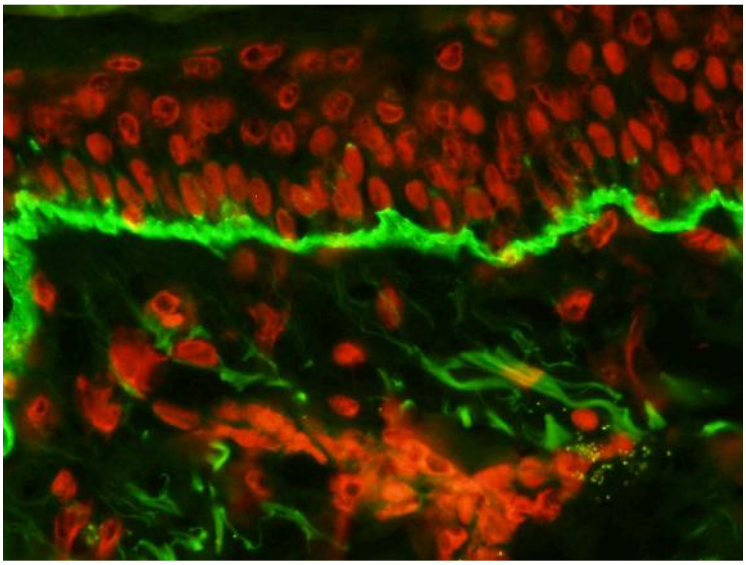
Control explants
without treatment

The labelling appears as a scalloped band relatively clear and relatively regular along the DEJ.



Treated explants
with 2% OKINACEA®

The marking is distinct and regular along the DEJ. It also appears in the basal keratinocytes



It proves that the application of a gel with 2% OKINACEA® induces a noticeable over-expression of the laminin-5 in the DEJ and in the basal keratinocytes

➤ OKINACEA® potentiates the production of laminin-5 and therefore contributes to maintain or repair normal epidermal basement membrane structure and its function.

➤ By influencing the DEJ, OKINACEA® supports the good skin cell communication between the epidermis and dermis and guarantees its functionality and integrity.

Renewal & enrichment of the dermal matrix

The dermis is a complex structure composed of two layers: the more superficial papillary dermis and the deeper reticular dermis.

The papillary dermis lies immediately beneath the epidermis and is about twice the thickness of the epidermis. It consists of loose connective tissue containing capillaries, elastic fibers, reticular fibers and some collagen fibrils organized into small bundles.

The reticular dermis consists of a thick layer of dense connective tissue containing large blood vessels, closely interlaced elastic fibers and coarse bundles of collagen fibers arranged in layers parallel to the surface. It is responsible for most of the mechanical properties of the skin.

The reticular dermis also contains fibroblasts, mast cells … and epidermal appendages.

Fibroblasts synthesize and secrete pro-collagens. These pro-collagens contain globular amino- and carboxyl-terminal domains which make these proteins soluble. After secretion of these pro-collagens, these domains are cleaved by specific proteolytic enzymes (R. Halila & L.Peltonen, 1986 - Biochem. J. 239: 47-52; Y. Hojima *&t al.* - 1989 J. Biol.Chem. 264: 11336-11345) resulting in formation of mature collagen.

This mature collagen spontaneously assembles into thin collagen fibrils. These tightly collagen fibers provide tensile strength and resistance to shear and other mechanical forces.

Surrounding the dermal components is the extracellular matrix, a gel-like ground substance composed of mucopolysaccharides (primarily hyaluronic acid), chondroïtin sulfates and glycoproteins.

During skin ageing, dermal changes are significant in the cellular and extracellular matrix components. The dermis thins. Senescent fibroblast changes include an increase in matrix metalloproteinase expression and a decrease in its inhibitors (K. Ghersetich *& al.*, 1994 – Int. J. Dermatol., 33: 119-122). The number of fibroblasts and their capacity decrease. New collagen production decreases and the dermal matrix declines. The dermis loses turgor due in part to a reduction of glycosaminoglycans synthesis. Elastic fibers also undergo important changes.

Therefore, to counteract these dermal ageing signs, it is important to re-activate skin own production of matrix macromolecules in order to improve cutaneous tonicity and to reduce wrinkles and skin sagging.

Stimulation of glycosaminoglycans (GAGs) synthesis

Proteoglycans (PGs) and glycosaminoglycans (GAGs) are minor components of normal human skin, making up only 0.1% to 0.3% of the total dry weight.

Proteoglycans are characterized by having a protein core covalently bound to carbohydrates called glycosaminoglycans (GAGs). They are involved in many of the cell processes occurring by means of

molecular interactions in the cell surface. They also act as tissue organizers. They facilitate cell growth and the maturation of specialized tissues. They play an essential role as biological filters and regulate the activity of growth factors (E. Ruoslahti, 1989 – J. Biol. Chem. 264: 13369-13372 ; R.V. Iozzo , 1998 – Ann. Rev. Biochem. 67: 609-652).

Due to their high content in acid groups, GAGs are negatively charged and tend to attract cations such as Na<+>. As they are osmotically active, they attract water and allow maintaining tissue hydration. Approximately 60% of the total weight of the dermis is water, retained largely as a result of the water-absorbing capacity of these molecules. Indeed, GAGs molecules can bind a volume of water in the dermis up to 1 000 times of the size of the molecule itself. Because of these water attracting properties, they are responsible for maintenance of skin hydration and turgor as well as the transport of nutritional material in the matrix.

Moreover, GAGs are also involved in a variety of functions *e.i.* in the orientation and structural arrangement of other matrix constituents and in cell communication events.

With age, significant reductions in the content of GAGs have been observed, that may lead to a reduction in water content and changes in skin thickness. The result of all this is that the aged skin appears dried and wrinkled.

So, GAGs are becoming original target in the treatment of skin ageing.

Overexpression of glycosaminoglycans

This *ex vivo* study has been performed at Laboratory BIO-EC (Longjumeau – France).

Method

Specific immunostaining of GAGs is performed by Mowry staining method (Alcian blue stain).

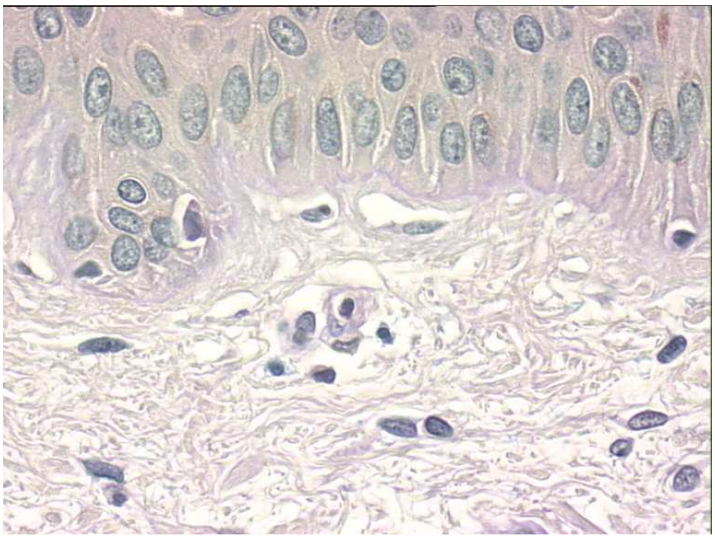
It is enables to visualize the GAGs present in the papillary dermis and along the dermal-epidermal junction due to pink-violet staining.

Results

Results are illustrated below.

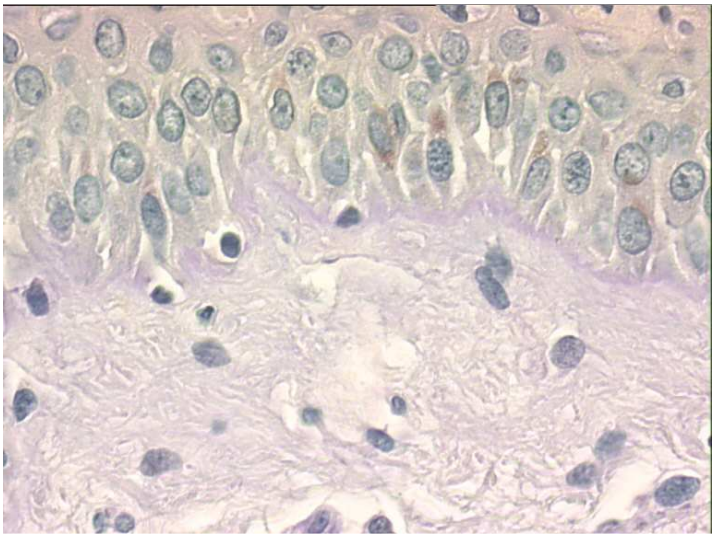
Control explants
without treatment

GAGs present along the DEJ form a pink-violet band, regular and thin in the papillary dermis.



Treated explants
with 2% OKINACEA®

The pink-violet staining is regular and variously important.



The application of 2% OKINACEA® formulation after 9 days treatment induces an overexpression of GAGs along the DEJ.

➤ OKINACEA® is able to stimulate the biosynthesis of glycosaminoglycans (GAGs) and thus helps to improve skin moisturizing and to replenishe the skin volume.

Stimulation of collagen synthesis

Collagen is a major structural protein in the skin.

Collagen has an amino acid composition which differentiates it from the other natural proteins. It contains around 25% glucose, 10% alanine, 12% proline and 10% hydroxyproline that is the amino acid that characterizes collagen. Alteration in this amino acid composition cause dysfunction and loss of the mechanical properties (E.M. Culav *et al.,* 1999 – Phys. Ther. 79: 308-319).

Collagen fibers consist of fibrils gathered together. The firmness of the dermis is principally due to the entanglement of these fibers packed together in all directions. The collagen fibers contribute to the elasticity and tonicity of the skin.

Mature collagen in skin undergoes continuous renewal throughout our lives to repair and replace damaged collagen or build cellular structures. The degradation and recycling of old or damaged collagen is a natural process used to build up protein fragments, needed to create new cellular structures such as in the healing process.

Intrinsic ageing has a dramatic effect on the network of collagen fibers. Likewise, the prolonged exposure to UV rays can damage the architecture of collagen.

Collagen increases and continues to build up until about the age of 35 when the skin reaches the peak of its mechanical strength. After that, it begins to deteriorate and cause the skin to become thinner and eventually sag. With age, the secretion of collagen decreases linearly with a 29% loss in secretion ability between 19 to 68 years (M. Dumas *et al*., 1994- Mech. Ageing Dev. 73 (3):179-187).

After damage, collagen biosynthesis remains at a level that is too low to allow mature skin to repair and to replace the collagen that has been lost. Therefore, the regulation of collagen synthesis can be potentially useful for cosmetics treatments.

So, the best ways to maintain a youthful, vital and healthy looking appearance are to promote and protect collagen synthesis.

Overexpression of collagen I

Method

This *ex vivo* study has been performed at Laboratory BIO-EC (Longjumeau – France).

Specific immunolabelling of Collagen I is performed thanks to monoclonal antibodies Anti-collagen I (MONOSAN ref. PS 047) applied for 1 hour at room temperature and revealed by FITC. Cells nuclei are stained with propodium iodine.

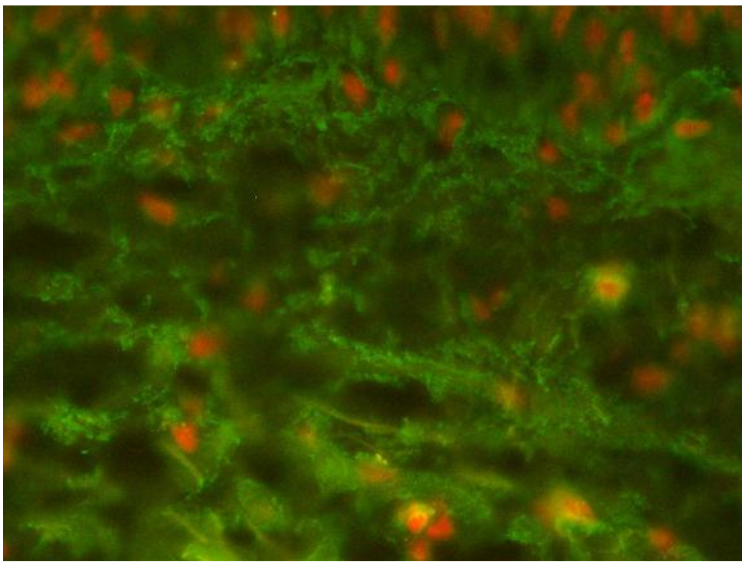
The analysis of epidermis thickness filled by basal K14 has been performed by using the software LEICA QWIN.

Results

None labelling has been observed when the saline buffer solution PBS can be used in substitute for the antibody.

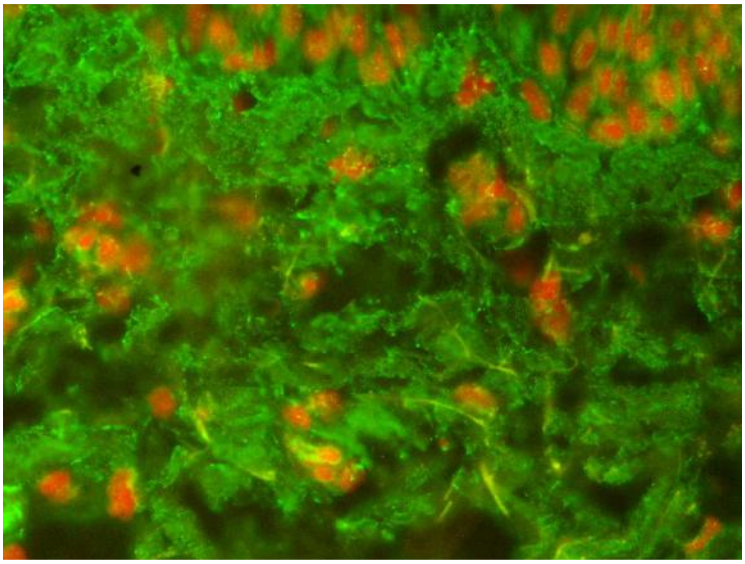
Control explants
without treatment

The marking is very weak and less dense in the papillary dermis.

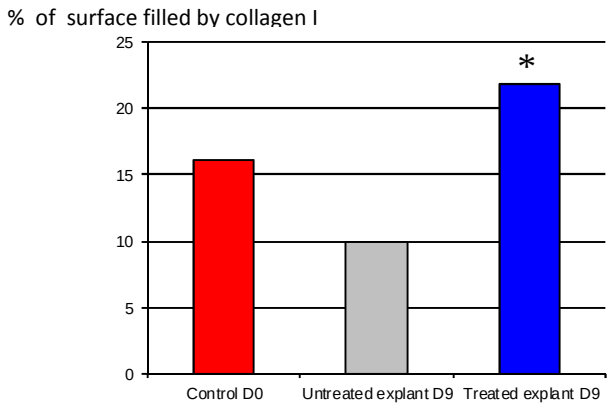


Treated explants
with 2% OKINACEA®

The marking is distinct with a network denser in the papillary dermis.



The percentage of the surface occupied by collagen I for the explants treated OKINACEA® after 9 days treatment reaches significantly 118% compared to untreated explants at Day 9.



* significant compared to untreated explants D9

➤ OKINACEA® is able to increase the synthesis of collagen and thus helps to restore youth appearance.

This result has been confirmed by *in vitro* study (next page).

Production of pro-collagen I

Collagen I is synthesized from a precursor molecule called “pro-collagen”.

The Type I pro-collagen is synthesized and secreted by fibroblasts which are specialized skin cells located in the dermis. It will form mature collagen which spontaneously assembles into thin collagen fibrils.

Because pro-collagen I is a precursor molecule of mature collagen, its level reflects the level of the content of synthesized collagen I (K. Haukipuro *& al*., 1991 – Ann. Surg. 213: 75-80).

Method

This *in vitro* study has been performed at the testing Company SEPhRA (Puteaux – France).

The synthesis of procollagen 1 has been quantified on the supernatant of the cultures of normal human fibroblasts after 48 H cultivation in the presence of 2% active by using the kit “Procollagen type 1C-peptide (PIP) EIA Kit - ref. MK101 –TANAKA.

The standard was vitamin C 50 µg/ml. –positive control). The total protein content was evaluated according the bicinchoninic acid (BCA) method.

Results

Results are obtained as a quantity (ng/ml) of pro-collagen I per quantity (ng/ml/ µg prot.) of total proteins.

	PIP (ng/ml)	ng/ml/µg prot.	% stimulation
Control	288.2 ± 65.0	71.8 ± 13.9	
OKINACEA® 0.5%	299.5 ± 31.7	108.2 ± 24.1 *p* = 0.007	51% **
OKINACEA® 1 %	400.8 ± 54.7	103.5 ± 179 *p* = 0.005	44% **
OKINACEA® 2 %	381.5 ± 38.9	107.9 ± 16.3 *p* = 0.002	50 % **
Vitamin C 50µg/ml	487.7 ± 50.1	155.2 ± 19.1	116 % **

** p < 0.01 Student test.

➤ At different concentrations tested, OKINACEA® is able to stimulate highly significant the synthesis of pro-collagen I by fibroblasts.

With 0.5% active the increase reaches more than 50%.

➤ By activating both GAGs and collagen synthesis, OKINACEA® appears as a true restructuring agent.

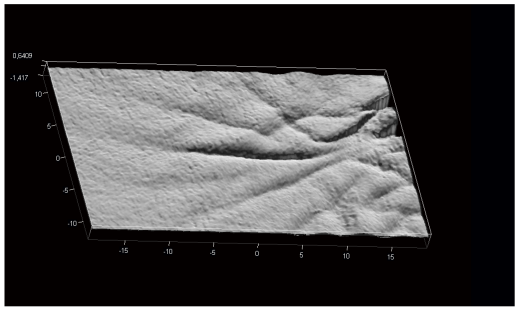
Anti-ageing effect

The first signs of ageing are seen in the skin of the face .The first areas affected are the eye corners where “crows’ feet” develop. They start at the eye external angle, as fine cracks, then spread out to form a network of wrinkles.

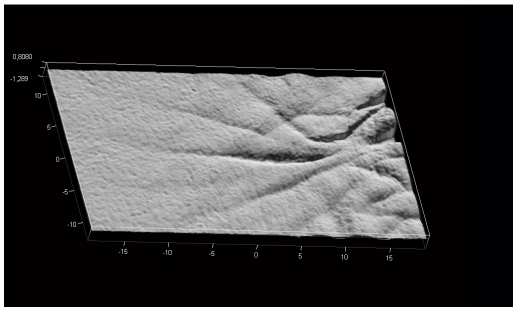
Reduction of skin roughness: Clinical study

To prove the efficacy of OKINACEA® , a study with 25 healthy women (age 40 to 59) has been performed at EUROFINS (France).
A formulation with OKINACEA® (5%) as a unique active ingredient have been applied twice daily for 28 days on crow ’s feet area.

The measurement of the skin roughness and 3D pictures has been performed by fringes projection using a GFM PRIMOS® device.



D0



D28

➤ OKINACEA® provides a significant reduction of 21% of the total roughness after only 28 days.

Improvement of skin appearance: Consumer test

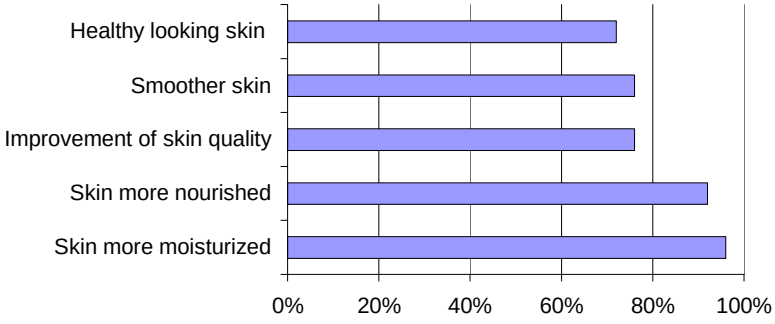
After 28 days treatment, positive opinion of

▶ 72% of volunteers for product satisfaction

▶ 84% of purchase intention.

In addition : good tolerance
non-toxicity.

Subjective consumer response



➤ Using OKINACEA® in a cosmetic formulation provides your skin with the tools it needs to maintain the surface of the skin more regular in appearance.

CONCLUSION & COSMETIC BENEFITS

OKINACEA® is an innovative association of Sea Grape and Hydrolyzed Rice Bran proteins.

Sea grape, also known as green caviar, is a green macroalga highly appreciated as delicacy in Okinawa, the Japanese island of centenarians and in Philippines, Malaysia and Indonesia.

Focused on skin anti-ageing, OKINACEA® targets both the dermal-epidermal junction and dermis.

The product efficacy has been demonstrated by several *ex vivo* and *in vitro* studies.

OKINACEA® offers the possibility of both

- ➤ to strengthen the DEJ functionality by stimulating both laminin-5 and collagen IV, therefore improving skin cohesion and increasing exchanges between the epidermis and dermis

- ➤ to enrich and renew the extracellular matrix by increasing the synthesis of GAGs and collagen

This finally contributes to improve the skin structure, to firm the skin and reduce the saggy skin and consequently to delay the major signs of skin ageing.

The complete anti-ageing effect of OKINACEA®, also demonstrated in clinical and consumer use tests, is an innovative answer to obtain visible benefits for combating skin ageing, reducing wrinkles and skin sagging, effects perceived by final consumers.

COSMETIC APPLICATIONS

Anti-ageing face care - Specific skin care for mature skin - Repairing and restructuring skin care – Firming body care.

Recommended use level: 1% - 5%.

Vérifié par ECOCERT MATIÈRE PREMIÈRE COSMÉTIQUES

Vérifié par ECOCERT MATIÈRE PREMIÈRE COSMOS APPROVED

Version OKINACEA EL

INCI names

water	CAS n° 7732-18-5	EINECS n° 231-791-2
algae extract	CAS n° 92128-82-0/ 68917-51-1	EINECS n° 295-780-4/-
Hydrolyzed Rice protein	CAS n° 156715-40-1	

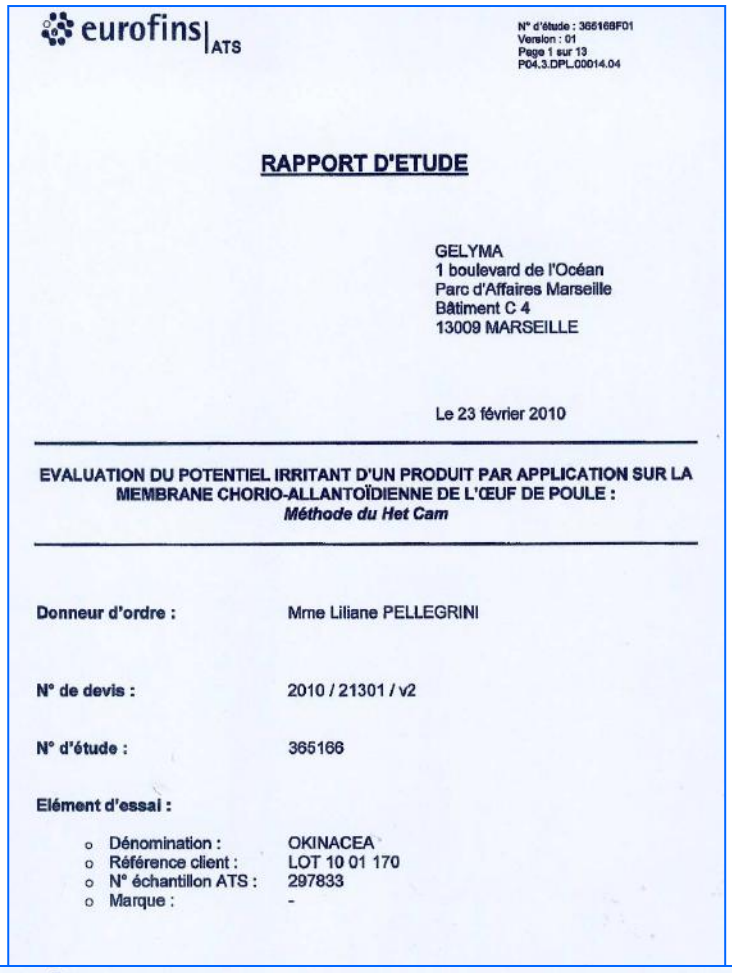
Preservatives by selection: microcare SB or phenoxyethanol.

CHINA LISTED 2014

algae extract

ANNEX

Evaluation of ocular irritation



eurofins | ATS

N° d'étude : 365166F01
Version : 01
Page 1 sur 13
P04.3.DPL.00014.04

RAPPORT D'ETUDE

GELYMA
1 boulevard de l'Océan
Parc d'Affaires Marseille
Bâtiment C 4
13009 MARSEILLE

Le 23 février 2010

EVALUATION DU POTENTIEL IRRITANT D'UN PRODUIT PAR APPLICATION SUR LA MEMBRANE CHORIO-ALLANTOÏDIENNE DE L'ŒUF DE POULE :
Méthode du Het Cam

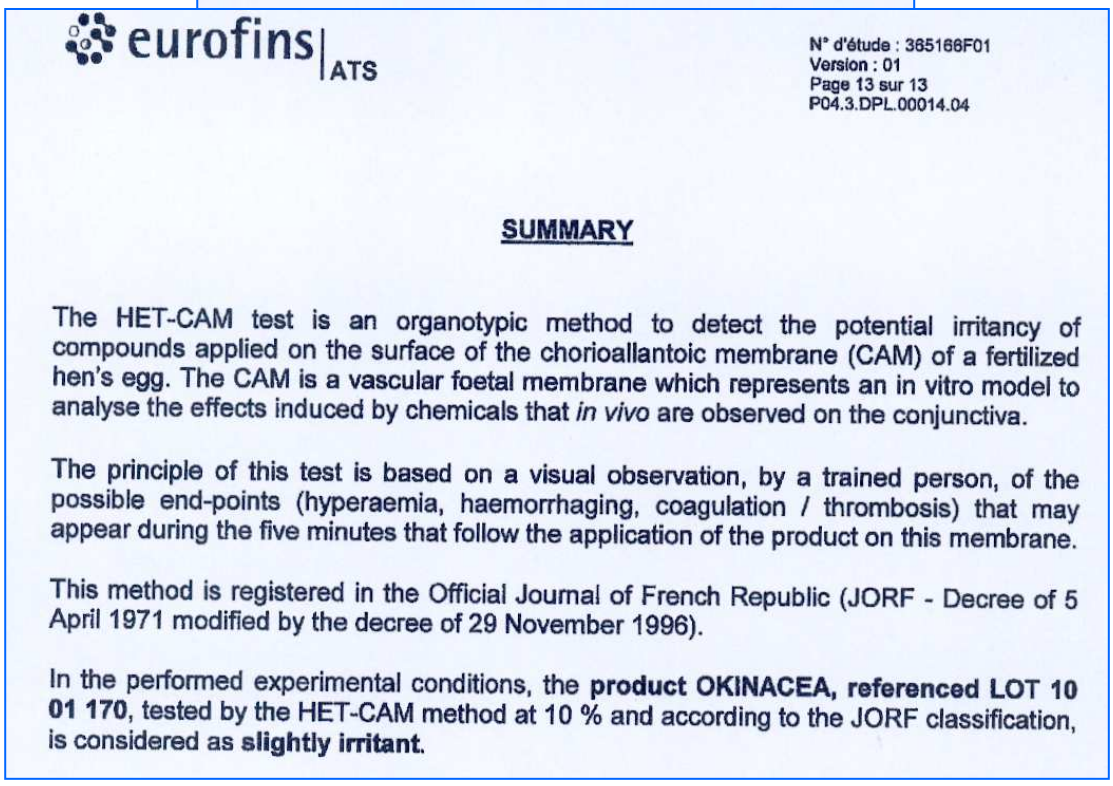
Donneur d'ordre : Mme Liliane PELLEGRINI

N° de devis : 2010 / 21301 / v2

N° d'étude : 365166

Elément d'essai :

- Dénomination : OKINACEA
- Référence client : LOT 10 01 170
- N° échantillon ATS : 297833
- Marque : -



eurofins | ATS

N° d'étude : 365166F01
Version : 01
Page 13 sur 13
P04.3.DPL.00014.04

SUMMARY

The HET-CAM test is an organotypic method to detect the potential irritancy of compounds applied on the surface of the chorioallantoic membrane (CAM) of a fertilized hen's egg. The CAM is a vascular foetal membrane which represents an in vitro model to analyse the effects induced by chemicals that *in vivo* are observed on the conjunctiva.

The principle of this test is based on a visual observation, by a trained person, of the possible end-points (hyperaemia, haemorrhaging, coagulation / thrombosis) that may appear during the five minutes that follow the application of the product on this membrane.

This method is registered in the Official Journal of French Republic (JORF - Decree of 5 April 1971 modified by the decree of 29 November 1996).

In the performed experimental conditions, the **product OKINACEA, referenced LOT 10 01 170**, tested by the HET-CAM method at 10 % and according to the JORF classification, is considered as **slightly irritant**.

Evaluation of cutaneous irritation

eurofins | ATS

N° Etude : 365167F01
Version : N° 1
Page: 14/16 + annexe 2
P05.0.DOC.00017.03

STUDY SUMMARY

EVALUATION OF SKIN TOLERANCE OF A COSMETIC PRODUCT AFTER A SINGLE APPLICATION UNDER OCCLUDED PATCH DURING 48H ON 12 VOLUNTEERS:
48 hours occluded patch tests

- **Product tested:** OKINACEA
- **Promotor:** LILIANE PELLEGRINI, GELYMA
- **Objective:** Assessment of the skin local tolerance of the studied product after an epicutaneous test performed in occluded conditions, during 48 hours.
- **Place of the study:** EUROFINS ATS
  Pôle d'activité Aix-Les-Milles - ACTIMART
  3 allée des Ingénieurs
  1140 rue André Ampère
  13851 AIX EN PROVENCE cedex 3
- **Investigator:** Doctor CREST MARY, DERMATOLOGIST
- **Dates of study:** from 02/02/2010 to 04/02/2010
- **Method:**

✓ ***Application:***
Area: on the back
Quantity of product: 0.02 ml
Frequency and duration: only one application during 48 hours
Conditions of application: product applied pure under occluded patch.

✓ ***Assessment method:***
A dermatologist performs the clinical observation, after the removal of the patches. The quantification of the skin irritation is given through a numeric scale (erythema, oedema, dryness/desquamation, vesicle). The average irritant score of the product to be tested is calculated from the average of the quotations obtained for each volunteer, allowing to rank the product from "non irritant to very irritant". The assessment is always made by comparison with the "negative" control.

- **Panel:** 12 healthy adult volunteers.
- **Result:** The average irritant score of the product is 0.08.
- **Conclusion:**

According to the experimental conditions of the study, **the OKINACEA product, referenced BATCH 10 01 170**, can be considered as **very slightly irritant regarding its primary skin tolerance.**

Eurofins ATS -Pôle d'activité d'Aix-en-Provence - Actimart - 1140, Rue Ampère - 13851 Aix-en-Provence Cedex 3 - France
TEL +33 (0)4.42.39.78.08 - FAX +33 (0)4.42.39.77.81
N° SIRET : 33761796300083 – Code APE :7120B

Evaluation of mutagenicity

vivotecnia FINAL REPORT B-01203

FINAL REPORT B-01203

BACTERIAL REVERSE MUTATION TEST

OKINACEA

Batch: 10 11 080

16 February 2011

SUMMARY

The bacterial reverse mutation test (Ames test) assesses the mutagenic or promutagenic potential of the test item OKINACEA in the several bacterial strains.

The test was performed in accordance with OECD Guideline 471 for the Testing of Chemicals (Bacterial Reverse Mutation Test. Adopted 21st July 1997) and the test Method B13/B14 of Commission Directive 2000/32/EC.

No cytotoxic activity was observed at a test item concentration of 50.0µL/mL.

Five test item doses ranged between 5.00 and 0.06 µL/plate were assayed.

None of the concentrations assayed for the test item showed an increase in the R value either with or without S9 metabolic activation regardless of the procedure.

No dose response for the test item OKINACEA was observed in any of the tested bacterial strains.

Based on the results obtained in this study it can be concluded that the test item does not induce point mutations or frame-shifts in the genome of the bacterial strains with or without metabolic activation regardless of the procedure.

Therefore, the test item OKINACEA is considered to be **NON MUTAGENIC / NON PRO-MUTAGENIC** under the experimental conditions assayed.

Test facility
VIVOTECNIA Research S.L.
Parque Científico de Madrid
C/Santiago Grisolía 2, (PTM)
28760 Tres Cantos, Madrid
Spain

Evaluation of sensitizing potential

ROBEN PRODUCTION GRUP SRL
CENTRUL DE CERCETARE A PLANTELOR
STRADA LUGOJ NR. 63 SECTOR 1, BUCURESTI, ROMANIA

EVALUATION DU POUVOIR SENSIBILISANT CHEZ LE VOLONTAIRE ADULTE SELON LA METHODE DE MARZULLI-MAIBACH

ASSESSMENT OF SENSITIZING POTENTIAL IN THE ADULT VOLUNTEER FOLLOWING THE METHOD OF MARZULLI-MAIBACH

Etude clinique sur 105 volontaires, tout type de peau
Clinical study on 105 volunteers, with all skin type

- Etude/ *Study*: 3.04
- Produit/ *Product*: RB10/0031

PRODUIT / *Product*	**: OKINACEA**
CODE PRODUIT / *Code product*	**: RB10/0031**
DILUTION / *Dilution*	**: PUR PURE**
INVESTIGATEUR / *Investigator*	**: DR. ANNE-MARIE MARINESCU**

CONCLUSIONS/ *CONCLUSIONS*

Dans les conditions d'une application répétée de la procédure de patch-test conduite auprès d'un panel de 105 volontaires présentant tout type de peau, le produit **OKINACEA, RB10/0031** a été «Testé dermatologiquement» et n'a pas présenté de risque d'irritation de la peau cliniquement significative ni montrer de réaction de type allergique au contact de la peau humaine.

Under the conditions of a repeated insult (occlusive) patch test procedure conducted in a panel of 105 subjects, with all skin type, the product **OKINACEA, RB10/0031** *was "Dermatologist-Tested" and did not induce clinically significant skin irritation nor show any evidence of induced allergic contact dermatitis in human subjects.*

Le produit **OKINACEA, RB10/0031** peut être considéré comme «hypoallergénique».

The product **OKINACEA, RB10/0031** *can be considered as "hypoallergenic"*

Parc d'Affaires Marseille Sud
1 Boulevard de l'Océan
13009 Marseille – France

www. gelyma.com

Contact

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e-mail gelyma @ wanadoo.fr