The first defensome enhancer tested on over 3 300 genes

Systemic protection and skin regeneration

OCEA HEALTH®

strengthens skin natural defensome with coordinated responses on

epidermal integrity

✦

cell resilience

✦

immune protection

✦

inflammation and wound healing

Gelyma

Patented

OCEA HEALTH®

Innovative approach to protect sensitive and reactive skin

An actual major question in skin dermatology is how skin cells function to maintain healthy metabolism and fight against ageing in the face of adverse exposome factors known to can change the visual appearance, physical properties and physiological functions of skin in undesirable ways.

The exposome includes the totality of specific and nonspecific external environmental exposures (external exposome *e.g*. environment, lifestyle, stress, nutrition, smoking and noise) to which an individual is subjected and their consequences at the organ and cell levels (internal exposome *e.g.* metabolism, psychological stress, lack of sleep). Therefore, the exposome is often divided into external and internal exposome [Vrijheid M. 2014 - Thorax 69: 876-878; Krutmann J. *et al.* 2017 - J. Derm. Sc. 85(3): 152-161].

Exposures vary on an hourly to yearly basis both in the external and internal environments.

The exposome is dynamic as opposed to the static genome. Genes and proteins participating in responses against such exposures may be considered as "defensome".

The term "defensome" has been used firstly in the plant infection literature (de Torres M. *et al*. 2003- Plant J. 33: 665–676) and the behavior of the « chemical defensome » studied by Goldstone J.V. *et al.* [2006- Dev. Biol. 300 (1): 366-384] in the marine animals.

The defensome concept appears to be almost universally applicable. It groups an integrated network of genes and pathways regulated by numerous transcription factors that allow an orchestrated defense against exogenous and/or endogenous stressors.

Skin is one of the major interfaces between the body and the external exposome factors.

Exposome factors affect the natural skin barrier and the skin immunity resulting in different skin changes *e.g*. homeostasis dysregulation, hyper keratinization and activation of the innate immunity thus inducing possible skin diseases *e.g*. atopic dermatitis and acne. These factors also potentiate skin ageing to trigger molecular processes inducing skin structural damage. Mechanical protection continually decreases and wound healing as well as immune response are delayed.

Therefore, it is important to maintain suitable skin functions against exposome factors.

GELYMA has created OCEA HEALTH® a smart patented marine active designed to maintain and restore healthy skin and subsequently limit the signs of damage from exposome factors.

Patents FR 2000229 and FR 2000230.

COMPOSITION

OCEA HEALTH® combines 1,3 propanediol (COSMOS grade) with a calibrated extract of the brown alga *Padina pavonica* collected in the Mediterranean Sea.

The algal extract is obtained from an aqueous based extraction under pressure according a green process with minimum consumption of energy in order to capture the richest content of molecules.

CONCEPT

OCEA HEALTH® is based on the « defensome concept » applied from exposome factors affecting the skin. It acts as a powerful defender able to modulate, in coordinated responses, a vast array of biological process to protect sensitive and reactive skins and repair damage.

MECANISMS OF ACTIONS

Efficacy has been demonstrated on NHEKs normal human keratinocytes after 24h treatment by a full genome transcriptome approach, without any preconceived view. Microarrays analyses have been performed by Affymetrix technique that allows identify multiple biological pathways modulated by OCEA HEALTH® and more interestingly under a coordinate fashion.

When human keratinocytes were grown in the presence of 3% active for 72h, the expression of 3363 genes was found modulated significantly (p-value < 0.05), that was highly unexpected and exceptional. The thematic analysis of these genes revealed the action of OCEA HEALTH® on biological processes distributed into 33 significant groups particularly relevant of skin biology. Only genes with fold changes (FC) ≥ 1.3 were selected.

Collaboration Strati CELL-Belgium.

Anti-microbial defense
T-Cell Immune response-
Toll-like receptor signal

Stress responses
Cellular stress response - Pollution stress - Antioxidant stress - Osmotic stress - Cellular senescence – Apoptosis

Epidermal homeostasis
Epidermal biology – Epidermal differentiation - Cornified envelope proteins - Desquamation

Cell-cell cohesion
Cell-cell functions - Differentiation markers - Cell mobility

Wound healing-Angiogenesis
Remodelling enzymes
Extracellular matrix components-

Inflammation response
Cytokines & chemokines
NF-Kp signalling

Transcriptome analysis has been completed by immunolabelling studies on normal human keratinocytes, *ex vivo* studies on human skin explants and clinical studies.

SKIN BENEFITS

Improvement of the epidermal integrity	⇨	Action on cornification and epidermal cohesion
Increase of the skin's capacity to handle major exposomes stressors	⇨	Response to HSP, oxidative, UV, pollution, osmotic stress
Support of the immune protection	⇨	Action on AMPs and TLRs
Modulation of inflammation	⇨	Inhibition of IL 1alpha
Improvement of wound healing	⇨	Regulation of chemokine balance
Amelioration of the comfort of sensitive skin		

OCEA HEALTH® offers high and innovative potential to protect the sensitive and reactive skins and repair deleterious damage caused by numerous exposome factors, therefore to prevent premature ageing.

PART I – The exposome affects the epidermal barrier

The skin barrier is essential for survival. More than 30% of the US population had been affected by skin disorders (Dehkharghari S. *et al.* 2003- J. Am. Acad. Dermatol. 48: 592-599). When this barrier is compromised, skin homeostasis is perturbated increasing the chance of infection and disarranged function.

OCEA HEALTH® reinforces epidermal integrity

Gene expression and immunolabelling studies

OCEA HEALTH® is able to up-regulate the expression of important genes playing major roles to maintain skin integrity and homeostasis in order (1) to improve cornification and (2) to increase epidermal cohesion and communication.

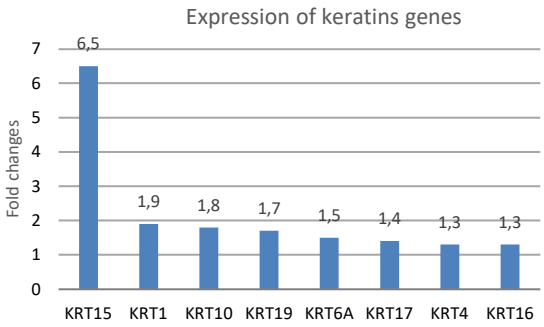
OCEA HEALTH® improves cornification

Cornification consists of different steps, specially the formation of the intracellular keratin cytoskeleton and the cornified layer preceding the maturation of the *stratum corneum.*

Impact on the formation of keratin cytoskeleton

The cytoskeletal architecture, made mainly of keratins, protects the epidermis against mechanical trauma.

By overexpressing major gene keratins, OCEA HEALTH® reinforces the resistance and the mechanical stability of the epidermis, providing efficient structural support as well as strong mechanical resilience.

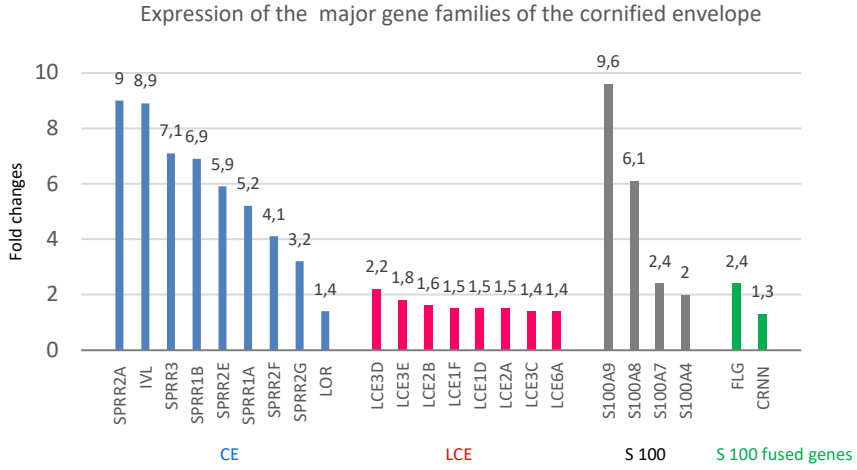


Impact on the formation of the cornified envelope

Cornification leads to the formation of the outermost skin barrier *i.e.* the cornified layer. This layer is constituted by different kinds of structural and regulatory proteins made from the gene cluster "epidermal differentiation complex" tightly coordinated by three major gene families (1) cornified envelope (CE) precursors including involucrin, loricrin and the complex cornifin/small proline-rich proteins (SPRRs) (2) late cornified envelope proteins (LCE) and (3) S 100A and S 100 fused genes.

OCEA HEALTH® modulates numerous genes belonging to the three major families participating to the formation of the cornified envelope.

The expression of a set of 33 genes was found modified significantly in the gene group "Epidermal differentiation".



Cornification also involves distinct enzymes such as transglutaminases and various transcriptions factors playing major roles in keratinocyte terminal differentiation.

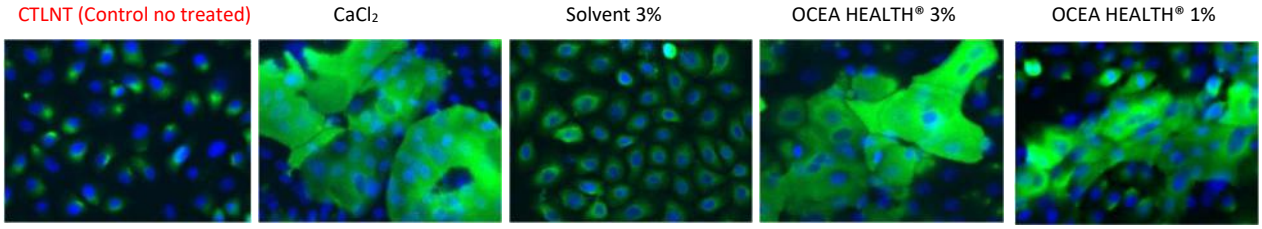
OCEA HEALTH® modulates transglutaminases and some transcription factors significantly:

TGM1	*transglutaminase 1*	FC	1.5	p-value	4.3E-003
TGM3	*transglutaminase 3*	FC	1.3	p-value	3.3E-02
CRCT1	*cysteine rich C-terminal 1*	FC	10.4	p-value	2.37E-08
GRHL3	*grainy head like transcription factor 3*	FC	9.7	p-value	1.3E-08
ZNF75	*zinc finger protein 750*	FC	9.4	p-value	3.2E-09.

Therefore, OCEA HEALTH® influences important genes participating to the formation of the cornified envelope. It supports tight integrity of the mature *stratum corneum* and maintains complete rebuilt of this envelope to avoid damage from environmental factors.

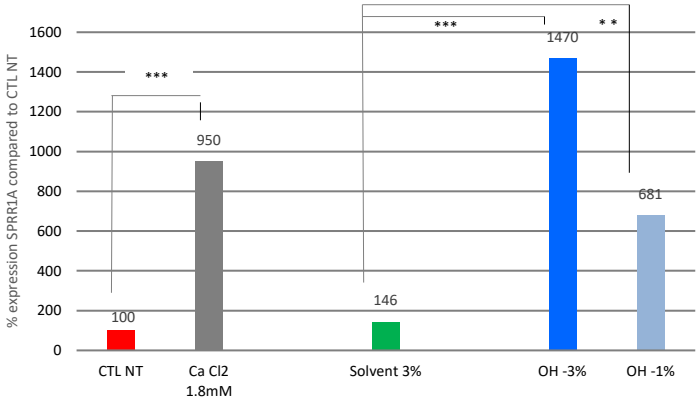
Immunofluorescence detection of SPRR1A on human keratinocytes

Besides their biomechanical functions, SPRRs take part in the adaptive tissue response through their anti-oxidant and detoxification properties.



SPRR1A was strongly stimulated when NHEKs were grown in the presence of 1.8 mM $CaCl_2$ as well as in the presence of the active (OH) under very highly significant manner for 3% and highly significant manner for 1%.

These results confirm the strong effect of OCEA HEALTH® on keratinocyte differentiation.



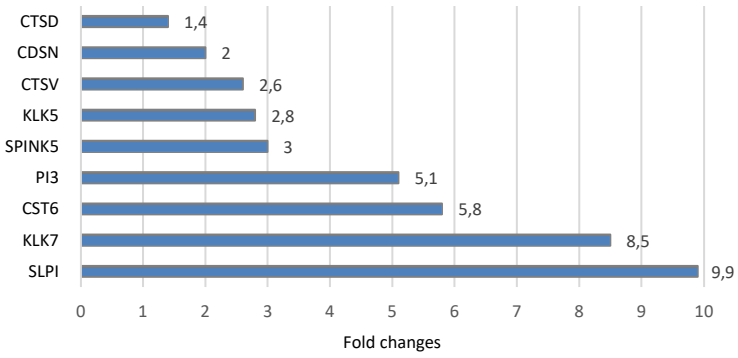
Impact on the maturation of the *stratum corneum* - Desquamation

Once, cornification process is completed, desquamation can starts mediated by a cascade of proteases to maintain skin homeostasis.

Several genes highly implicated in desquamation are up-regulated, specially kallikrein 7 (KLK7) and cystatin (CST6) known to control proteolysis.

OCEA HEALTH® regulates epidermal maturation and homeostasis under a controlled and balanced way.

Expression of genes invoved in desquamation

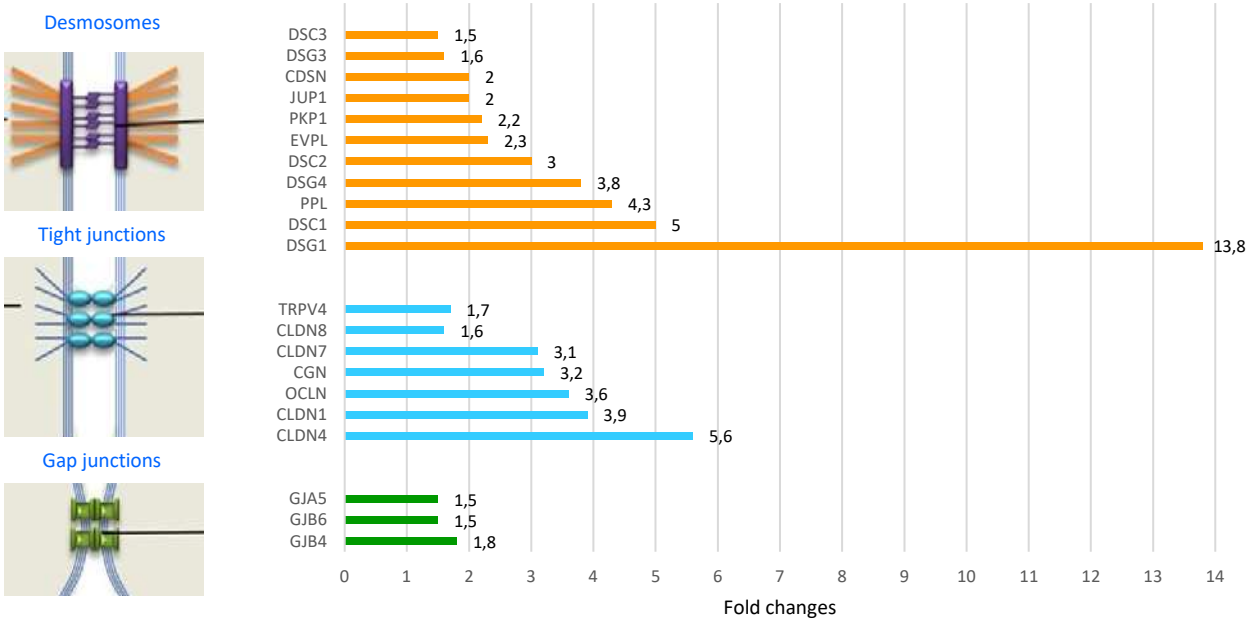


OCEA HEALTH® strengthens epidermal cohesion and communication

Impact on the components of cell junctions

Cell junctions link cells to each other in order to regulate homeostasis.

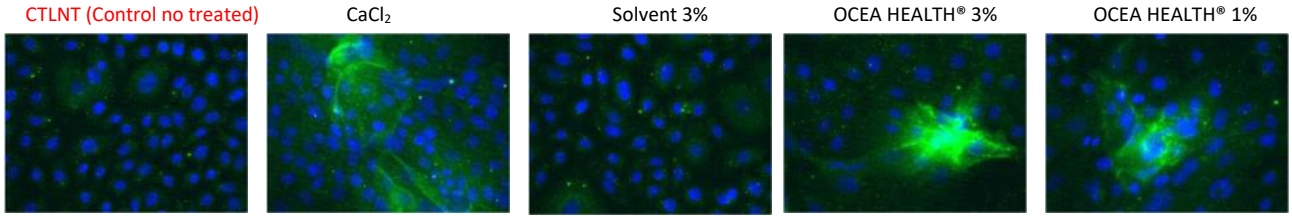
OCEA HEALTH® acts on the formation of the three main cell junctions.



OCEA HEALTH® stimulates the expression of 63 genes belonging to the group « cell-cell junctions ». It increases the formation of the components of desmosomes, tight junctions and gap junctions to reinforce epidermal cell adhesion and communication for better cell synchronization and metabolic coordination while to increase homeostasis maintenance.

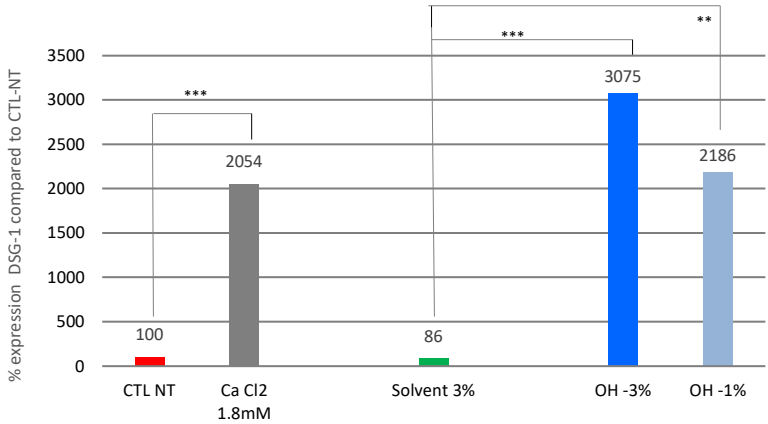
Immunofluorescence detection of DSG1 on human keratinocytes

Desmoglein 1 (DSG1) is a major cadherin playing a major role in cell-cell adhesion.



The expression of DSG1 is strongly over-expressed by OCEA HEALTH® (OH) with a superior effect than $CaCl_2$ alone.

OCEA HEALTH® improves keratinocyte adhesion and epidermal integrity.



PART II – The exposome induces cellular stress

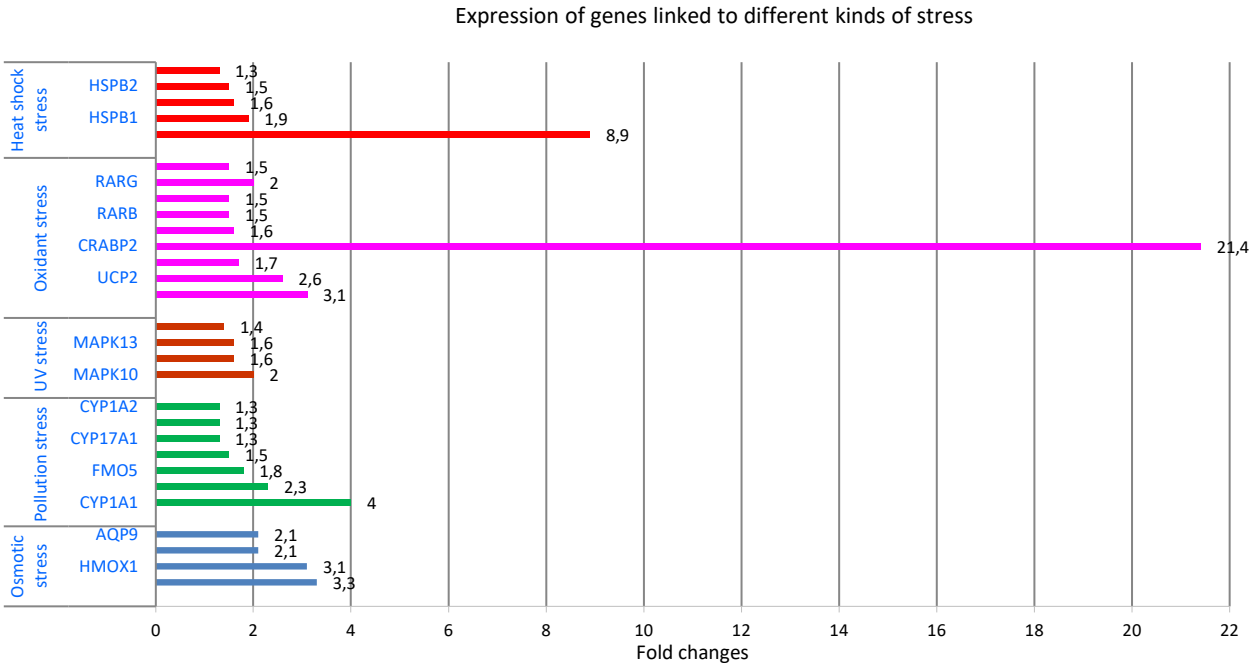
The skin is submitted to constant stressors exposures that can deteriorate homeostasis and induce structural damages. Skin cells respond to stress through the activation of numerous genes and pathways constituting the «chemical defensome».

Gene expression

OCEA HEALTH® increases the skin's capacity to handle exposome stressors

OCEA HEALTH® modulates numerous genes belonging to the major gene groups of stress *e.g.* heat shock stress, oxidant stress, UV stress, pollution stress and osmotic stress.

Note the important fold change (FC: 21.4) of CRABP 2 (*cellular retinoic acid binding protein 2*) known to play an important role in the transport of retinoid acid, an important molecule in skin biology.



OCEA HEALTH® activates appropriate defense responses to reinforce skin protection against major exposome factors.

OCEA HEALTH® reinforces immune protection

The skin is not only a physical barrier from external stressors, it also plays as an immune organ to protect it from invading microbial pathogens

OCEA HEALTH® is able to regulate numerous genes belonging to the immune defense gene group: 55 genes of anti-microbial defense, 45 genes of T-Cell immune response and 27 genes of Toll-like Receptor signal.

OCEA HEALTH® acts as an efficient protector of the immune skin barrier to boost the anti-microbial defense by over-expressing the gene expression of major AMPS

SLPI	*secretory leukocyte peptidase inhibitor*	FC	9.9	p-value	6.08-10
DEFB1	*defensin beta 1*	FC	5.5	p-value	6.54E-07

and Toll like receptors

TLR1	*toll like receptor 1*	FC	1.8	p-value	0.0045
TICAM1	*toll like receptor adaptor molecule 1*	FC	1.6	p-value	0.0079
TLR2	*toll like receptor 2*	FC	1.5	p-value	0.0032
THR7	*toll like receptor 7*	FC	1.3	p-value	0.2029

Therefore, OCEA HEALTH® offers an exceptional defensive mechanism against skin injury.

PART III – Exposome factors induce inflammation and slows down wound healing

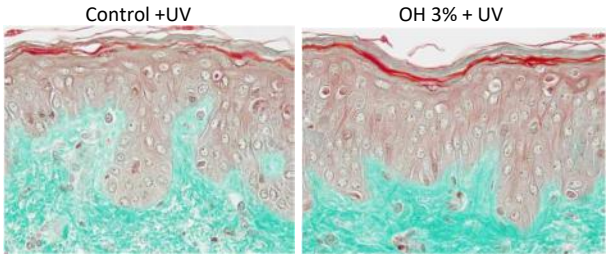
Environmental factors are tightly associated with increased inflammation that at the skin level is characterized by redness, heat, pain, swelling and loss of tissue function. The inflammatory response is coordinated by the activation of signaling pathways to regulate mediator levels in order to maintain tissue homeostasis.

OCEA HEALTH® reduces inflammation

Ex vivo study

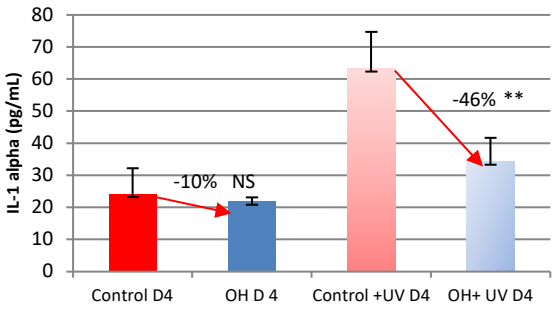
Inflammation can be induced by UV radiation that remains one of the biggest environmental stressors.

Ex vivo studies on human explants treated with 3% active in a basic gel then submitted to UV radiation (UVA 18 J/cm² + UVB 0.6 J/cm² = 4 DEM). Observations after 4 days cultivation (D4).



OCEA HEALTH® (OH) at 3% in a basic gel does not induce morphological changes. It preserves cell structure after inflammation caused by UV radiations.

Inhibition of the release of IL-1 α



OCEA HEALTH® (OH) at 3% in a basic gel decreases significantly by 46% the release of IL-1 α. Therefore, it decreases inflammation.

OCEA HEALTH® improves wound healing

Healing of a wound follows a predictable chain of events that occurs in a carefully regulated fashion, reproducible from wound to wound. It is critically affected by ageing. It includes four overlapping phases, namely hemostasis, inflammation, cellular proliferation and remodeling. Success in the latest phase is highly dependent on preceding phases.

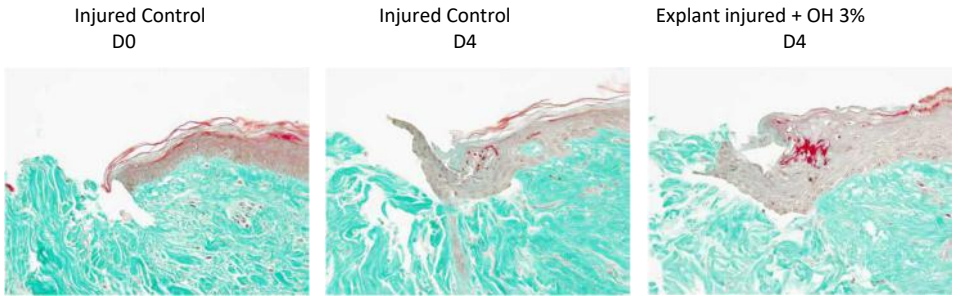
OCEA HEALTH® is able to act during all wound healing phases.

Histological observations

Ex vivo study

The normal healing response begins the moment the tissue is injured. It would appear important to check the behavior of OCEA HEALTH® in injured conditions.

Histological studies on human skin explants treated with 3% active in a basic gel then submitted to mechanical injured cultured in controlled conditions.
Observations at D0 and D4.



After 4 days cultivation, human skin explants treated with 3% OCEA HEALTH® (OH) presents an increase of the thickness at the growth bud that implicates the proliferation of neo-keratinocytes to start tissue repair.

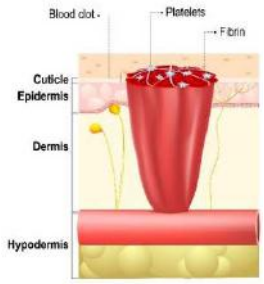
OCEA HEALTH® promotes the healing process as soon as 4 days after mechanical damage.

Regulation of the chemokine balance

Gene expression

Chemokines are involved in all stages of wound healing. Therefore, given the importance of chemokines to the wound healing process is very important to successful faster healing.

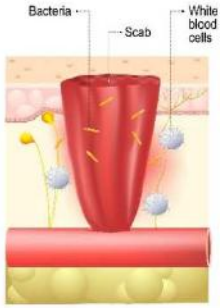
Hemostasis



Symbols	Names	Fold changes	p-values
CCL5	*C-C motif chemokine ligand 5*	3,9	3,22E-07
CXCL5	*C-X-C motif chemokine ligand 5*	1,5	0,0064
CCL2	*C-C motif chemokine ligand 2*	1,5	0,0238

OCEA HEALTH® over-expresses various chemokines that allow to recruit inflammatory cells and promote angiogenesis.

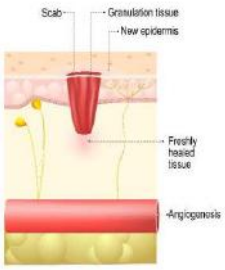
Inflammatory response



Symbols	Names	Fold changes	p-values
CXCL8	*C-X-C motif chemokine ligand 8*	7,1	4,03E-09
CXCL1	*C-X-C motif chemokine ligand 1*	2,01	2,46E-05
CXCL6	C-X-C motif chemokine ligand 6	2,01	5,46E-05
CXCR2	*C-X-C motif chemokine receptor 2*	1,8	0,00420
CCL2	*C-C motif chemokine ligand 2*	1,5	0,0238
CXCL3	*C-X-C motif chemokine ligand 3*	1,5	0,0097

These chemokines also allow cells recruitment that will remove dead cells, debris and promote the release of pro-angiogenic molecules to facilitate cell migration and differentiation.

Cellular proliferation phase



Symbols	Names	Fold changes	p-values
CXCL8	*C-X-C motif chemokine ligand 8*	7,1	4,03E-09
CXCL16	C-X-C motif chemokine ligand 16	3,0	1,15E-06
CXCL11	*C-X-C motif chemokine ligand 11*	2,3	0,00149
CXCL10	*C-X-C motif chemokine ligand 10*	1,9	0,00307
CXCR2	*C-X-C motif chemokine receptor 2*	1,8	0,00420

The modulation of these chemokines permits to control angiogenesis that is vital for the reconstruction of wound microvasculature to restore nutrient supply.

Remodeling phase

Symbols	Names	Fold changes	p-values
MMP9	*matrix metallopeptidase 9*	6,7	9,46E-09
MMP1	*matrix metallopeptidase 1*	2,3	4,05E-05
MMP2	*matrix metallopeptidase 2*	0,5	7,44E-06
TIMP2	*TIMP metallopeptidase inhibitor 2*	2,4	2,26E-05
PLAUR	*Plaminogen activator, urokinase receptor*	2,45	1.30E-05
CSF2	*colony stimulating factor 2*	2,1	3,39E-05

The action of these molecules allows to create new tissue.

Due to the efficient activity of chemokines playing major roles in all steps of wound healing, OCEA HEALTH® mediates a normal healing cascade to prevent impairments and reduce host-susceptibility to infection.

PART IV – Effect on the status of sensitive and reactive skins

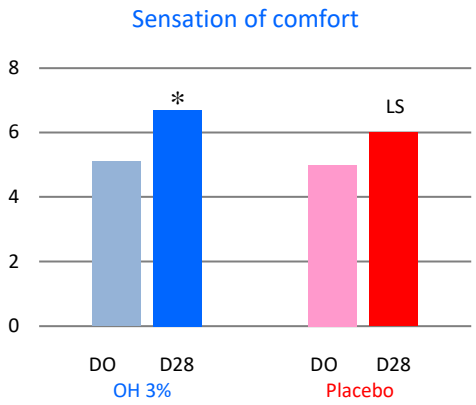
In vivo study

Formulations including 3% OCEA HEALTH® were applied on the half-face and half-neck chosen randomly, twice daily, during 28 consecutive days on a panel of 23 female Caucasian volunteers from 38 to 65 years old with sensitive skin and phototype (Fitzpatrick): from I to III.

Sensitive skin: 23 subjects (100%): Normal skin: 5 subjects (20.8%) - Dry skin: 8 subjects (37.5%)-Dry combination skin: 4 subjects (16.7%) - Oily combination skin: 4 subjects (16.7%) - Oily skin: 2 subjects (8.3%).

OCEA HEALTH® improves the sensation of comfort

Self-scoring performed on the skin status before then after applications using a scale scored in 10 points (from 0 not comfortable to 9 very comfortable) in order to determine its cosmetic efficacy.



OCEA HEALTH® at 3% offers a significant increase (*) of 30,51% (p = 0.002)

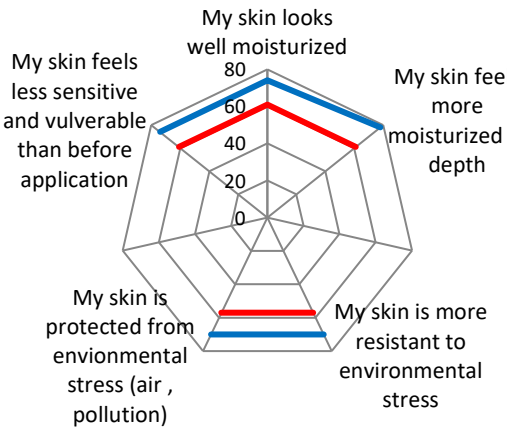
Placebo shows a limit significant increase (LS) of +18,10 % (p= 0.074)

at D28 compared to D0.

OCEA HEALTH® ameliorates skin qualities

Self-assessment of the cosmetic qualities (n=23)

OH 3% Placebo



Benefits against exposome factors

Improvement of the skin beauty

OCEA HEALTH® improves the skin status of sensitive and reactive skin better than placebo.

CONCLUSION & COSMETIC BENEFITS

Thanks to the conjugated properties of the brown seaweed *Padina pavonica* with propane 1,3 diol (COSMOS grade), OCEA HEALTH® offers important benefits to take care to sensitive and reactive skins against exposome factors.

Sensitive and reactive skins are influenced by numerous exposome factors leading to numerous disorders difficult to combat to balance biological homeostasis and defective protective and immunological functions.

OCEA HEATH® is able to bring systemic protection and skin regeneration in coordinated responses at different levels.

At the epidermal barrier level,

➔ OCEA HEATH® reinforces epidermal integrity.

- it improves cornification: action on the formation of the keratin cytoskeleton and of the cornified envelope, action on the maturation of *stratum corneum*.
- it strengthens epidermal cohesion and communication: action on the components of desmosomes, tight junctions and gap junctions.

At cellular stress level

➔ OCEA HEATH® increases the skin's capacity to handle environmental stressors.

- it modulates the expression of several kinds of stress: HSP stress, oxidative stress, UV stress, atmospheric pollution stress and osmotic stress, with appropriate defense responses.

➔ OCEA HEATH® reinforces the immune protection against external toxins and microbes.

- it regulates the genes of various antimicrobial peptides AMPs and Toll-like receptors TLRs.

At inflammation and wound healing level

➔ OCEA HEATH® decreases inflammation and inhibits the release of IL 1alpha.

➔ OCEA HEATH® improves wound healing: regulation of the chemokine balance essential in wound healing.

Clinical studies (n= 23) demonstrates that OCEA HEATH® at 3% ameliorates, *versus* placebo, the status of sensitive skin to increase comfort and skin qualities.

OCEA HEATH® brings a new dimension to manufacturer with a natural marine active presenting superior and proven efficacy to protect sensitive and vulnerable skin from numerous exposome factors and to prevent premature ageing.

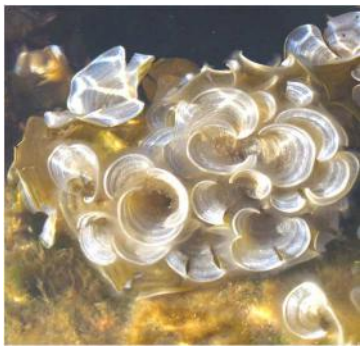
COSMETIC APPLICATIONS

- sensitive and reactive skin products
- age perfecting products
- cosmetic products with a repair concept against exposome care approach.

Recommended use levels : 3%

ADDITIONAL INFORMATIONS

Algal source



Morphology of *Padina pavonica*

Padina pavonica shows an erect thallus divided into whitish to brownwish color fronds that are fan shaped. It is attached to substratum by a rhizoidal holdfast. It can reach up to 15 cm length in summer time.

This alga is quite unique because it is one of the two calcified brown algae known today, the second one being *Newhousia imbricata* (Silberfeld T. *et al.* 2013 - J. Phycol. 49: 130-142; Johnson V.R. *et al*. 2012 - Global Change Biol. 18: 2792-2803).

Padina pavonica grows on hard substratum in the infralittoral level in sheltered or exposed sites. It is known to be very sensitive to physical disturbances of water.

This brown alga is widely distributed from warm-temperate to tropical shores in Atlantic Ocean, Adriatic Sea, Mediterranean Sea, South and Central America, Asia (India, Taiwan, Japan, Indonesia), Australia and New Zealand.

Padina pavonica offers numerous interesting bioactivities: antioxidant, antimicrobial and antifungal properties, anticancer and other medical properties. It may also serve as bioinsecticide pollution bio monitor or else for the production of biodiesel.

Specifications

Limpid liquid dark amber colored, with possible brown small precipitates with the time.

Transparency of this extract may evolve after production, without affecting the properties of the product. In case of turbidity, filter before using.

Additives by selection: microcare SB, phenoxyethanol, emollient PTG.

Packing size: 1kg - 5kg - 10 kg.

Regulatory data

INCI names	CAS n°	EINECS n°	China listed 2015		
Water	7732-18-5	231-791-2	06260	水	WATER
Padina pavonica thallus extract			02331	粉团扇藻（PADINA PAVONICA）叶状体提取物	PADINA PAVONICA THALLUS EXTRACT
Bio-propanediol	504-63-2	207-997-3	00006	1,3-丙二醇	PROPANEDIOL
Additives	as required				

Additions possible by selection: phenoxyethanol, microcare SB.

Paraben free.

The data presented in this document are offered solely for your consideration and investigation. No guaranty is expressed or implied. No responsibility or liability for any consequence arising from the use of these data can be accepted, including possible infringement of any patent.

GELYMA Parc d'Affaires Marseille Sud (C4) - 1 Boulevard de l'Océan - 13009 Marseille - France
Phone: +33 4 96 14 09 82 - e-mail: gelyma@wanadoo.fr – contact @gelyma.com