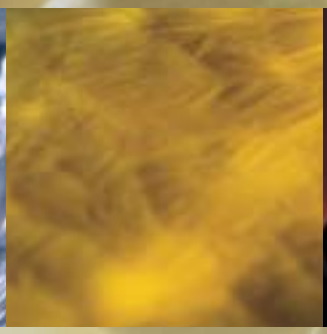
GATULINE® DERMA-SENSITIVE

A Touch of Serenity

GATTEFOSSÉ

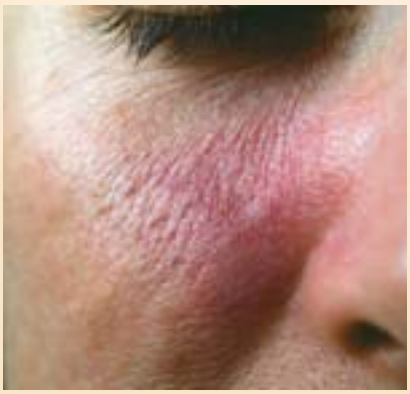
A sophisticated and technical range, GATULINE® once again takes its inspiration from gemmotherapy in order to bring peace and serenity to delicate skins.

Skin inflammation is the most commonly found disorder in dermatology and many products are now aimed at treating sensitive or reactive skin.

Skin tissue is practically constantly under aggression – thermal shock, UV rays, mechanical or chemical stress. This recurrence induces many pro-inflammatory signals in the cells.

Clinically, the deterioration of symptoms due to pain and/or burning is observed. These symptoms produce a feeling of discomfort, dry tightness, itching or swelling.

physical signs:
redness, swelling, oedema…



tactile signs:
dry tightness, burning

The soothing function has thus become inseparable from all claims put forward by cosmetic care today: anti-ageing, moisturising or even revitalising or firming.

GATULINE® DERMA-SENSITIVE is precisely positioned as the new ultra-specific active fighting the clinical symptoms of hypersensitive skin.

Tested on reconstructed skin then *in vivo* on a panel of people with sensitive skin, **GATULINE® DERMA-SENSITIVE** significantly reduces the production of pro-inflammatory factors as well as the expression of the resulting clinical symptoms.

physical signs:
clear and uniform skin tone

tactile signs:
suppleness and skin comfort

What is sensitive skin?

A sensitive skin is an inflammation-prone skin.

The inflammatory reaction is an adapted response, strictly controlled and protective, that contributes to the natural defence process and repair of damaged tissues. The skin, through its barrier role, plays a decisive part in this immunity system.

The inflammatory response consists of three sequences of complex and overlapping events:

- a vascular-sanguine initiation phase in the attacked zone within seconds following the aggression, broken down into four known clinical signs: tumor (œdema), calor (burning), rubor (redness), dolor (pain).
- an amplification phase during which the inflammatory action is developed with the migration of the different type of cells within the inflammatory pocket to remove any foreign elements or cellular debris.
- and finally, a resolution phase aiming to restore the integrity of the aggressed tissue. The inflammatory response then leads to its "*ad integrum*" restoration.

Under stress, the keratinocytes, prime target cells of several aggression factors, secrete a large number of pro-inflammatory mediators such as cytokines.

So-called primary cytokines, TNF-α and Interleukine 1 (IL-1), are non-specific to the inflammatory agent. These are capable of activating, directly or indirectly, all the cells of the epidermis (Langerhans cells, melanocytes, Merkel cells) and dermis (fibroblasts).

This is also the case of IL-8, a chemokine produced by practically all skin cells and induced under the action of various stimuli. IL-8 is specialized in polynuclear neutrophile and T lymphocyte recruitment.

Generally speaking, the inflammatory response is limited in time thanks to a system that controls the amplification phase (anti-inflammatory cytokines, anti-proteases, anti-free radicals).

However, if the inflammatory response is not adapted or poorly controlled, it can become aggressive.

Whereas cytokine production by skin cells is low and even non-existent in normal conditions, the keratinocyte production of cytokines increases considerably under stress conditions.

The merger of science and tradition

To develop this new **GATULINE®**, Gattefossé has aimed to determine precisely which vegetal fractions can activate the modulation mechanisms of the inflammatory processes.

Gattefossé has selected *Capparis spinosa*, a member of the Capparaceae family, traditionally picked and used in decoctions to treat bouts of arthritis.

This gemmotherapy extract uses caper bud, an embryonic tissue containing all the biological power of the future plant.

A preliminary study [1] shows that the caper bud offers significant anti-inflammatory activity in presence of stimulated inflammation. Tested against a positive reference produced by pharmacology, oxyphenbutazone, the extract induces a 50% reduction in inflammation, as opposed to 66% for the pharmaceutical reference.

The active fractions of caper were then identified [2]: these are mainly cappaprenols 12, 13 and 14 (number of isoprene chains), and Gattefossé has used a supercritical CO_2 extraction technique to optimise the production of these fractions.

Why supercritical CO_2?

Supercritical CO_2 extraction technology has unrivalled advantages in terms of quality and ecology. Supercritical CO_2 is used to totally or selectively extract compounds with low polarity and small molecular masses.

CO_2 has several advantages as a supercritical fluid:

- use at temperatures close to room temperature and at acceptable pressures (from 8 to 20 MPa)
- non-toxic and “natural”, it does not contribute to the greenhouse effect as the CO_2 is recycled, hence the term “green chemistry”, often used in relation to the supercritical extraction process
- non-combustible, chemically inert
- the extracts obtained have low colour and contain no metallic ions.

Cappaprenols, the chemical compounds partly responsible for the anti-inflammatory activity of capers, are lipophilic compounds. These compounds can be extracted by the supercritical CO_2 extraction technique.

Gattefossé has shown that the lipophilic compounds sought are optimally extracted, in qualitative and quantitative terms, by applying supercritical CO_2 extraction in the presence of a MOD (Octododecyl Myristate) co-solvent and using dried capers.

Efficacy on reconstructed epidermis

The influence of the formulated extract on the production of pro-inflammatory cytokines (IL-8 and TNF-α) by reconstructed epidermis subjected to topical inflammatory stress (PMA or Phorbol-12-Myristate-13-Acetate) has been evaluated.

The principle of the test lies in the dosing of pro-inflammatory cytokines released by reconstructed epidermis treated beforehand by the active formula or the excipient then subjected to stress by the topical application of PMA.

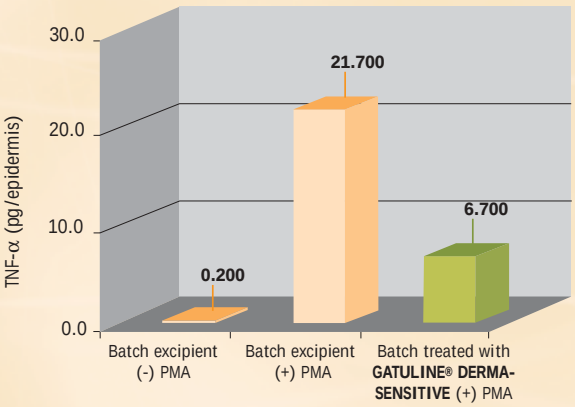
The test was carried out on epidermis separated into three batches:

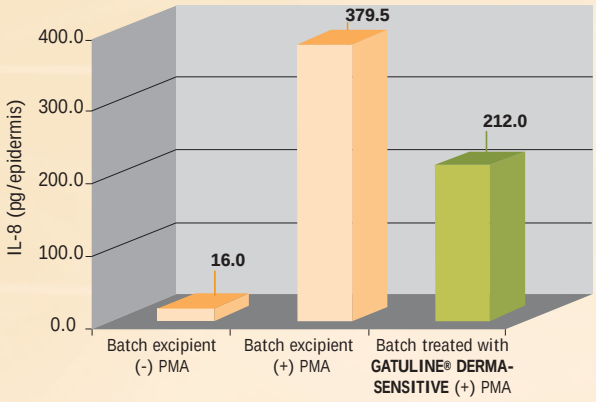
- an "Excipient + PMA" batch consisting of epidermis treated with the formulation excipient without **GATULINE® DERMA-SENSITIVE** and subjected to inflammatory stress
- an "Excipient – PMA" batch consisting of epidermis treated with the formulation excipient without **GATULINE® DERMA-SENSITIVE** but not subjected to inflammatory stress
- a "**GATULINE® DERMA-SENSITIVE** + PMA" treated batch composed of epidermis treated with the active formulation (2% **GATULINE® DERMA-SENSITIVE**) and subjected to inflammatory stress.

The test was conducted in triplicate.

Dosage of epidermal cytokines - Production of IL-8 and TNF-α

The topical application of PMA induces a very high release of IL-8 and TNF-α in the epidermis treated by the formulation excipient.





Treatment of the epidermis with the formula containing 2% GATULINE® DERMA-SENSITIVE helps significantly reduce (44% and 70% respectively) the production of IL-8 and TNF-α induced by PMA.

GATULINE® DERMA-SENSITIVE shows clear anti-inflammatory potential.
This potential is highlighted in the *in vivo* study presented on the following page.

In vivo efficacy

The aim was to assess, in standard use conditions, the efficacy and cosmetic acceptability of a soothing protective cream containing 2% **GATULINE® DERMA-SENSITIVE**.

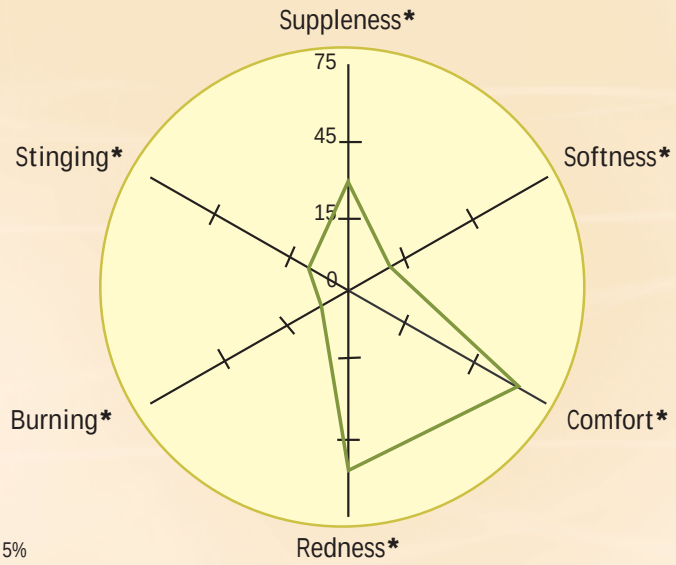
A panel of 20 members was used, all women with sensitive, reactive skin, subject to discomfort and diffuse redness. The product was applied to one side of the face, twice a day for 28 days. A cream containing a reference calming active, Bisabolol at 0.5%, was applied using the same protocol to the other side of the face.

Three series of results are presented:

- Clinical assessment at T0 then T4 weeks by the dermatologist, of efficacy criteria noted on an analogue scale of 10 points from 0 to 9 (the closer one gets to 9, the better the improvement)
- Self-assessment at T0 then T4 weeks, according to the same protocol
- Answers by the panel to an acceptability questionnaire on the two products at T4 weeks.

Clinical assessment

This graph presents the average improvement percentages obtained for the cream containing 2% **GATULINE® DERMA-SENSITIVE**, evaluated by the dermatologist at T0 and at the end of the study.



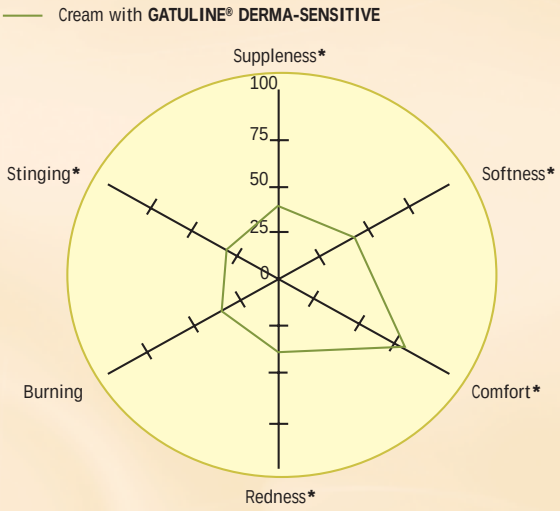
(*) significant improvement $p < 5\%$

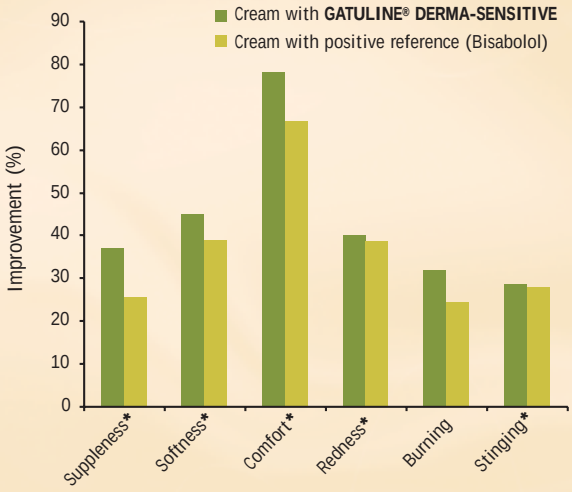
After 4 weeks of twice-daily application of the cream containing 2% GATULINE® DERMA-SENSITIVE, a significant improvement in all parameters was observed with, depending on the criteria, improvement of between 10 and 70%.

In particular, the assessment parameters of comfort and redness, very often associated with reactive skin, showed a very clear difference before and after treatment.

Self-assessment

This evaluation has the advantage of illustrating more specifically the benefits perceived by the user. The efficacy criteria and method of notation are the same as in the clinical assessment.





(*) significant improvement $p < 5\%$

After 4 weeks of twice-daily application of a cream formulated with 2% of **GATULINE® DERMA-SENSITIVE**, a significant improvement was noted in the perception of the parameters studied, with the exception of the burning sensation. These results confirm those of the clinical evaluation and clearly demonstrate the soothing effect of **GATULINE® DERMA-SENSITIVE**.

In parallel, comparison of the results obtained for the **GATULINE® DERMA-SENSITIVE** containing cream and the Bisabolol containing cream shows, for each of the criteria studied, a favourable tendency for the **GATULINE®** active.

Acceptability questionnaire

At the end of the study, the panelists used 4 levels of answers – "I agree", "I quite agree", "I tend not to agree" and "I don't agree at all" – to complete an acceptability questionnaire. On the basis of these results, a satisfaction percentage grouping together the "I agree" and "I quite agree" responses was calculated.

Question	Satisfaction percentage
The skin is more comfortable	60%
The skin is soothed and less reactive	75%
The skin is supple	80%
Redness is attenuated	65%
Sensations of discomfort and dry tightness are attenuated	90%

The cream containing **GATULINE® DERMA-SENSITIVE** obtained high satisfaction percentages for all criteria.

Conclusion

Combining bibliographic sources and experimental data, Gattefossé has selected, then developed, a new **GATULINE®** reference: **GATULINE® DERMA-SENSITIVE**, a touch of serenity.

Like all the other references in the range, this active ingredient has been tested *in vivo*, under normal conditions of use.
Its activity has been demonstrated using specific efficacy tests and strict statistical analysis.

In parallel, Gattefossé has identified the physiological and/or molecular mechanisms at the origin of this efficacy. In the case of **GATULINE® DERMA-SENSITIVE**, the cappaprenols, produced by capers using specific extraction, are clearly named as the ingredient responsible for its soothing properties.

Aimed at sensitive and reactive skin, 2% **GATULINE® DERMA-SENSITIVE** very significantly reduces the production of IL-8 and TNF-α cytokines. These cytokines are the major physiological mediators of inflammation, secreted by keratinocytes in situations of stress. Inhibiting their production or action helps limit the inflammatory response, particularly when this becomes uncontrollable.

User tests, as well as the clinical study, illustrate the expected benefits of regular use of a product containing **GATULINE® DERMA-SENSITIVE**.

The significant improvement encompasses sensations of stinging, burning, redness, suppleness and general comfort of the skin, parameters associated with reactive, irritated and environmentally stressed skin.

Applications

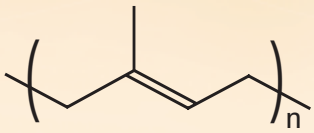
Active designed for sensitive and reactive skin products. Soothing activity. **GATULINE® DERMA-SENSITIVE** reduces cutaneous hypersensitivity. Ideal for preventive and protective suncare formulations.

For all types of emulsions, gel-creams, anhydrous bases or rinsable products. Recommended to be added at room temperature at the end of the manufacturing process. Suggested concentration of use: 2%.

Glossary

Cappaprenols: *long chain isoprenoid alcohols with numerous and long isoprene units.*

- Isoprene unit:



Chemokine: *type of cytokine with chemotactic ability.*

Chemotaxis, chemotactism: *cell movement due to a concentration gradient of a chemical substance.*

Cytokines: *group of regulating polypeptides and glycoproteins (non immunoglobulins) that act locally as cell communication messengers.*

Inflammation: *group of reactions triggered by aggression from a pathogenic element.*

Langherans cells: *epidermal dendritic cells with a sentinel role against exogenous antigens.*

Melanocytes: *epidermal cells whose function is to produce melanin pigments.*

Merkel cells: *epidermal neuro-endocrine cells involved in sensitivity.*

Supercritical state: *state of a fluid simultaneously exposed to a temperature and a pressure respectively superior to its critical temperature and its critical pressure.*

Bibliography

[1] Ageel A.M. *et al.* Anti-inflammatory activity of some Saudi Arabian medicinal plants. Agents and Actions. 17(3-4), 1985: 383-384.

[2] Al-Said M.S. *et al.* Isolation and identification of an anti-inflammatory principle from *Capparis spinosa*. Pharmazie. 43(9), 1988: 640-641.

SPECIFICATIONS

Organoleptic characteristics:

Aspect .....green limpid liquid
Odour .....characteristic
Colour (gardner scale) (LICO 50) .....5.0 to 8.0

Physico-chemical characteristics:

Specific gravity at 20°C (D20/4) .....0.85 to 0.86
Refractive index at 20°C .....1.452 to 1.456
Intrinsic viscosity at 20°C .....30 to 40 mPa.s
Acid value .....2.5 to 4.0 mgKOH/g
Solubility .....soluble in oils, insoluble in water
Water content.....< 0.30%
Linoleic acid (C18:2) .....> 0.05%
Pathogenic organisms .....none
Total aerobic germs.....< 100/g

Transport and storage conditions:

This product does not contain preservative. Prevent exposure to light. Store at room temperature.

Packing:

Industrial standard pack .....plastic packing of 800 g, 4 kg or 20 kg
Samples.....brown plastic bottle of 50 g

Regulatory:

INCI name .....Octyldodecyl Myristate (and) Capparis Spinosa Fruit Extract
CAS n° 22766-83-2/89958-23-6
EINECS n° 245-205-8/289-646-4
Japan .....Approved for cosmetic use

Toxicological profil:

Local toxicity on the skin.....not classified
Local toxicity on the eyes .....not classified
Phototoxicity.....without phototoxic effect
Immuno-toxicity .....without allergic effect
Photosensitization.....without photoallergic effect
Systemic toxicity.....not classified
Mutagenic effect (Ames test).....without mutagenic effect

FORMULAS

SOOTHING STICK — **JB 1879/C**

	INCI name	Trade name	%
I	ISOSTEARYL ISOSTEARATE (and) OZOKERITE (and) CASTOR (*Ricinus Communis*) OIL (and) HYDROGENATED PALM KERNEL GLYCERIDES (and) PROPYLENE GLYCOL DIPELARGONATE (and) POLYGLYCERYL-2 SESQUIISOSTEARATE (and) POLYGLYCERYL-2 SESQUISTEARATE (and) PEG-8 BEESWAX (and) PHENYL TRIMETHICONE (and) PROPYLENE GLYCOL ISOSTEARATE (and) CETYL LACTATE (and) HYDROGENATED PALM GLYCERIDES	LIPSTICK BASE PL 1916	96.20
	MINERAL OIL (and) VEGETABLE OIL (and) ALOE EXTRACT	VEGETOL® ALOE GR335 OILY	1.00
II	OCTYLDODECYL MYRISTATE (and) CAPPARIS SPINOSA FRUIT EXTRACT	GATULINE® DERMA-SENSITIVE	1.00
	MICA (and) TITATIUM DIOXIDE		1.50
	PERFUME		0.30
			100.00

Melt phase I at about 80°C. Stir and let cool down. At about 70°C, add the ingredients of phase II. Stir and pour into molds.

PROTECTIVE SOOTHING CREAM — **ALE 1920/B**

	INCI name	Trade name	%
I	CETYL ALCOHOL (and) GLYCERYL STEARATE (and) PEG-75 STEARATE (and) CETETH-20 (and) STEARATEH-20	EMULIUM™ DELTA	6.00
	OCTYLDODECYL MYRISTATE	MOD	5.00
	CYCLOMETHICONE		4.00
	PRESERVATIVE		0.70
II	DEMINERALIZED WATER		60.00
	CARBOMER		0.15
	XANTHAN GUM (SOL. 2%)		15.00
	GLYCERIN		3.00
III	AMINOMETHYL PROPANOL (SOL. 50%)		0.15
IV	ALUMINIUM STARCH OCTENYL SUCCINATE		4.00
V	OCTYLDODECYL MYRISTATE (and) CAPPARIS SPINOSA FRUIT EXTRACT	GATULINE® DERMA-SENSITIVE	2.00
			100.00

Sprinkle carbomer over water, leave to stand. Heat I and II to 75°C. While mixing, pour II into I. Neutralize with III. Cool while mixing. At 45°C, add IV. At 35°C, add V. Complete cooling under stirring.

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Worldwide Position

GATTEFOSSÉ is an independent, multinational company headquartered in France which creates, manufactures and distributes specialty products used as ingredients by the cosmetic and pharmaceutical industries.

Present in almost 50 countries worldwide, GATTEFOSSÉ enjoys a strong know-how and position in lipochemistry, biology and extraction from natural sources.

GATTEFOSSÉ offers the cosmetic industry a variety of high performance products classified as:

- Bases & Additives: emulsifiers, coemulsifiers, emollients, dispersers, solubilizers, thickeners…
- Traditional Plant Extracts
- Substantiated Active Ingredients from vegetable and marine origins.

GATTEFOSSÉ GROUP