DEFENSIL®-PLUS

First Aid for Inflamed Skin

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Content

I feel comfortable
in my own skin

There is a broad spectrum of terms associated with sensitive skin: sensitive, irritated, stressed, intolerant, irritable, reactive or hyper-reactive. In most cases it is red, itchy, painful, burning, swollen or feels hot, meaning it is, or was, exposed to inflammatory processes. There are different factors which cause inflammation of the skin. Usually they include physical stimuli (UV exposure, climate, shaving), chemicals (detergents, cosmetics), psychological stress and hormonal factors.

Studies from the major cosmetics markets of the United States, Germany and France show a high prevalence of symptoms for sensitive skin; approximately 60% of women and 40% of men regard their skin as sensitive. Depending on the severity, sensitive skin can have a strong influence on the quality of life of an individual. Those suffering from atopic dermatitis are probably affected the most, with 5%–20% of children and 1%–3% of adults suffering from the condition in developed countries.

In a French study, more people indicated having sensitive or very sensitive skin in the summer rather than in winter. They named climatic factors such as the sun and temperature changes due to air conditioners as a reason. Similarly, sensitive skin is found more frequently in paler skin tones [1].

Inflammatory processes in the skin occur more frequently in older people and, according to recent findings, they are a cause of skin ageing. The buzzwords “inflammation ageing” or inflamm-ageing are becoming more common.

The cosmetic market for sensitive skin prone to inflammation is multifaceted and affects all segments: Products for face and body, from baby care to anti-ageing cosmetics, from scalp to foot care. With the right ingredients, the inflammatory symptoms can be markedly diminished. This leads to a new sense of well-being and a significant improvement in the quality of life of the people affected.

Inflammation –
protective reaction of the body

An inflammation is a characteristic response of the skin tissue to an external, potentially harmful irritation. Its job is to eliminate this irritant to prevent its spread and to potentially repair any resultant damage (Figure 1). Inflammation comes from the Latin word inflammatio. There is a specific nomenclature for inflammations which are restricted to specific regions of the body: They are named after the combination of the Greek term for the affected organ and the Greek ending -itis: for example, dermatitis (skin inflammation) or arthritis (joint inflammation). Inflammations can be either acute or chronic. The acute inflammations have a dramatic start, reach their climax in a short amount of time and the reaction usually ends within minutes or a few days maximum. If the body is unable to rapidly neutralise the irritating agent, the acute form can develop into an insidious, chronic condition.

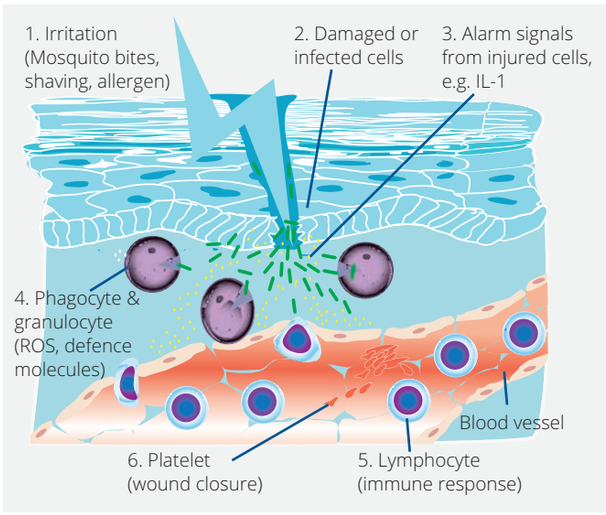


Figure 1: The inflammatory reaction in the skin. If the cells are damaged by trauma or foreign substances penetrate into the tissue, the cells of the skin react with the release of alarm signals. They thereby initiate an inflammatory response, which aims to protect the body from invaders and to repair the damage.

The acute
inflammatory response

The trigger of an inflammatory response is always an irritation of the tissue which can be caused by the following stimuli:

- Mechanical stimuli (foreign body, pressure, injury)
- Physical stimuli (ionising radiation, UV light, heat, cold),
- Chemical stimuli (alkalis, acids, heavy metals, bacterial toxins, allergens)
- Biological stimuli (bacteria, viruses, fungi, worms, insects)
- Other stimuli, including abnormal metabolism, abnormal enzymes, malignant tumour

If the stimulus exceeds a certain threshold, the body reacts with an inflammatory response. The lipids of the cell membrane usually are at the very beginning of the inflammatory cascade. Due to the irritation of the tissue, arachidonic acid is released from them (Figure 2a). Arachidonic acid is the basic building block for the formation of most of the alarm signals or inflammatory mediators (eicosanoids: leukotrienes and prostaglandins) that now follow. These and other mediators initiate and drive the next steps of the inflammatory response (Figure 2b): phagocytes (such as monocytes and Neutrophils) migrate through the vessel walls into the tissue to eliminate the inflammatory stimulus and the damaged cells. Other cells such as mast cells or basophils release substances (such as histamines or cytokines) that act as mediators of inflammation, specifically in terms of recruitment (= attract) of other blood cells such as lymphocytes and monocytes. Lymphocytes are the most important agents of the specific immune system; they are also responsible for the formation of specific antibodies against the inflammatory stimulus.

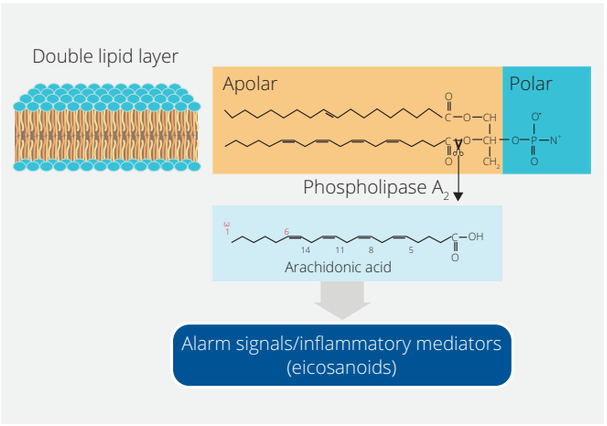


Figure 2a: The release of arachidonic acid is one of the first steps in the inflammatory response. Arachidonic acid is released by the enzyme phospholipase A_2 from the cell membrane lipids. An example of a phosphatidyl-choline with arachidonic acid and of the unsaturated oleic acid is shown. Arachidonic acid is the starting substance for a variety of inflammatory mediators. The enzyme phospholipase A_2 is also present in some insect poisons, which explains the severe skin reaction after a wasp sting, for example.

All of these processes combined together lead to the expression of the known signs of inflammation: the so-called cardinal signs of acute inflammation:

- Rubor/erythema. Inflammatory substances ensure that the vessels dilate, sending more blood to the affected area. The skin subsequently turns red due to the increased blood supply.
- Calor/warmth. The metabolism is stimulated by inflammatory substances. The tissue temperature increases along with the blood flow.
- Tumor/swelling. Inflammatory substances make the vessels located in the tissue more permeable. Escaping immune cells and blood flow swell the tissue.
- Dolor/pain. Immune cells and fluid in the tissues increase the pressure in the tissue. Combined with the formation of pain-triggering inflammation products, it explains the pain associated with inflammation.
- Functio laesa/dysfunction.

Inflammation is thought to protect the body from potentially harmful substances. We pay a high price for this protection because it creates substantial collateral damage. The skin and tissue are disturbed and damaged. Sensations such as burning, itching, tightening, etc. are the result.

Examples from the "cosmetic" practice are: mosquito bites, razor burn due to shaving or hair removal, nappy rash and allergic reactions. Allergic reactions can be seen as a special form of acute inflammatory response. An allergic reaction is characterised by an excessive response of the immune system to specific and normally harmless environmental substances (allergens), which is expressed in typical symptoms often associated with inflammatory processes. Allergy sufferers therefore carry a comparatively huge arsenal of weapons to combat tiny amounts of microscopic allergens. This disproportionate large-scale operation also mobilises defence units that damage an organism by inflammation. For hay fever, the nasal and ocular mucous membranes are affected; in the case of eczema itchy rashes develop on the skin.

If the various steps of the inflammatory response are manipulated or even prevented, this can result in cosmetic possibilities to intervene in the acute inflammation and to influence it positively. If the emerging inflammation is caught at the beginning (i.e. during the release of arachidonic acid), the inflammatory response may be less intense. If subsequent steps are mitigated (for example, the release of cytokines, tissue upset), the duration of the inflammatory response can be considerably shortened.

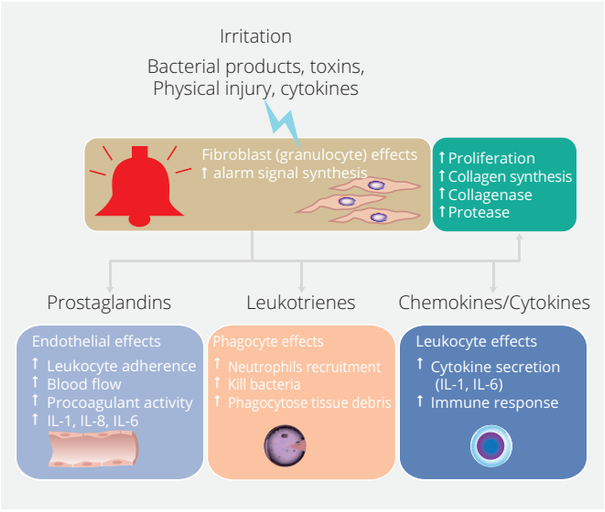


Figure 2b: The steps of the acute inflammatory response. The rapid formation and respective release of alarm signals arises at the beginning of the inflammatory response. The alerted cells then release more inflammatory mediators, which increases the reaction and orchestrates the tasks of all the cells.

Chronic inflammation
and sensitive skin

Chronic inflammations are more difficult to describe and treat. By definition, the chronic inflammation is characterised by a longer duration. The reasons for the long duration of inflammation are diverse:

- Sustained stimulus (such as ongoing infection)
- Inability of the body to resolve the acute inflammation (abscesses, scars)
- Hypersensitivity/disturbed barriers (sensitive skin)

The chronic inflammatory response is persistent and recurrent. Chronic inflammations affect people of all ages and backgrounds. There is a wide range of inflammatory skin disorders which can range from mild itching to severe medical forms. On the one hand, the visual impact of chronic disorders can be disfiguring, cause discomfort and anxiety for the affected individuals. On the other hand, the associated physical discomfort such as itching significantly worsens the quality of life and in extreme cases can lead to sleep problems.

Examples of chronic inflammation of the skin include eczema, neurodermatitis and psoriasis. We would also like to emphasise sensitive skin in this context: Sensitive skin is a skin condition in which the skin has a reduced threshold for irritative reactions. This means even small stimuli trigger inflammatory and immune reactions. This leads to a vicious circle: The inflammatory response triggers additional cell damage and as such induces a progressive deterioration of the skin barrier. Inflammations become even more easily initiated (Figure 4).

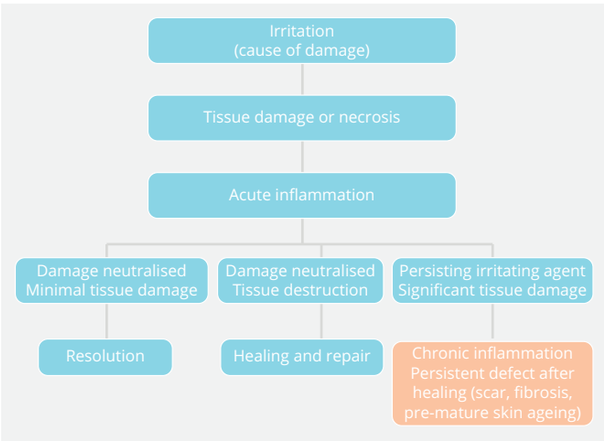


Figure 3: Chronic inflammation is a long-term inflammation (weeks or months to years). If an acute inflammation is unable to heal or the triggering stimulus remains for a long time, the inflammation develops into the chronic form. A predisposition to disproportionate, excessive immune system reactions (hypersensitivity) or a sensitive skin condition may also encourage the development of unfavourable chronic inflammation of the skin.

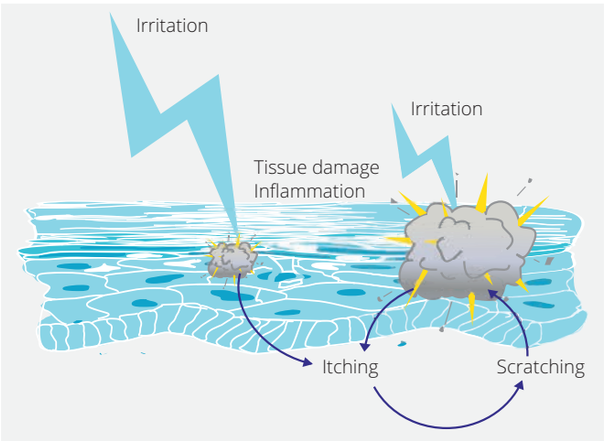


Figure 4: The vicious cycle of chronic inflammation. A stimulus induces tissue disruption and inflammation. This triggers itching and a desire to scratch. The tissue and skin barrier are further damaged by scratching leading to increased inflammation, itching and even greater sensitivity. The more sensitive the skin, the smaller the initial stimulus required to initiate the vicious cycle.

The frequently used terms “sensitive, hypersensitive or hyper-reactive skin” are indeed subjectively interpreted differently, but “sensitive skin” is still a significant problem: 44 % of consumers in Germany and 52 % in America stated in surveys that they suffer from a sensitive skin condition. Women seem to have more sensitive skin than men, with pre-menopausal women most commonly affected. Asians are more sensitive to acute irritation than Caucasians; in the case of chronic irritation, this is less pronounced for them.

The typical sensations described by those surveyed with sensitive skin include itching, burning, stinging, feelings of tension and even pain after exposure to certain environmental factors. The subjective sensations and the subjective distress can be very strong, even if no objective skin changes are detectable.

An impaired epidermal barrier function with easier penetration of irritants is a plausible cause of sensitive skin because a functioning, undisturbed barrier is a prerequisite for effective protection against potentially damaging environmental influences. A disruption of the skin barrier can be facilitated by various factors such as removal of epidermal lipids, or an excessively low water content of the stratum corneum. There is also an increased susceptibility in damp skin, which explains why irritations often manifest themselves in skin folds and bends of joints (occlusion). The trans epidermal water loss (TEWL) is an important indicator of the skin barrier function.

Moreover, an increased prostaglandin E_2 concentration and an increased IL-1α concentration was found in test subjects with sensitive skin after topical application of different irritants. Sensitive skin can therefore be caused not only by factors such as an easy-to-disturb skin barrier, but also by an increased response to irritants, respective to the presence of a pro-inflammatory environment [2].

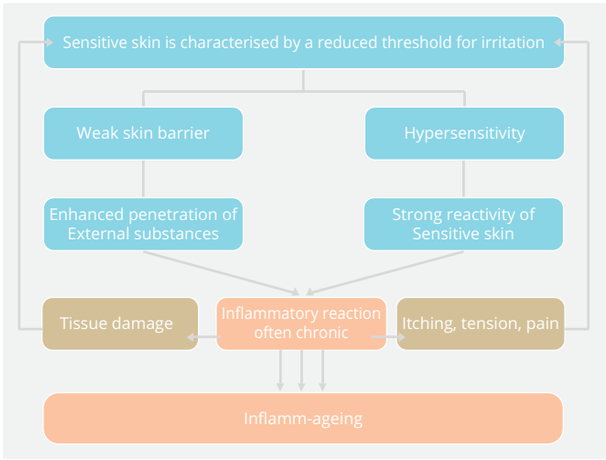


Figure 5: Sensitive skin is characterised by an easy-to-disturb barrier and overreaction to stimuli. The skin is continuously in defence mode and underlying, chronic inflammatory reactions are constantly taking place. As a result, the skin condition deteriorates rapidly and inflamm-ageing occurs. Active ingredients for sensitive skin should therefore not only have anti-inflammatory properties, but also help to maintain the skin‘s barrier and reduce sensitivity.

Inflammation and ageing:
inflamm-ageing

Inflammatory processes can have a significant impact on skin ageing. This fact is reflected in the term inflamm-ageing or inflammation ageing [3]. It is essential to be able to fend off foreign substances with acute inflammatory reactions, especially at a young age. Intense inflammation reactions improve the chances of survival against pathogens considerably and enable people to survive, at least until the end of their reproductive phase.

With advancing age, we pay the price for this defence system because the disadvantages gradually prevail. It is now believed that inflammatory reactions stand in the way of successful ageing because the immune system produces more inflammatory messengers with increasing age. This leads to an imbalance which favours inflammation. It is not characterised by classical, acute inflammations, but rather underlying, on-going processes, which permanently stress the skin and slowly but inexorably cause damage. One could also describe this effect as a "smouldering" in the skin. The skin ageing gains momentum and successful ageing is made more difficult (Figure 6).

This leads to interesting opportunities for "sustainable" anti-ageing products. The reduction of inflamm-ageing or slowing its development can significantly enhance the prevention of skin ageing. To counteract inflamm-ageing, the stimulus threshold for sensitive skin must be increased and inflammatory processes controlled. DEFENSIL®-PLUS meets these requirements perfectly!

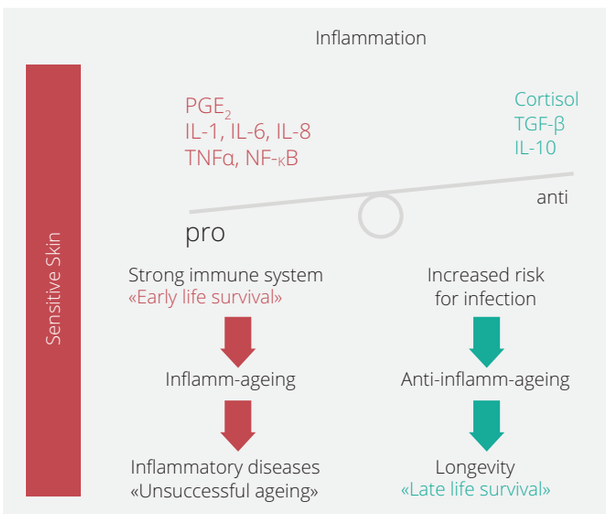


Figure 6: Inflamm-ageing. With age, the balance between pro-and anti-inflammatory signalling pathways shifts towards a pro-inflammatory environment. Likewise, there also is a pro-inflammatory imbalance in sensitive skin. The resulting chronic, underlying inflammatory condition is described by the term inflamm-ageing. Inflamm-ageing is suspected to be the basis for a variety of age-related diseases. If the inflammatory processes are reduced, that is, the balance returned to the right side, it not only has a positive effect on ageing and skin ageing, but can also help to normalise sensitive skin.

Active ingredients

Blackcurrant seed oil *(Ribes nigrum)*

The blackcurrant owes its German name (Johannisbeere) to its harvest time which begins around Johannitag (24 June). Blackcurrants belong to the gooseberry plant family. Botanically, they are gooseberries which have lost their spines [4]. The blackcurrant, with its aromatic bitter taste, is a woodland plant that grows wild in the Eurasian forests. It was previously used mainly for medicinal purposes. Mediaeval monastery medicine described the fruits as having a strong cooling and moisturising effect; they were also prized for their thirst-quenching effect during fever. Its juice is rich in vitamin C; vitamins B, E, anthocyanins and derivatives of hydroxycinnamic acid can also be found. [5].

Figure 7: *Ribes nigrum*, the blackcurrant

The oil is extracted from the seeds and is characterised by a particularly high content of polyunsaturated, (semi)essential fatty acids. It is difficult or impossible for our body to manufacture such (semi)essential fatty acids so they must therefore be supplied from outside. Blackcurrant seed oil has extremely high levels of linoleic acid, γ-linolenic acid, α-linolenic acid and stearidonic acid [6, 7]. Notably, it is one of the natural oils with the highest γ-linoleic acid content [8]. Because of their involvement in processes such as Eicosanoid synthesis, cholesterol metabolism, as well as the functionality of the cell membrane, these fatty acids play a crucial role in human metabolism. It is therefore not surprising that the blackcurrant fruit offers many health benefits [9], in which the anti-inflammatory effect is probably the most significant [10].

Barrier strengthening and anti-inflammatory

Fatty acids perform a variety of tasks in the skin. They are an element of phospholipids, which are part of the structure of the cell membrane and keratinocytes. Fatty acids are also important for the Epidermal barrier function of the skin because they have great importance as intercellular lipids of the stratum corneum – both as free fatty acids as well as bound to ceramides (sphingolipids). Ceramides make up approximately 50% of the major component of the epidermal lipids. Linoleic acid is the one of the most important ω-6 fatty acids for the skin since an insufficient amount of this essential fatty acid results in not enough ceramide I being formed (ceramide I is structurally an ester of linoleic acid). Ceramide I, because of its unique chain length and the position of the double bonds, is critical for the proper arrangement and stabilisation of the intercellular lipid lamellae and, thereby, critical for a functional skin barrier. A lack of ω-6 fatty acids leads to skin disorders and dry, flaky skin. However, no skin changes due to ω-3 fatty acid deficiency are known.

For example, the skin of those with atopic dermatitis has a significantly lower ceramide I content and increased incorporation of oleic acid instead of linoleic acid in ceramide I. This leads to structural changes in the lipid lamellae. Moreover, atopic skin exhibits increased linoleic acid values as well as decreased γ-linolenic acid (GLA) and dihomo-γ-linolenic acid values (DGLA), indicating a lack of the enzyme Δ-6-

C 18:2	**Linoleic acid**	diunsaturated ω-6-fatty acids (essential)	~ 50%
C 18:3	**α-linoleic acid**	triunsaturated ω-3-fatty acids (essential)	~ 15%
C 18:3	**γ-linolenic acid**	triunsaturated ω-6-fatty acids	~ 15%
C 18:4	**Stearidonic acid**	tetraunsaturated ω-3-fatty acids	~ 3%

Figure 8: Typical fatty acid spectrum of the blackcurrant seed oil used in DEFENSIL®-PLUS. Only evening primrose and borage oil achieve similarly high γ-linolenic acid concentrations (about 10% and 20%).

Desaturase. The result is a reduced formation of the anti-inflammatory linoleic acid metabolite prostaglandin E_1. Through the use of oral or topical linoleic and γ-linolenic acid, epidermal deficits can be compensated for. The use of blackcurrant oil is ideal for this purpose thanks to the high content of γ-linolenic acid. With topical application of γ-linoleic acid-containing formulations, an improvement in the barrier properties as well as a significant increase in skin moisture can be achieved [9, 11].

The anti-inflammatory effect is partly due to the local induction of an altered formation of inflammatory eicosanoids, such as prostaglandins and leukotrienes. The γ-linolenic acid (see above) and the stearidonic acid (inhibits the pro-inflammatory enzyme 5-Lypoxygenase) are of particular importance here [12–14]. The modified eicosanoid production has in turn an influence on the production of pro-inflammatory cytokines such as IL-1 [9].

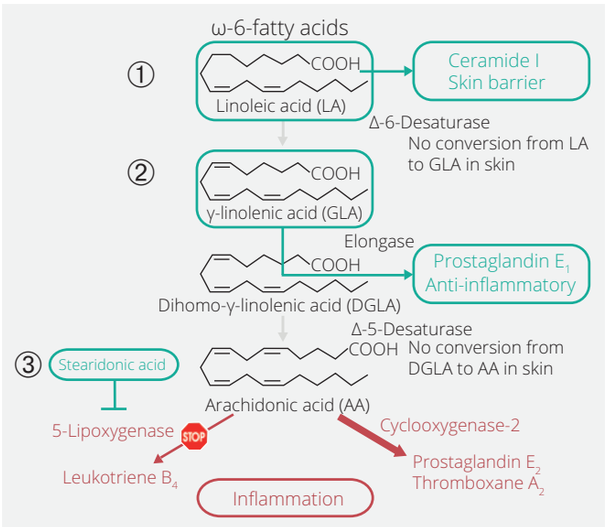


Figure 9: The blackcurrant seed oil's barrier-nourishing and anti-inflammatory mechanism of action. Blackcurrant seed oil is successfully used in cosmetics to combat dry, chapped and ageing skin, as well as in atopic eczema and psoriasis. 1) linoleic acid is a substrate for ceramide I. The skin barrier is subsequently strengthened and regenerated. 2) γ-linolenic acid (LA) and dihomo-γ-linolenic (DGLA) acid are converted to series 1 prostaglandins with anti-inflammatory properties. Supplementation with GLA and DGLA is especially important if these fatty acids are not formed sufficiently due to a Δ-6-desaturase deficiency. This is often the case in atopic dermatitis. 3) Stearidonic acid inhibits the enzyme 5-lipoxygenase.

The above mentioned studies also demonstrate the toxicological safety and tolerability of the blackcurrant seed oil, consistent with the assessment of the cosmetic ingredient review (CIR) expert panel which has certified plant-based, edible oils including blackcurrant seed oil "safe for use in cosmetics".

The oil used in DEFENSIL®-PLUS is produced with supercritical CO_2 extraction.

Balloon vine extract *(Cardiospermum halicacabum)*

The balloon vine *Cardiospermum halicacabum* is a creeper from the soapberry botanical family (Sapindaceae). Originally from the warmer regions of America, it is now common in all tropical areas. A hanging balloon-like fruit develops in autumn from the ovary; the seeds carry a heart-shaped, white spotted navel. The Latin name "*Cardiospermum*" (cardio = heart, spermum = seed) can be derived from this description. The name "halicacabum" is Greek and means "salt shaker". It refers to the inflated fruit. In German-speaking areas, *Cardiospermum halicacabum* is also called heart seed.

In its tropical homeland, the plant is primarily used as a traditional remedy. African natives use it as an anti-rheumatic drug and against indigestion; in India, it is used to stimulate contractions and helps nursing mothers in lactation while in Brazil, it is used for scaling of the skin.

In the 19th century, the balloon vine was discovered by homoeopathy and found use in rheumatic diseases as well as itchy eczema and skin rashes. In 1956, *Cardiospermum* was brought to Germany as a souvenir of a tropical trip by a German pharmacist, who then analysed and investigated its properties.

Figure 10: *Cardiospermum halicacabum*, the balloon vine

Skin-soothing and allergy-reducing

Cardiospermum is commonly used in folk medicine for various dermatological problems. It is therefore no surprise that anti-inflammatory, analgesic and anti-itch properties are recognised when it is applied to the skin [15]. Corresponding products are promoted as non-prescription alternatives to hydrocortisone. Since 1970, scientific publications have appeared which conduct critical studies on the therapeutic use of *Cardiospermum* [16]. 512 patients with atopic dermatitis participated in one of these studies. They were treated two to four times daily with a *Cardiospermum* ointment over a period of three or four weeks. In comparison to an ointment base, a significant improvement of the barrier function and a decrease of erythema were demonstrated. The need for other drugs decreased significantly: 90% of patients required hydrocortisone drugs initially; at the end of the study, only 10% had a requirement [17].

Meanwhile, the effect of *Cardiospermum* is also being studied by modern laboratory methods. In the above-ground parts of the plants, saponins and tannins could be detected;

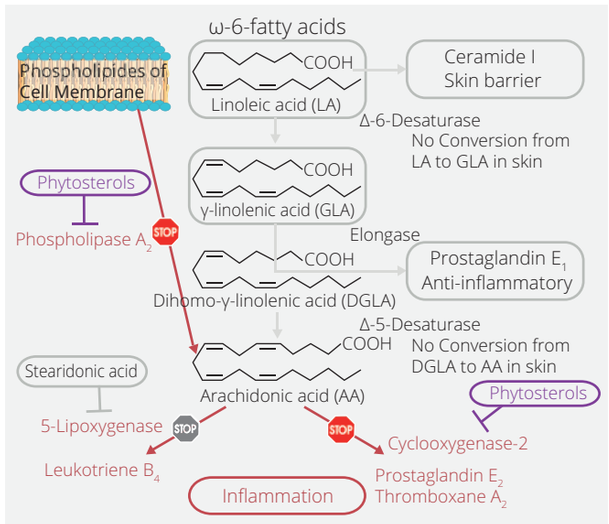


Figure 11: Inhibition of phospholipase A_2 and cyclooxygenase-2 is the anti- inflammatory mode of action of *Cardiospermum halicacabum*. Unlike other body cells, hardly any arachidonic acid (AA) is formed from linoleic acid in the cells of the skin, since the desaturation steps do not take place there. Instead, AA is temporarily stored in the membrane lipids of the epidermal cells in considerable quantities. If the enzyme phospholipase A_2 is activated by stress or environmental stimuli, AA is released and inflammatory reaction cascades are switched on.
Steroidal anti-inflammatory drugs such as hydrocortisone are potent anti-inflammatories, regardless of the inflammation's cause; their primary anti-inflammatory mechanism is phospholipase A_2 inhibition. Notably, phospholipase A_2 inhibition also has been reported for *Cardiospermum halicacabum*.
Non-steroidal anti-inflammatory drugs (NSAIDs such as aspirin, diclofenac, ibuprofen, etc.) are one of the most commonly prescribed drugs due to their high efficacy in the treatment of pain, fever and inflammation. However, the use of these drugs is associated with the occurrence of adverse effects. It is widely accepted that both the beneficial and adverse effects of NSAIDs are attributable to their ability to inhibit prostaglandin synthesis through a direct blockage of cyclooxygenases (COX). Of the two isoforms of COX, COX-1 is a constitutively expressed form required for normal physiologic functions whereas COX-2 is induced only during inflammatory processes. Selective COX-2 inhibition – as is reported for *Cardiospermum halicacabum* – can help to avoid these toxic effects.

flavonoids and phytosterols (β-sitosterol, campesterol and stigmasterol) were found later.

The anti-inflammatory and anti-itch effects are probably based on the modulating effect of phytosterols on phospholipase A_2, which cleaves arachidonic acid from cell membrane lipids, and cyclooxygenase-2, a rate-determining enzyme in the prostaglandin metabolism [16, 18, 19]. In this way, the formation of leukotrienes and prostaglandins on one hand and thromboxanes on the other is positively influenced.

A stabilisation of the lysosomal membrane is suspected as a second mechanism. Lysosomes are enclosed by a membrane-containing vesicle which contains digestive enzymes, including Phospholipase A_2. After contact with an inflammatory agent, the contents of these vesicles are normally released and the surrounding tissue is damaged [20]. If the lysosomal membrane is strengthened, less damaging enzymes are then released. This can have a calming influence on the development of allergic reactions.

In summary, *Cardiospermum* offers inflammation-regulating care for sensitive skin and is ideal for irritated skin prone to hypersensitivity. Balloon vine extract is an alternative for those with slightly inflamed skin who are reluctant to immediately apply "something chemical" such as hydrocortisone. Optionally, treatment with hydrocortisone can be delayed.
In DEFENSIL®-PLUS, an oily, phytosterol-containing extract from the balloon vine is used. β-sitosterol, stigmasterol and campesterol account for the highest proportion of phytosterols. It is assumed that *Cardiospermum halicacabum* is toxicologically safe: Dried, powdered plant material was orally administered to rats at a dose of 40 g/kg body weight with no side effects [20, 21].

Sunflower oil concentrate *(Helianthus annuus)*

The sunflower originally came from North America and has been used to produce oil there for 3000 – 4000 years. The Indians cultivated it long before the New World was discovered. It is believed that it found its way to Europe via Spanish immigrants. In the 17th century, the seeds were used for baking or roasting as a substitute for coffee or hot chocolate. Today, the sunflower is one of the most important oil crops with the world's fourth-highest production volume.
It is a prime example of heliotropism: on sunny days, the bud follows the sun from east to west, during the night it resumes its starting state facing east.

In folk medicine, sunflower oil was given internally for constipation and externally for poorly healing wounds, psoriasis and rheumatism [8].

Valuable nutrients

Sunflower oil is rich in unsaturated fatty acids. Linoleic acid (50 % – 75 %) and oleic acid (~ 25 %) are the main component of the fatty acids present. The saturated fatty acids palmitic and stearic acids are also present in large quantities, each with about 5 %.

The sunflower oil concentrate used in DEFENSIL®-PLUS is made of plants coming from certified organic cultivation. It is characterised by a particularly high standardised portion of unsaponifiable lipids. Unsaponifiable substances are components of oils and fats which cannot be split into fatty acids and alcohol (Figure 13). The unsaponifiable fraction is a valuable source of bioactive components such as phytosterols, tocopherols and other vitamins. These unsaponifiable substances contribute significantly to the beneficial properties of sunflower oil. In particular, the especially long shelf life and low oxidative deterioration of sunflower oil is mainly based on its exceptionally high content of tocopherols, for example.

The sunflower oil concentrate used in DEFENSIL®-PLUS supplements the activity spectra of blackcurrant seed oil and *Cardiospermum halicacabum* extract perfectly.

As mentioned previously in the case of blackcurrant seed oil, essential fatty acids, linoleic acid (the main component of sunflower oil) in particular, play an important role in maintaining the epidermal barrier and in minimising the TEWL [22, 23]. The similar lipid composition of sunflower oil and the lipid matrix of the epidermal skin barrier bodes well for

the potential treatment of various skin conditions. In fact, the benefits of sunflower oil as a skin care product have already been demonstrated in several studies: sunflower oil is ideal for topical application to treat a lack of essential fatty acids and associated effects such as extremely dry skin or increased TEWL [24]. Interestingly, olive oil produced no such improvements.

Premature babies are particularly vulnerable and have increased skin care needs. In this group, the daily application of sunflower oil resulted in 40% fewer nosocomial (hospital-acquired) infections and a 25% decrease in mortality. Barrier-enhancing skin care should be paid particular attention [23].

In recent studies, sunflower oil was increasingly attributed to anti-inflammatory and anti-oxidant activity. The unsaponifiable components seem to be responsible for this [25]. The activation of PPARα, a lipid sensor and inflammation regulator, is discussed as an underlying mechanism [26].

In summary, these results suggest that sunflower oil with a high content of unsaponifiable substances is best suited to calm inflammatory skin disorders which are characterised by an impaired barrier or a lipid deficit.

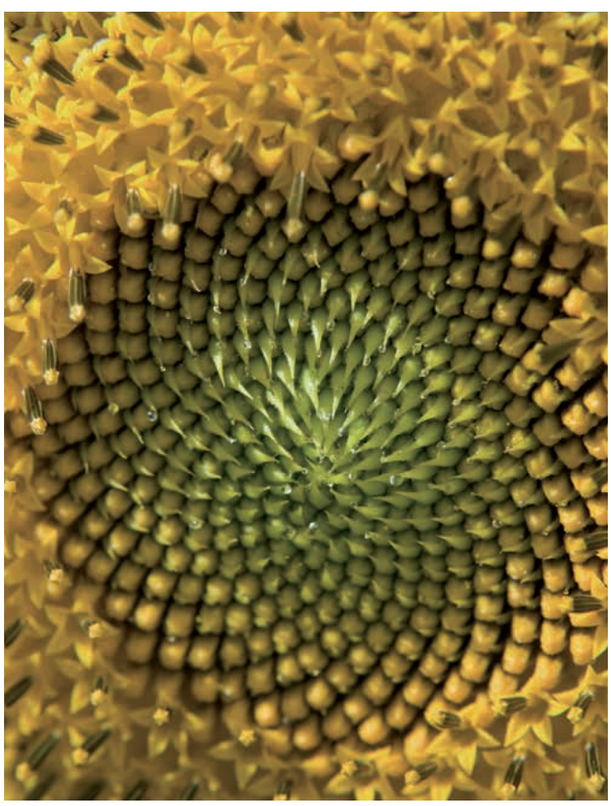


Figure 12: *Helianthus annuus*, the sunflower

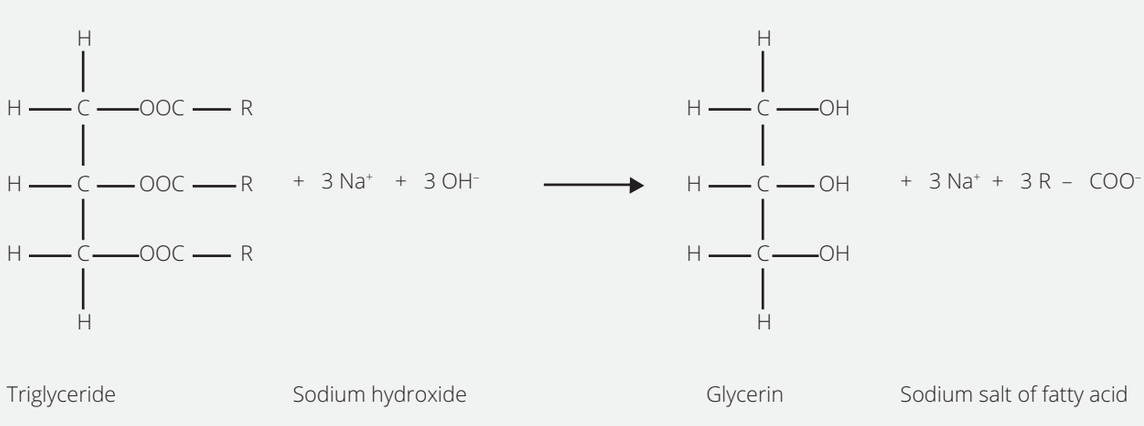


Figure 13. Saponification. Saponification refers to the basic hydrolysis of triglycerides (such as animal fats or plant-based oils) with alkalis, especially sodium hydroxide. This produces the trivalent alcohol, glycerol and the respective alkali metal salts of fatty acids occurring in fats. The salts of the fatty acids are called soaps. R = fatty acid residue.

A SMALL DIGRESSION

Atopic eczema

Atopic eczema, also called neurodermatitis or atopic dermatitis, is an inflammatory skin disease with recurrent episodes and chronic progression. It is usually accompanied by severe itching. The disease often begins in early childhood and has an 8%–16% incidence in this age group and is rising; within the last 50 years, the number has quintupled! As the child gets older, the disease spontaneously cures itself in most cases. One third of those affected suffers a relapse at some point in their lives and develop eczema once again. There are different degrees of severity, with most affected suffering only from mild forms, although the quality of life is still significantly reduced over a long period of time. Infants with atopic eczema often suffer from very red, oozing and crusted rashes on the face (cradle cap), arms and legs. Later, the so-called "bending eczema" with redness, scaling and coarsened skin (lichenification) at the elbows, wrists and knees is typical. Scratch marks are frequently found on the skin; nodules can form from itching in adults. Infections are common complications.

The causes of such conditions are still poorly understood. In about half of all those affected, the disease is due to an allergy to extrinsic factors. This is different from the intrinsic form in which no sensitisation is demonstrated. A genetic predisposition that determines the skin quality as well as the regulation of the immune system is critical to the development of atopic eczema. Factors such as Δ-6-desaturase deficiency, barrier disruptions as a result of abnormal composition of skin lipids, and the disturbance of keratinocyte functions play a role here.

Treatment

1. Reducing individual and unspecific provocation factors such as pollen or food allergens but also unsuitable textiles, incorrect skin cleaning, extreme climatic conditions, etc.

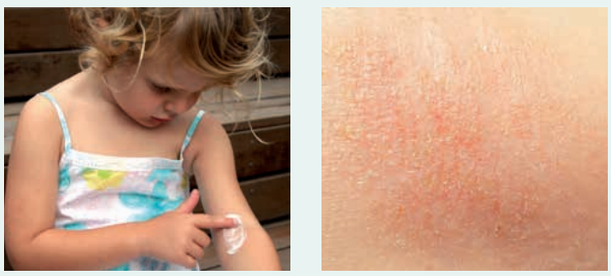


Figure 14: Gentle and calming. DEFENSIL®-PLUS, the cosmetic First-Aid Kit.

2. Lipid-replenishing therapy. In patients with atopic eczema, the skin is very dry and rough. Dry skin leads to itching and barrier defects. The disturbed barrier leads to increased sensitivity to environmental factors and promotes sensitisation. Therefore, gentle cleaning and regular lubrication of both the affected skin and symptom-free skin are necessary.

3. Anti-inflammatory therapy. Curbing inflammation is necessary to alleviate the skin symptoms and itching. An externally applied therapy of corticosteroids and calcineurin inhibitors (tacrolimus and pimecrolimus inhibit cytokine release) is usually prescribed.

4. Itch relief. The most agonising itching is a major symptom of atopic eczema and presents a particular challenge. Itching leads to scratching, this in turn leads to deterioration of the skin condition and hence new itching (itch-scratch-spiral). Since itching is caused by many different mechanisms, it often requires multiple therapeutic approaches to control it, such as consistent anti-inflammatory therapy, anti-histamines, distracting activities, autogenic training, etc. [27].

DEFENSIL®-PLUS is ideal for adjunctive skin care in the treatment of atopic skin: By easing inflammatory processes DEFENSIL®-PLUS not only reliefs sensitivity and itching, but also supports the recovery of the irritated skin barrier.

Treatment concept
and efficacy studies

Concept

The body's way of protecting itself against potentially harmful substances is to trigger inflammation. In sensitive skin, which often is characterised by an impaired skin barrier, inflammation is triggered more easily causing the skin to become inflamed, hot and itchy. Excessive inflammation exacerbates skin barrier function and eventually leads to accelerated skin ageing (inflamm-ageing) as well as impaired quality of life.

DEFENSIL®-PLUS is a highly effective first-aid kit to alleviate stressed, sensitive and irritable skin. The special properties of blackcurrant seed oil and balloon vine extract in combination with sunflower oil concentrate effectively reduce inflammatory processes and replenish the damaged skin barrier.

DEFENSIL®-PLUS soothes various forms of skin irritation; acute irritation as a result of razor burn, or from mosquito bites are both significantly reduced. Chemically irritated skin also is protected and gently regenerated. In summary, DEFENSIL®-PLUS markedly relieves dry, itchy, allergy-prone skin and gives those plagued by eczema a new lease of life.

Scientifically confirmed effects:

- Nips inflammatory processes in the bud (*in-vitro* study)
- Reduces allergic reactions (*in-vitro* study)
- Reduces tissue damage resulting from mosquito bites (*in-vivo* study)
- Soothes the skin after shaving and epilation (*in-vivo* study)
- Protects and regenerates the damaged skin barrier (*in-vivo* study)
- Improves the quality of life of those suffering from atopic eczema (*in-vivo* study)
- Reduces the severity of couperose (*in-vivo* study)

Mode of action

"Sensitive skin" is a skin condition which is particularly susceptible to irritation. Sensitive skin has a great commercial importance, as 50% of respondents suffer from sensitive skin and report subjective discomfort - but do not necessarily exhibit visible symptoms of skin irritation.

The main causes are excessive inflammatory responses, compounded by a weak skin barrier and with a tendency to react hyper-sensitively. Inflammatory reactions are a particular issue for skin with a damaged or weak barrier. This promotes uncomfortable sensations such as itching leading to a vicious cycle and chronic progression. The consequences can range from premature skin ageing and accelerated inflamm-ageing to serious skin diseases.

Sensitive skin needs inflammation-relieving skin care that not only reduces irritated inflammatory processes, but also helps replenish and stabilise the physiological skin barrier. The extremely high contents of γ-linolenic acid in the blackcurrant seed oil and linoleic acid in sunflower oil concentrate compensate for lipid deficits in the outermost layers of the skin and help the skin barrier function to recover. Stearidonic acid (blackcurrant seed oil) and high levels of phytosterols (oily *Cardiospermum halicacabum* extract and sunflower oil concentrate) assist in soothing inflammatory processes and as such counteract the underlying causes of skin disorders, inflamm-ageing, and discomfort.

DEFENSIL®-PLUS effectively soothes acute inflammatory reactions such as razor burn or allergic response to mosquito bites, as well as more persistent inflammatory processes caused by chemicals, such as SLS (found in laundry products) as well as skin conditions like atopic eczema.

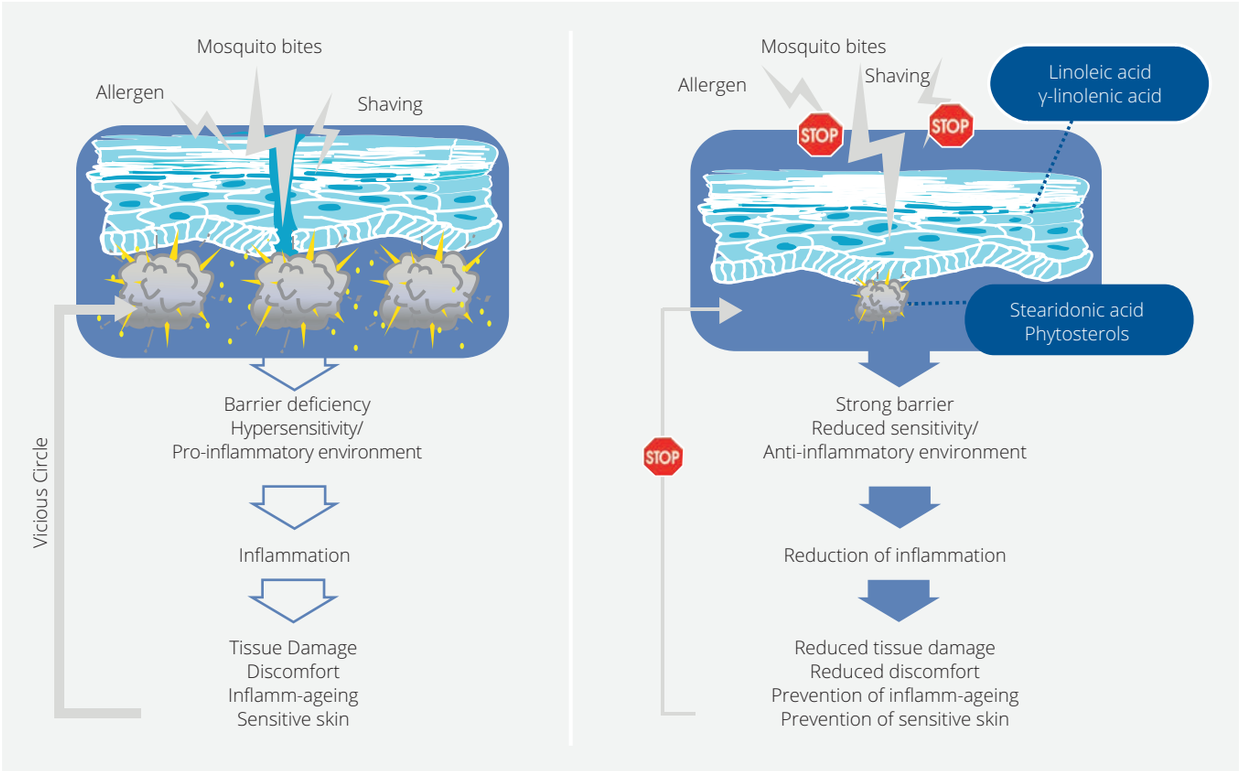


Figure 16: DEFENSIL®-PLUS eases inflammatory processes and supports the recovery of the skin barrier.

DEFENSIL®-PLUS NIPS INFLAMMATORY PROCESSES IN THE BUD (*in-vitro* study)

Aim

To demonstrate that incubation with the components of DEFENSIL®-PLUS (*Cardiospermum Halicacabum* Extract and blackcurrant seed oil) and DEFENSIL® (echium oil) leads to a weakening of the inflammatory processes.

Method

Provoking an inflammatory reaction through incubation with Interleukin-1α (IL-1α), then determining the content of inflammatory mediators (IL-1α, IL-1β and IL-8) by means of flow cytometry (FACS analysis).

Interleukins are the body's own signalling substances that allow communication between the cells of the immune system and other cells involved in the immune reaction. IL-1 α is primarily a pro-inflammatory signalling substance which orchestrates the initial ignition of local inflammatory reactions (i.e. formation of further pro-inflammatory Interleukins/cytokines and recruitment of immune cells into the inflamed tissue). The cells of the skin and the tissue are stressed here, particularly in the case of chronic inflammation. IL-1α is often used as an end point in assays to determine the potential for irritation of the skin.

Implementation

Human keratinocytes were incubated with 0.0025% of the ingredients found in DEFENSIL®-PLUS (black currant seed oil, balloon vine extract, control: echium oil) corresponding to approx. 0.01% DEFENSIL®-PLUS. Immediately afterwards, the cells were stimulated with IL-1α (2.5 ng/ml) and 24 hours later the content of inflammatory signal substances in the remaining cells was quantitatively determined.

Result

The addition of *Cardiospermum Halicacabum* Extract and of blackcurrant seed oil respectively, clearly reduced the formation of inflammatory mediators after induction of an inflammatory reaction.

This showed that blackcurrant seed oil in particular possesses a potent anti-inflammatory effect and has an even greater anti-inflammatory potential than echium oil. Due to its excellent anti-inflammatory properties, echium oil has been successfully used in DEFENSIL® for years.

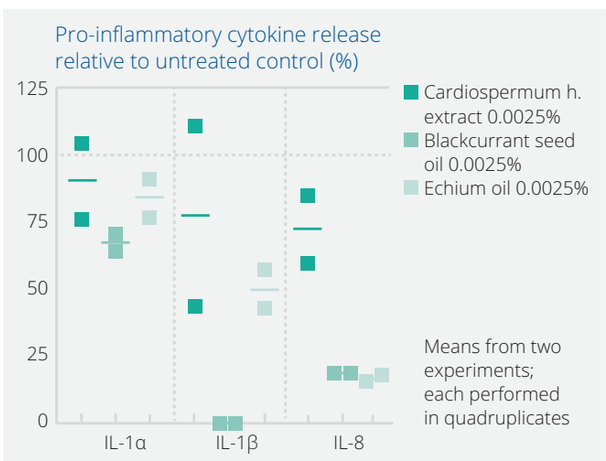


Figure 17: The DEFENSIL®-PLUS and DEFENSIL® contents stem inflammatory processes. Human keratinocytes were mixed with the individual components of DEFENSIL®-PLUS and DEFENSIL®. An inflammatory reaction was then provoked by means of IL-1α stimulation. After 24 hours, the content of inflammatory mediators was determined and calculated relative to the control without components. The figure shows the results from two independent experiments and the respective mean value. Quadruplicates were used in each experiment. These were combined before the FACS analysis.

DEFENSIL®-PLUS REDUCES ALLERGIC REACTIONS (*in-vitro* study)

Aim

To prove that treatment with DEFENSIL®-PLUS leads to a weakening of allergic reactions.

Method

Basophil activation test [28]: basophils are a subgroup of white blood cells which are involved in certain allergic reactions. An allergy is an immunological over-reaction: The allergic reaction occurs as a consequence of an immune response to actually harmless molecules, which the immune system wrongly sees as threatening or exogenous (referred to as antigens or allergens).

Contact with an allergen typically initiates a massive release of toxic inflammatory mediators, e.g. histamine, through mast cells and basophils. This process is called degranulation. Degranulation ultimately leads to an allergic reaction characterised by itching, burning, swelling, etc. In the basophil Activation Test, the number of degranulated basophils after incubation with an allergen is determined using flow cytometry.

Implementation

Basophil activation test was performed using Flow2 CAST® kit. Briefly, human blood was pre-incubated for 15 minutes at 37°C in the presence of 0.05% DEFENSIL®-PLUS (dissolved in 1% EtOH), solvent control (1% EtOH) or degranulation inhibitor (3 mM Cromoglycate). Then, the allergen f-MLP (a formyl tri-peptide: f-Met-Leu-Phe) was added or not (non-stimulated control) and blood was incubated for 10 additional minutes in the presence of labeling antibodies. Notably, basophilic cells can be identified by using CCR3-PE labelling; and

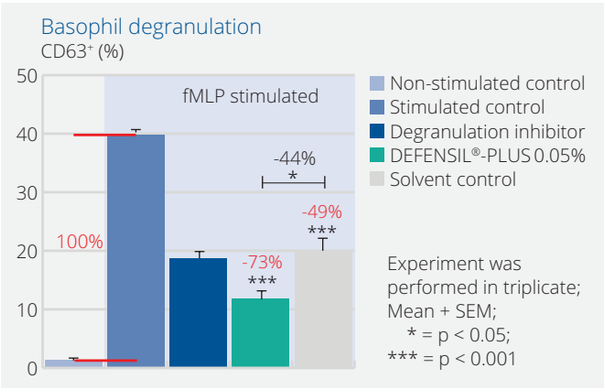


Fig. 18: DEFENSIL®-PLUS acts as an anti-allergen. When basophils were pre-treated with DEFENSIL®-PLUS in an *in-vitro* allergy model, fewer inflammatory mediators were released after the allergy was triggered. Stimulation with fMLP induced the degranulation of basophils, i.e. a greater number of cells were positive in terms of the degranulation marker CD63 (stimulated control). Degranulation could be prevented by the degranulation inhibitor cromoglycate. A pretreatment of the cells with 0.05% DEFENSIL®-PLUS significantly reduced the number of CD63-positive, degranulated cells and thereby reduced the excess release of disadvantageous inflammatory mediators. The calculated anti-allergy effect of 0.05% DEFENSIL®-PLUS was 73% (in red). The solvent alone (solvent control) also showed a certain effect, but the anti-allergy effect of DEFENSIL®-PLUS was significantly greater (by 44%). Two-sided, unpaired t-test. The experiment was carried out in triplicate.

degranulated cells can be identified by CD63-FITC labeling. CD63 is an intracellular transmembrane protein, which is exposed to the cell surface upon degranulation. At the end of the incubation time, red blood cells were lysed, and cells were analyzed for CCR3/CD63 expression using flow cytometry.

Result

DEFENSIL®-PLUS prevents allergic reactions: When basophils were pre-treated with 0.05% DEFENSIL®-PLUS before irritation through the allergen, the degranulation thereof was reduced by 73% and 44% respectively (compared to the solvent control)! It must therefore be assumed that, thanks to the pretreatment with DEFENSIL®-PLUS, fewer inflammatory mediators are released and hence allergic reactions will be far less severe.

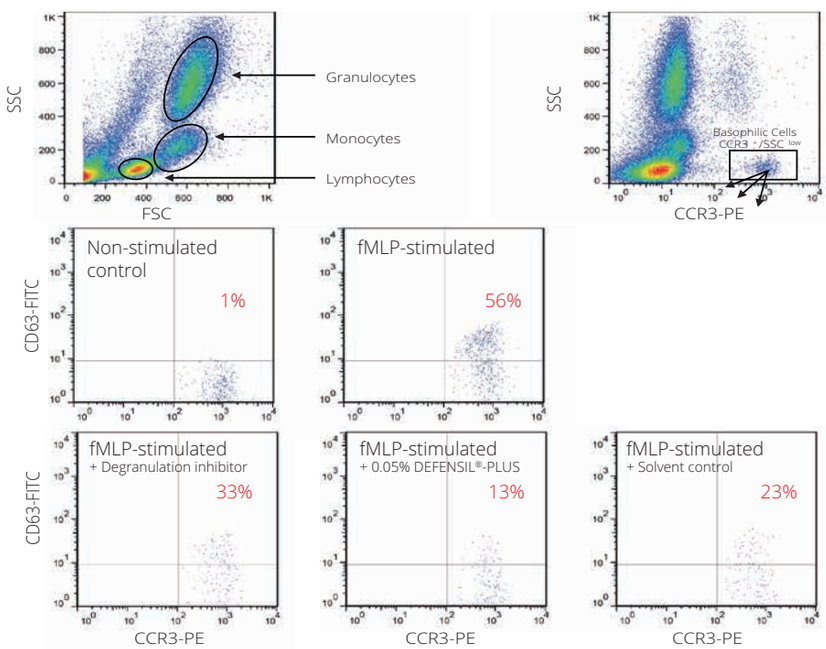


Figure 19: Representative illustrations of the flow cytometry analysis: blood cells can be classified on the basis of their size (FSC) and their granularity (SSC) **(top left)**. Basophils are characterised by SSClow/CCR3+ (top right). Without fMLP, no degranulation of basophils takes place, i.e. the staining for CD63 is negative **(middle left)**. On the other hand, the addition of fMLP induces considerable degranulation (middle right), which is less severe on prior addition of the degranulation inhibitor cromoglycate **(bottom left)**. With the prior addition of 0.05% DEFENSIL®-PLUS, a clear anti-allergy effect is discernible: Now only 13% of all basophils degranulated.

DEFENSIL®-PLUS REDUCES TISSUE DISORDER RESULTING FROM MOSQUITO BITES *(in-vivo* study)

Aim

Insect bites cause unpleasant inflammatory or allergic reactions characterised by swelling and itching. We wanted to demonstrate that DEFENSIL®-PLUS can reduce the manifestation of painful mosquito bites.

Method

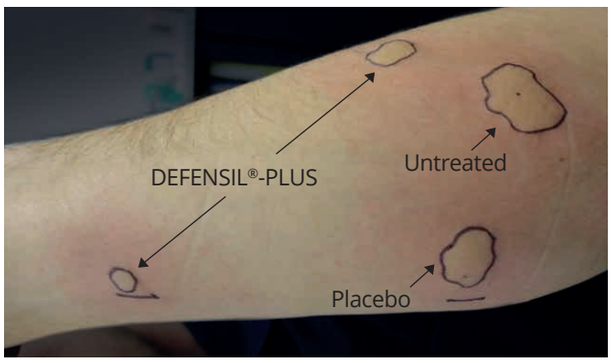
Self-experiments with Culex pipiens (common house mosquito). Culex pipiens, which is found all over the world, is the most frequent type of mosquito in Europe. A short time after the bite, an allergic reaction limited to the area bitten usually occurs. This reaction is caused by proteins which the mosquito injects into the suction area in order to prevent blood clotting. The immune system wrongly sounds the alarm, releases inflammatory mediators and causes a local inflammation reaction for a number of hours. The reaction manifests itself in the form of a visible swelling at the injection point and is often accompanied by itching. The severity of the allergic reaction was determined by measuring the swelling.

Implementation

The subjects held out their arm for 3 minutes into a cage containing over 100 female Culex pipiens mosquitoes, resulting in about 10 bites. As soon as the first symptoms became noticeable, a cream containing either 5% DEFENSIL®-PLUS or 0% DEFENSIL®-PLUS (placebo) was randomly applied [DEFENSIL®-PLUS 1]. After half an hour, when the swelling had become fully pronounced, the boundary of the wheel was defined, photographs were taken and the area of the swelling was measured by means of in-silico analysis.

Result

The problem of mosquito bites is not the injected poison, but rather the inappropriate immune response to the bite. Treatment with DEFENSIL®-PLUS immediately after the mosquito bite led to a marked relief of inflammation, i.e. the swelling caused by the bite was on average 35% less pronounced!



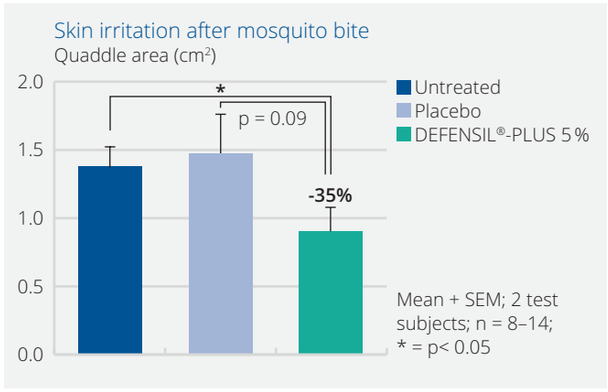


Figure 20: DEFENSIL®-PLUS reduces the manifestation of mosquito bites. Top: a subject allows himself to be bitten by Culex pipiens for a duration of 3 minutes. **Centre:** immediately afterwards, the bite areas were treated either with a placebo or with DEFENSIL®-PLUS. Untreated bitten areas served as a control. The signs of inflammation were most pronounced after approx. 30 minutes. **Bottom:** photographs were then taken and the size of the swollen areas was measured on the computer. 2 subjects; 8–14 bites per condition. Two-sided, paired t-test.

DEFENSIL®-PLUS SOOTHES THE SKIN AFTER SHAVING AND EPILATION (*in-vivo* study)

Aim

To show that razor burn is prevented or reduced by the application of DEFENSIL®-PLUS.

Method

An inflammation is a characteristic response to an external, potentially harmful irritation. The skin reacts with classic signs of inflammation such as pain, reddening or hyperthermia.

1. In the male subject, the facial skin was irritated by wet shaving. The degree of hyperthermia was determined by means of a thermal imaging camera and acted as an indicator of razor burn and subsequently a soothing effect on the skin.

2. In the female subject, the skin of the legs was irritated by epilation. The degree of skin reddening and swelling was also a sign of "razor burn" or a soothing effect on the skin here.

Implementation

1. Wet shaving (face) in men

Curative test design: Usual wet shaving and subsequent drying of the face by the subject. A cream containing 5% DEFENSIL®-PLUS was then applied to one half of the face [DEFENSIL®-PLUS 1], and a placebo to the other half. 10 minutes later, photographs were taken using a thermal imaging camera (Thermo Shot F30; NEC Avio Infrared Technologies) and the temperature differences were determined using the associated software (InfReC Analyzer NS9500).

Preventive test design: Twice-daily pre-treatment of one half of the face with a cream containing 5% DEFENSIL®-PLUS [DEFENSIL®-PLUS 1] for one week; placebo on the other half of the face. Usual wet shaving, every second day over this period; no additional cosmetics. Then wet shaving by the subject and taking of thermal imaging pictures 10 minutes after shaving.

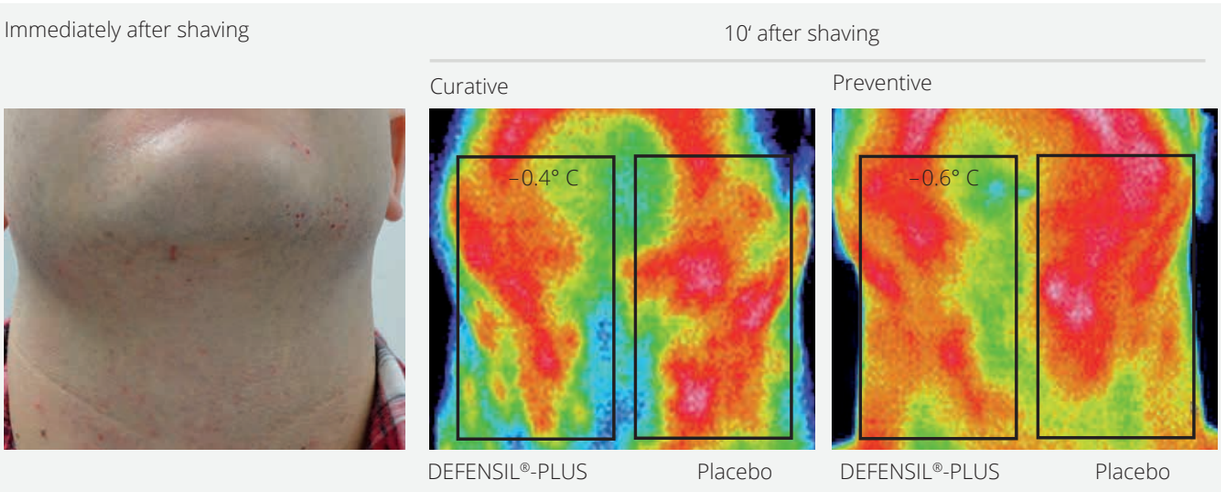


Figure 21: DEFENSIL®-PLUS reduces razor burn. Left: usual wet shaving by the subject irritates the skin. Reddening and lesions are clearly visible. **Centre:** DEFENSIL®-PLUS immediately soothes the skin and protects it from excessive heating. Curative test design. Single application of DEFENSIL®-PLUS or a placebo immediately after shaving, with the taking of a thermal image 10 minutes later. In the picture, the hottest areas are shown in white, followed by red, yellow, green and finally blue for the coldest areas. The temperature differences and hence the anti-irritant effect of DEFENSIL®-PLUS is clearly visible. **Right:** DEFENSIL®-PLUS prevented razor burn and reduced excessive irritant responses. Preventive test design. The skin pre-treated with DEFENSIL®-PLUS was much less warm (= less irritated) after shaving than the skin treated with the placebo.

2. Epilation (leg) in women

Mixed test design: pretreatment for one week with a cream containing 3% DEFENSIL®-PLUS [DEFENSIL®-PLUS 2] on one leg; placebo on the other leg. The last application was made in the evening before epilation of the legs. The epilation was made the next morning, followed by further application of DEFENSIL®-PLUS or the placebo. Any discomfort was photographically documented 10 minutes later.

Result

1. Wet shaving (face) in men

Even if the skin is used to regular and always identical shaving, it reacts to this irritation by burning, reddening or heating up. In our tests, we found that the skin heats up by about 0.5°C after shaving. Razor burn is usually at its most severe after 10–20 minutes and gradually declines thereafter (not shown).

A single application of a cream containing 5% DEFENSIL®-PLUS soothes the skin immediately and reduces irritation or heating of the skin almost completely: The area of the face treated with DEFENSIL®-PLUS remained 0.4°C cooler. If DEFENSIL®-PLUS was used daily as a cure for razor burn, the soothing effect on the skin was even more pronounced: The skin was protected and hardly reacted to external irritations at all.

2. Epilation (leg) in women

DEFENSIL®-PLUS allowed more comfortable and gentle epilation of the legs. The leg treated with 3% DEFENSIL®-PLUS showed fewer negative side effects, i.e. markedly less reddening and less swelling. It was also reported that the hairs on the leg treated with DEFENSIL®-PLUS could be removed more easily.

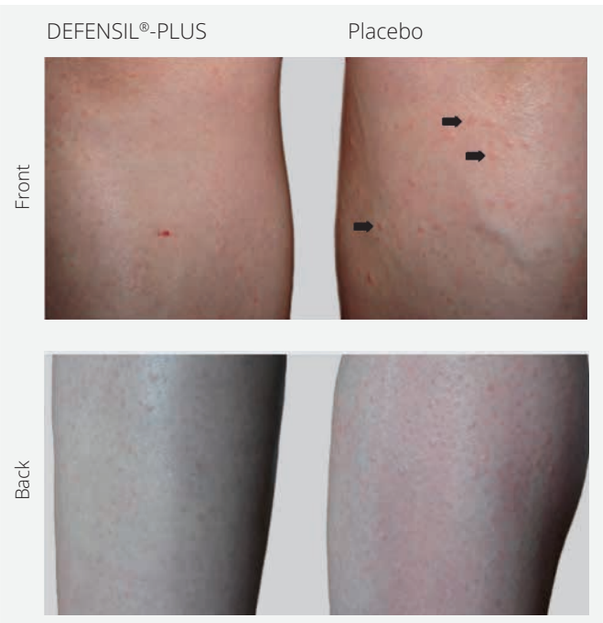


Figure 22: DEFENSIL®-PLUS for soothing skincare. The skin reacts to epilation with discomfort such as swelling (top right picture, arrows; front view of the shin) and reddening (bottom right picture; calf). When the leg was treated with DEFENSIL®-PLUS, epilation was gentler and discomfort less pronounced.

DEFENSIL®-PLUS PROTECTS AND REGENERATES THE DAMAGED SKIN BARRIER (*in-vivo* study)

Aim

To demonstrate a regenerative and protective effect of DEFENSIL®-PLUS on SLS-induced skin irritations. SLS (Sodium Lauryl Sulfate) is a detergent that disturbs the epidermal barrier. Measuring the reddening of the skin and the TEWL has proved to be a good way of determining the severity of the irritation.

Method

Determining the reddening of the skin: Skin irritation was measured by determining the reddening of the skin using a Minolta Chromameter CR 400 (L*a*b colour system). In the L*a*b system, a colour is displayed in a three-dimensional coordinate system with axes for green-red (a*), blue-yellow (b*) and brightness (L*). Where the skin has reddened, the a* value rises.

Determining the TEWL: Tissue damage, i.e. the integrity of the skin barrier, was investigated by determining the TEWL using a Courage & Khazaka Tewameter TM 2010. TEWL shows the amount of water discharged by the skin to the outside world per hour and cm^2. If the skin barrier is damaged or irritated, the TEWL value rises dramatically and then gradually falls as the tissue begins to regenerate.

Implementation

20 subjects of Caucasian skin-type took part in the study (6 men and 14 women). Their ages ranged from 29 to 58 (an average of 42.4).

To study the regenerative properties of the DEFENSIL®-PLUS, skin irritation was induced by 1 week of twice daily washing of the forearms with 5% SLS in distilled water. Skin redness and TEWL were recorded at baseline and 6 hours after the last SLS washing (after SLS). Then, creams containing 1%, 2%, 4% DEFENSIL®-PLUS or placebo were applied twice daily [DEFENSIL®-PLUS 3]. Another area was left untreated and served as control. Measurements were taken after 1, 2, 4 and 7 days of treatment to study the effect of DEFENSIL®-PLUS on the recovery process of the skin.

To study the protective properties of the DEFENSIL®-PLUS, the subjects were asked to continue the application of respective test product application and to resume the SLS washing routine. SLS washing was done with a 1 hour delay after test product application. Skin redness and TEWL were determined before and after the 7-day SLS washing/treatment phase.

Result

Skin reddening regeneration:

SLS washing induced measureable skin reddening in all six test areas. Skin redness was found to have returned to its original level (in statistical terms, $p < 0.05$) on day 2 in areas treated with DEFENSIL®-PLUS creams. In stark contrast, in untreated and placebo treated areas, the original level was not achieved before day 4. Thus, without DEFENSIL®-PLUS twice as much time was needed for regeneration!

TEWL regeneration:

SLS washing induced a measurable increase in TEWL in all six test areas. During the following application phase, TEWL was found to decrease statistically faster in areas treated with 1% and 4% DEFENSIL®-PLUS (after 2 and 4 days of treatment against untreated and after 4 days against placebo). Therefore, we can deduce DEFENSIL®-PLUS, accelerates recovery from barrier disturbance!

Skin reddening protection:

When SLS washing and product were resumed, a repeated increase in skin redness was observed. The increase in skin reddening, however, was statistically significantly less pronounced in areas treated with 2% and 4% DEFENSIL®-PLUS than the increase in the untreated, SLS washed, control area. To conclude, DEFENSIL®-PLUS efficiently protects against skin redness upon irritation.

TEWL protection:

When SLS washing and product were resumed, again, an increase in TEWL was observed. Barrier damage, however, was statistically and significantly less pronounced in areas treated with 2% and 4% DEFENSIL®-PLUS. In essence, DEFENSIL®-PLUS powerfully protects from induced barrier damage!

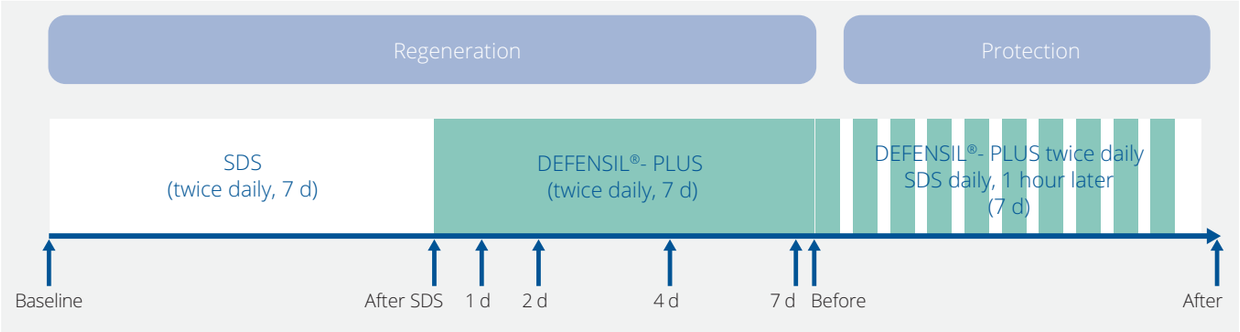


Figure 23: Experimental set up to determine the regenerative and protective properties of DEFENSIL®-PLUS.

Figure 24: DEFENSIL®-PLUS provides regeneration and protection in the event of irritation by SLS. Top left: the 7-day SLS washing led to a reddening of the skin. When the areas were then treated with DEFENSIL®-PLUS cream, the skin was soothed within two days, i.e. the reddening of the skin returned to the original level. However, in untreated or placebo-treated areas, it took four days for the reddening to disappear. # means "no significant difference from the original level"; **Top right:** the 7-day SLS washing led to an increased TEWL. The subsequent application of 1% and 4% DEFENSIL®-PLUS accelerated the regeneration of the skin barrier compared to the placebo-treated and untreated areas. **Bottom left:** a further 7-day SLS washing led again to reddening of the skin. When the skin was treated with 2% or 4% DEFENSIL®-PLUS one hour before washing in each case, the skin was protected and reddening was far less severe. **Bottom right:** further 7-day SLS washing also led to another rise in the TEWL. When the skin was treated with 2% or 4% DEFENSIL®-PLUS one hour before washing in each case, the skin barrier was protected and the rise in the TEWL was far less severe. * means $p < 0.05$. Two-sided, paired t-test.

DEFENSIL®-PLUS IMPROVES THE QUALITY OF LIFE OF THOSE SUFFERING FROM ATOPIC ECZEMA (*in-vivo* study)

Aim

To evaluate the efficacy of DEFENSIL®-PLUS on subjects with atopic dermatitis to reduce the local SCORAD, as assessed by a dermatologist, as well as pruritus and quality of life, as assessed by the subjects.

Atopic eczema, also known as atopic dermatitis or neurodermitis, is the most common skin disease. It is an intermittently occurring chronic inflammation reaction of the skin.

Method

Local SCORAD (SCORing Atopic dermatitis)

SCORAD is used as a standardised method of assessing the severity of atopic eczema and has proven itself as a parameter for clinical follow-up in clinical studies. A slightly modified local SCORAD was used for this study. It represents the sum of various parameters and is only ascertained locally in a diseased area on a scale of 0–3. An assessment was made of the reddening of the skin (erythema), oedemata and papules, discharges and crusts, attrition (excoriation), coriaceous changes in the skin (lichenification), dryness and itchiness.

Subjects' Questionnaires

On each day between days –5 to 14 itchiness was evaluated on a daily basis in a diary. On days 0 and 14 the subjects filled in a questionnaire regarding their quality of life. Finally at the end of the study, the subjects rated the product traits.

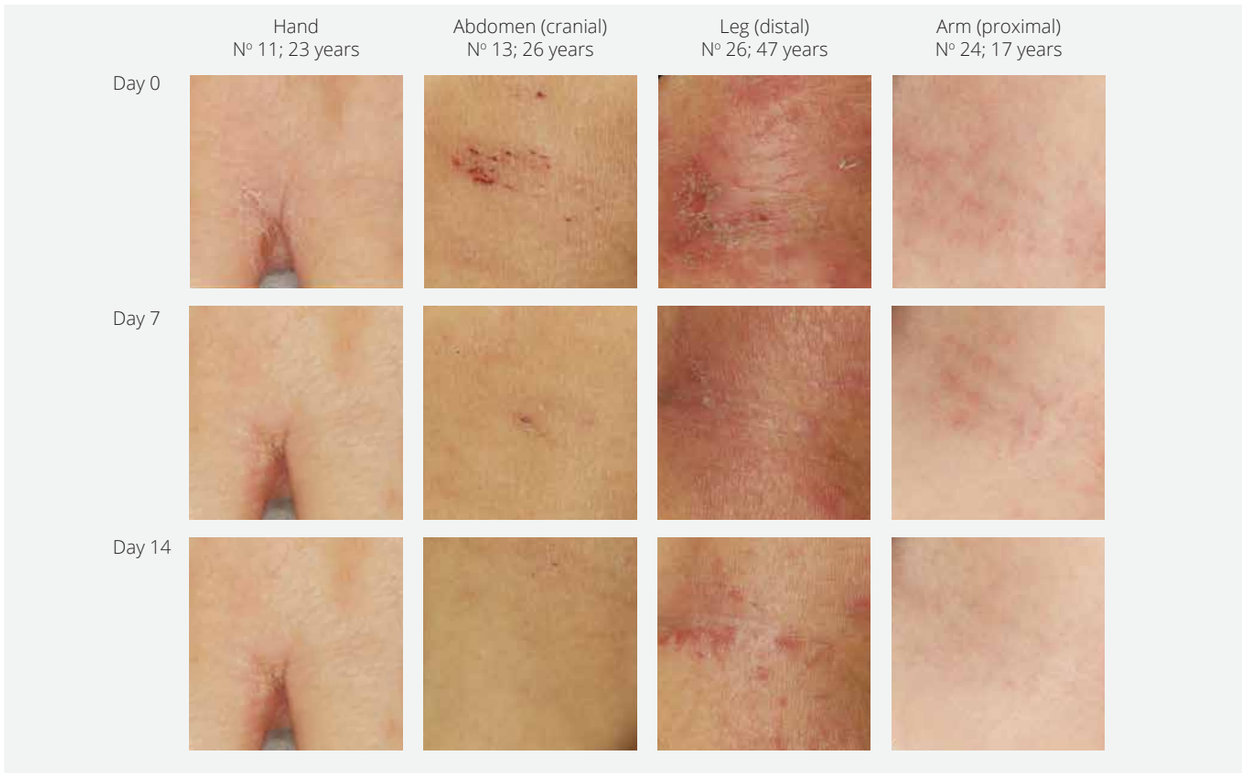


Figure 25: Change in the skin condition by use of DEFENSIL®-PLUS.

Implementation

After screening 47 subjects, 35 subjects having slight, suitable eczema areas and a SCORAD > 4 were included in the study. 34 subjects (8 men and 26 women) completed the study. Their ages ranged from 17 to 60 (an average age of 32.4).

A cream containing 3% DEFENSIL®-PLUS [DEFENSIL®-PLUS 4] was applied over a period of two weeks, respectively twice (arms, legs, trunk) and four times (hands) a day in the area of the lesions. On the examination days of Day 0, Day 7 and Day 14, an objective assessment (local SCORAD) of the skin condition was carried out by a dermatologist and a subjective assessment (itchiness) was carried out by the subject. The subjects also assessed their quality of life (QoL) before and after use and cosmetic acceptability at the end of the study by filling in a questionnaire.

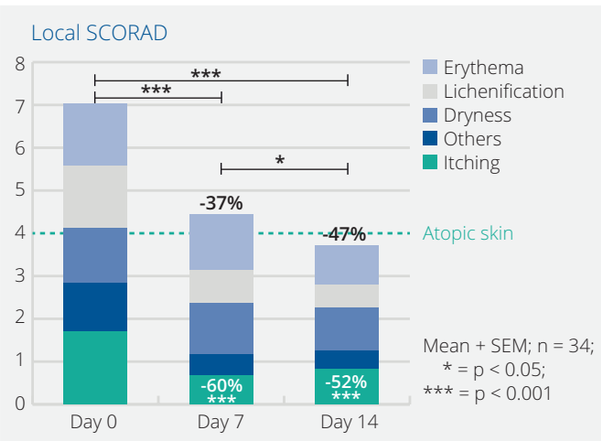


Figure 26: DEFENSIL®-PLUS leads to a reduction in the local SCORAD. On treatment with 3% DEFENSIL®-PLUS, significantly lower local SCORAD values were found on Day 7 and Day 14 compared to the baseline. The local SCORAD was significantly lower again on Day 14 than on Day 7. In particular, a reduction in the itchiness parameter was also confirmed by the dermatologist (shown in black and white). Wilcoxon signed ranks test. * = p < 0.05; *** = p < 0.001.

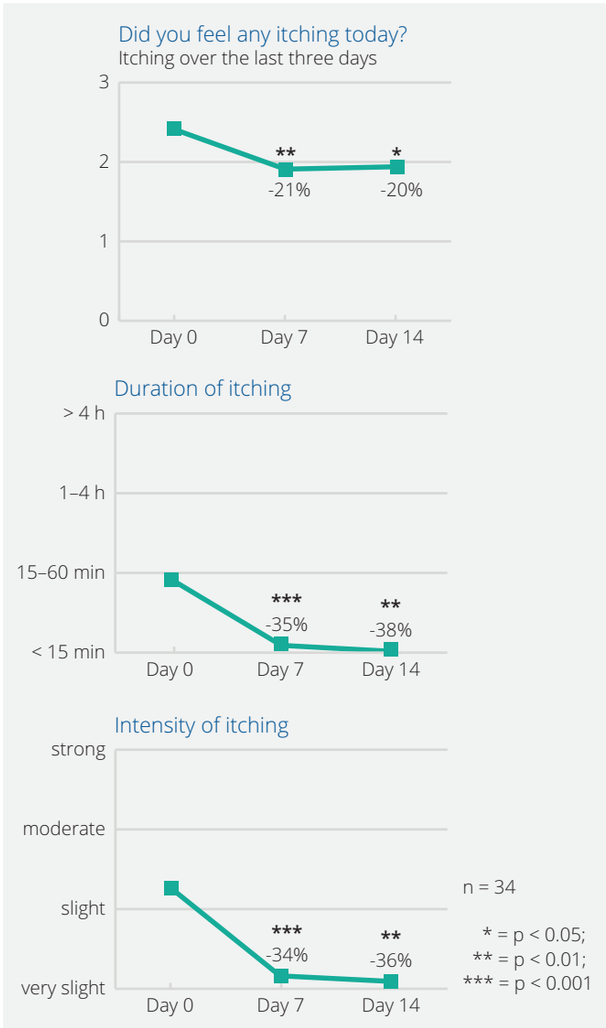


Figure 27: DEFENSIL®-PLUS leads to a subjectively perceived reduction in itchiness. Top: Mean values of accumulated pruritus over the last 3 days before visits, as documented by the subjects in their diaries (0 = no pruritus today; 1 = pruritus occurred today). According to the scale, possible mean values of pruritus over the last 3 days ranged between 0 (= no pruritus on neither of the 3 days before the visit) and 3 (= pruritus on all 3 days), i.e. lower mean values indicate a decrease of pruritus. Mean values of duration and intensity of pruritus over the last 3 days before visits, as documented by the subjects, are shown in the **middle** and **bottom** panel, respectively. Wilcoxon signed ranks test. * = p < 0.05; ** = p < 0.01; *** = p < 0.001.

Result

The local SCORAD lay in the middle at the beginning of the study at 7.03 and fell to 4.44 (–37%) after just 7 days of use. After 14 days use, it was already 3.74 (–47%) and below the threshold for atopic skin. In particular, a reduction of itchiness was noted (Figure 26).

Subjective discomfort also clearly fell during the observation period and therefore also provided convincing evidence of the efficacy of DEFENSIL®-PLUS: itchiness (Figure 27) and negative effects on the quality of life (Figure 28) were reduced on average by approx. 40%. The cosmetic acceptability of the product was also high (Figure 29).

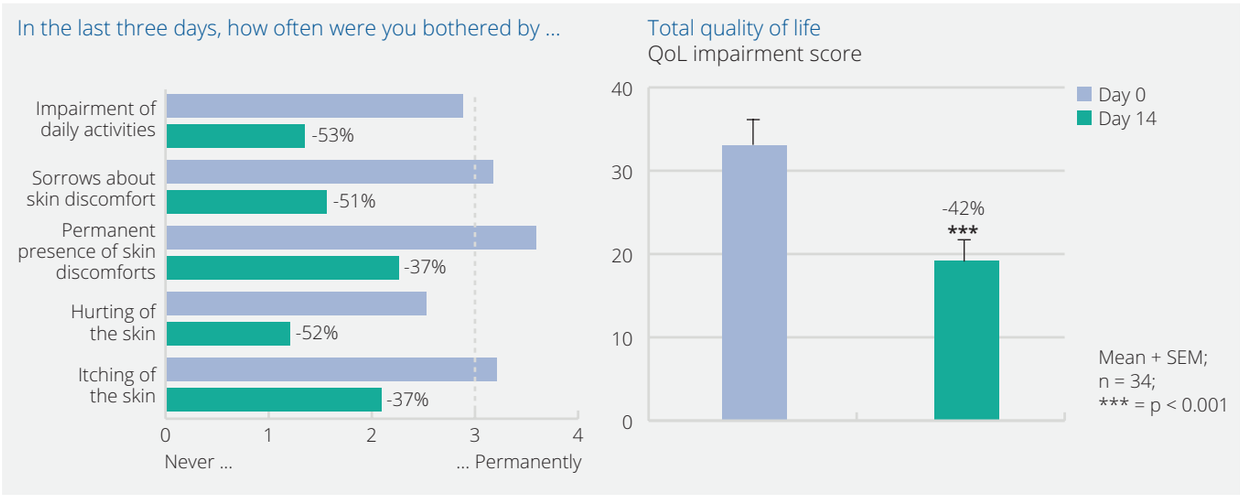


Figure 28: DEFENSIL®-PLUS restores the quality of life. Left: at the beginning and the end of the study, the subjects filled in a questionnaire regarding their quality of life (QoL). The scale ranged from 0 (= did not bother me at all/never bothered me) to 6 (bothered me permanently), i.e. lower mean values indicate an increase of the quality of life. Indeed, a significant increase of the quality of life was documented after two weeks of treatment with DEFENSIL®-PLUS in comparison to baseline. 5 out of 11 questions are shown. **Right:** a total QoL impairment score was calculated as sum of all gradings of the QoL evaluation. The treatment with 3% DEFENSIL®-PLUS reduced this score respectively improved the quality of life of atopic-dermatitis plagued consumers by reducing skin discomfort and dispelling fears – overall by 42%. Wilcoxon signed-ranks test. Mean + SEM.

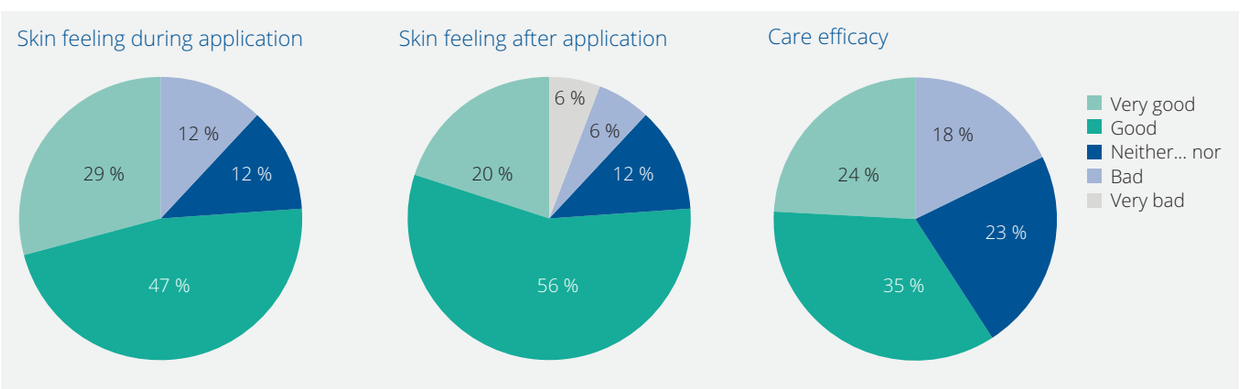


Figure 29: Product assessment by subjects. The skin feeling parameters both during and after application and care efficacy produced convincing assessments.

A SMALL DIGRESSION

Couperose – Rosacea
Definitions of terms

Couperose is a French expression and can be translated as "copper-rose" or "copper acne". The technical term facial erythrosis is also used. Couperose denotes a **persistent** dilation and relaxation of the blood vessels in the facial region and is characterised by a typical copper-red colouration which can result in visible small blood vessels (telangiectasia), particularly in the area of the cheeks, but also on the nose or forehead. If the damage progresses, it can lead to severely inflammatory changes in the blood vessels, also known as rosacea.

Causes and progression

Pre-stages: blood vessels in the surface of the skin dilate and then slowly constrict in response to stress, excitement, alkaloids (coffee, tea), alcohol, strong spices and exterior temperature influences. The temporary dilation of the vessels is visible and leads to skin redness which occurs spontaneously and then subsides, and which can continue for hours or days. Frequent and intense dilation reactions in case of a corresponding predisposition lead to the progressive slackening of and damage to the vessel walls. Over time, the hyperreactive blood vessels become damaged and the redness increasingly persists in the affected areas. Subsequent symptoms include persistent telangiectasia (visible small vessels) and ultimately inflammatory processes.

Couperose: if the now permanently dilated vessels become overfilled with blood, this manifests itself in the form of a fine, visible vascular plexus and intensified redness. In the early stage, the redness fades away, if light pressure is applied to the skin. The skin colour changes, because the pressure forces the dammed-up blood in the dilated but intact blood vessels deeper into the skin. In a later stage, the redness no longer fades away but remains. This is explained by the increasing damage to the vessel walls, which facilitates the exit of the blood into the surrounding tissue. New vessels are also formed with reduced elasticity and increased permeability. As a result of the increased collection of blood in the tissue, the skin redness now becomes more intense and widespread. If a bright red hue is dominant, then arteries are affected; when veins are affected, the skin appears bluish.

Rosacea: couperose can also be understood as an early form of rosacea. Couperose is often seen not as a disease, but rather as a cosmetic problem. In contrast, rosacea is a medical problem that also includes pathological changes such as red papules, isolated pustules over a pronounced pustular area and a coarsened complexion due to proliferation of the sebaceous glands which can lead to rhinophyma (bulbous nose).

Preventative measures and cosmetic treatment

Couperose usually appears after the age of 30 and affects women far more frequently than it does men. Treatment requires patience and perseverance. As couperose and telangiectasia are typically persistent, prevention is particularly important if a person has a recognizable predisposition. The following preventative measures are recommended:

- All stimuli that promote rapid dilation and constriction of the blood vessels should be consistently avoided: extreme temperatures or temperature fluctuations (e.g. when washing), excessive cooling of the surface of the skin in the winter due to cold, dry wind, overheating of the skin due to direct infrared radiation from sunlight (e.g. due to prolonged sunbathing; be sure to use ample sunscreen) or sauna, cosmetics containing alcohol, menthol, etc., wet shaving (ensure that blades are sharp, or better still, use an electric razor).
- Barrier-strengthening skincare products help to minimize external stimuli.
- Anti-inflammatory skincare products help to suppress internal stimuli as subthreshold inflammatory reactions continually weaken the blood vessels.

A final option is corrective (typically in green hues) or concealing cosmetics, which do improve the appearance but not the condition of the skin.

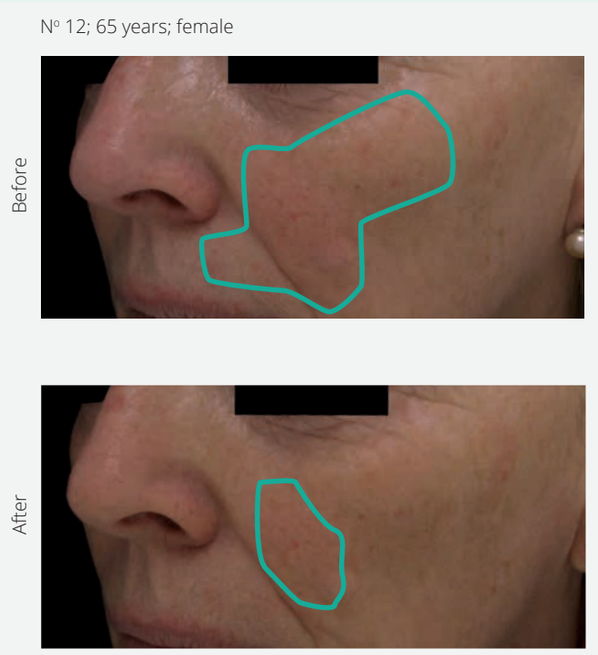


Figure 15: With its barrier-strengthening and inflammation-reducing characteristics, DEFENSIL®-PLUS is able to improve the appearance of couperose. Above: before application of DEFENSIL®-PLUS; **Below:** 6 weeks after application of a cream containing DEFENSIL®-PLUS.

DEFENSIL®-PLUS REDUCES THE SEVERITY OF COUPEROSE (*in-vivo* study)

Aim

The aim of the study was to prove that DEFENSIL®-PLUS could positively influence the severity of couperose, an early form of rosacea.

Method

1. Objective assessment of main parameters such as degree of redness, degree of inflammation and general appearance by dermatologists using a 100 mm analogue scale ranging from "poor condition" to "excellent condition". A numerical value was obtained by measuring the mark on the scale. The min./max. values were 0 and 100 units respectively. Areas of approx. 5 cm diameter in the area of the cheeks were assessed.
2. Determination of skin redness using a Minolta CM 700d spectrophotometer (L*a*b colour system). In the L*a*b system, a colour is represented in a three-dimensional coordinate system. The system uses three axes, one for green-red (a*), one for blue-yellow (b*) and one for brightness (L*). A falling a* value corresponds to less redness and thus to an improvement in the severity of the couperose.
3. In addition, the VISIA system was used to take digital photographs of 10 randomly selected test subjects before and after 6 weeks of application.

Implementation

Double-blind, placebo-controlled study. 20 volunteers (2 men, 18 women) with couperose and Caucasian skin type took part in the study. The age range was 23 – 65 years (average 49.2 years).

On one half of the face, a cream containing 3 % DEFENSIL®-PLUS [DEFENSIL®-PLUS 5, see test formulations for the efficacy studies] was applied twice daily over a period of 6 weeks. Placebo was applied on the other half of the face. Objective assessments of the skin condition as well as instrumental determination of skin redness before the start of the application period, after three weeks of application and at the end of the test.

Result

After just 3 weeks, the dermatologist confirmed that there had been significant improvements and after 6 weeks, the severity of visible and perceptible skin parameters such as degree of redness, degree of inflammation and general appearance had practically halved!

These findings were confirmed by the instrumental measurement of the skin redness: the degree of redness of the skin (a* value) decreased markedly within 3 weeks. The cream containing DEFENSIL®-PLUS was twice as effective as the cream without DEFENSIL®-PLUS.

Conclusion

DEFENSIL®-PLUS was very well tolerated in applications according to clinical-dermatological criteria. Therefore, DEFENSIL®-PLUS is ideally suited for concomitant care alongside couperose treatment.

This is true not only for the face, but also for the upper and lower thighs – there the condition is also known as spider veins – or for the feet. Dark circles around the eyes are also part of this condition.

The causes of underlying couperose skin often lie in adolescence – a time when fashion concerns may outweigh preventative health concerns. Wearing unsuitable footwear is one example worth mentioning here: the constant mechanical pressure is a frequent cause of couperose-like changes to the edges of the feet as people get older. Prevention is thus very important and DEFENSIL®-PLUS is ideal for that.

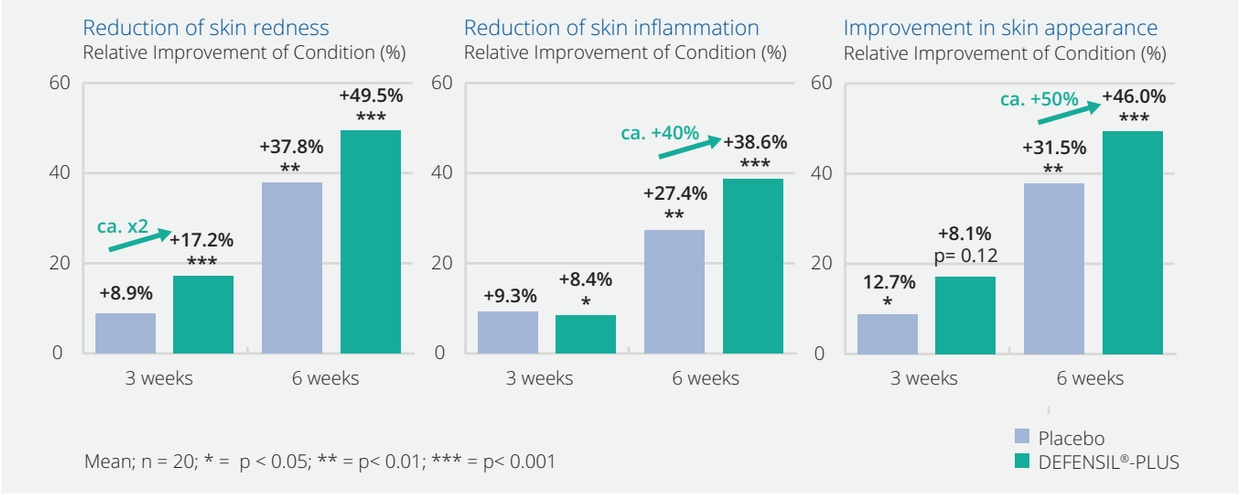


Figure 30: DEFENSIL®-PLUS improves the skin condition for people with couperose skin. The severity of visible and perceptible skin parameters such as degree of redness, degree of inflammation and general appearance were objectively assessed by dermatologists over time. **Left:** within just 3 weeks, 3 % DEFENSIL®-PLUS improved the degree of redness in comparison to the initial condition by a significant 17.2 % – thus the improvement is twice as pronounced as that achieved after application of placebo. After 6 weeks' application of DEFENSIL®-PLUS, the improvement was an impressive 49.5 %, i.e. the degree of redness was almost halved. **Centre and right:** there was also evidence of a marked reduction in the degree of inflammation (by 38.6 %) and a significant improvement in the general appearance (by 46.0 %), especially after 6 weeks. The statistical values refer to the comparison with the initial condition; mean; n = 20; two-sided, paired t-test; * means p < 0.05; ** means p < 0.01; *** means p < 0.001.

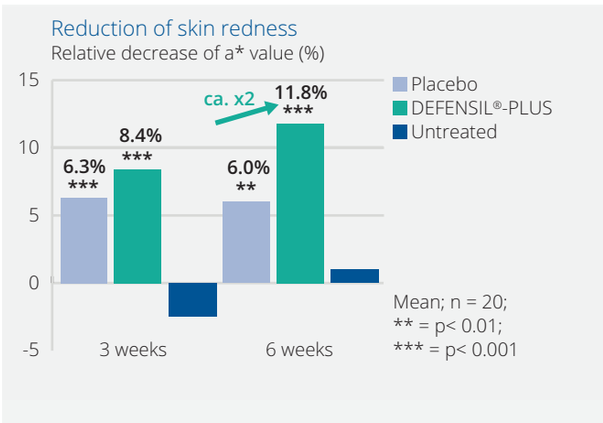


Figure 31: DEFENSIL®-PLUS leads to normalisation of skin redness in people with couperose skin. Treatment with 3 % DEFENSIL®-PLUS resulted in significantly lower measured a* values (= red portion) after 3 and 6 weeks in comparison with the initial values. In areas treated with placebo, the measured reduction was only half as significant. Untreated test areas showed no change. The statistical values refer to the comparison with the initial condition; two-sided, paired t-test; mean; n = 20; ** means p < 0.01; *** means p < 0.001.

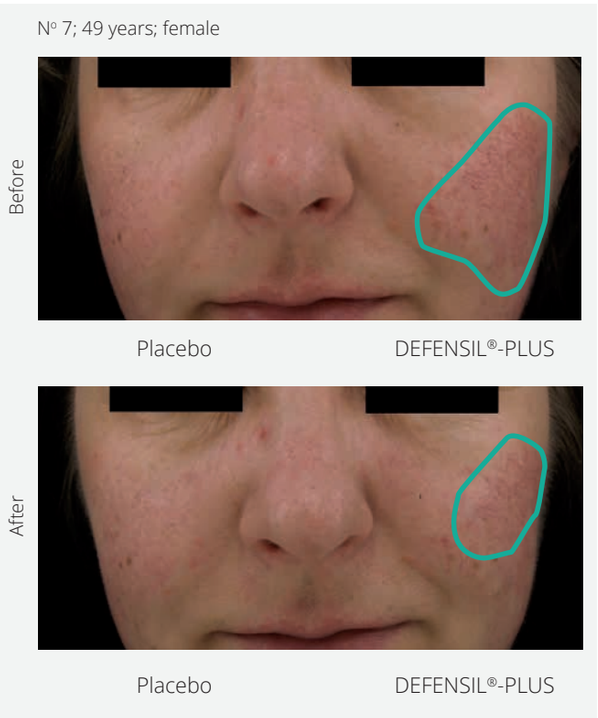


Figure 32: DEFENSIL®-PLUS provides a visible remedy for reddened, couperose-prone skin. Illustrative example.

Test formulations
for the efficacy studies

DEFENSIL®-PLUS 1 (700005.0005 | 0013)

St	Substance	INCI name USA	% [w/w]	Manufacturer
1	Water demin.	Water	Ad 100	several
	Euxyl PE 9010	Phenoxyethanol, Ethylhexylglycerin	1.00	Schuelke & Mayr, DE
2	Carbopol ETD 2020	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.40	Lubrizol, US
	Keltrol CG-SFT	Xanthan Gum	0.10	CP Kelco, US
3	DEFENSIL®-PLUS	Octyldodecanol, Ribes Nigrum (Black Currant) Seed Oil, Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables, Cardiospermum Halicacabum Flower/Leaf/Vine Extract, Tocopherol, Helianthus Annuus (Sunflower) Seed Oil, Rosmarinus Officinalis (Rosemary) Leaf Extract	0.00 or 5.00	RAHN AG, CH
4	NaOH solution 10%	Sodium Hydroxide, Water	1.20	several

Production
Mix 1 / Mix 2, add to 1 while stirring / Add 3 while stirring / Add 4 while stirring

DEFENSIL®-PLUS 2 (700005.0005 | 0014)

St	Substance	INCI name USA	% [w/w]	Manufacturer
1	Water demin.	Water	Ad 100	several
	Euxyl PE 9010	Phenoxyethanol, Ethylhexylglycerin	1.00	Schuelke & Mayr, DE
2	Carbopol ETD 2020	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.40	Lubrizol, US
	Keltrol CG-SFT	Xanthan Gum	0.10	CP Kelco, US
3	NaOH solution 10%	Sodium Hydroxide, Water	1.20	several
4	DEFENSIL®-PLUS	Octyldodecanol, Ribes Nigrum (Black Currant) Seed Oil, Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables, Cardiospermum Halicacabum Flower/Leaf/Vine Extract, Tocopherol, Helianthus Annuus (Sunflower) Seed Oil, Rosmarinus Officinalis (Rosemary) Leaf Extract	0.00 or 3.00	RAHN AG, CH

Production
Mix 1 / Mix 2, add to 1 while stirring until the phase is homogenous / Add 3 to neutralise / Add 4 while stirring, homogenise shortly

DEFENSIL®-PLUS 3 (700005.0006 | 0008 | 0009 | 0010)

St	Substance	INCI name USA	% [w/w]	Manufacturer
1	Water demin.	Water	Ad 100	several
	Glycerin 85%	Glycerin, Water	4.00	several
	Euxyl PE 9010	Phenoxyethanol, Ethylhexylglycerin	1.00	Schuelke & Mayr, DE
2	Keltrol CG-F	Xanthan Gum	0.20	CP Kelco, US
	Carbopol ETD 2020	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.40	Lubrizol, US
3	Cetiol SN	Cetearyl Isononanoate	2.50	BASF, DE
	DEFENSIL®-PLUS	Octyldodecanol, Ribes Nigrum (Black Currant) Seed Oil, Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables, Cardiospermum Halicacabum Flower/Leaf/Vine Extract, Tocopherol, Helianthus Annuus (Sunflower) Seed Oil, Rosmarinus Officinalis (Rosemary) Leaf Extract	0.00 or 1.00 or 2.00 or 4.00	RAHN AG, CH
4	NaOH solution 10%	Sodium Hydroxide, Water	1.20	several

Production

Mix 1 / Mix 2, add to 1 while stirring / Mix 3, add while stirring / Add 4 while stirring

DEFENSIL®-PLUS 4 (700005.0001)

St	Substance	INCI name USA	% [w/w]	Manufacturer
1	Water demin.	Water	Ad 100	several
	Glycerin 85%	Glycerin, Water	4.00	several
	Euxyl PE 9010	Phenoxyethanol, Ethylhexylglycerin	1.00	Schuelke & Mayr, DE
2	Carbopol ETD 2020	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.40	Lubrizol, US
	Keltrol CG-SFT	Xanthan Gum	0.20	CP Kelco, US
3	Cetiol SN	Cetearyl Isononanoate	2.50	BASF, DE
	DEFENSIL®-PLUS	Octyldodecanol, Ribes Nigrum (Black Currant) Seed Oil, Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables, Cardiospermum Halicacabum Flower/Leaf/Vine Extract, Tocopherol, Helianthus Annuus (Sunflower) Seed Oil, Rosmarinus Officinalis (Rosemary) Leaf Extract	3.00	RAHN AG, CH
4	NaOH solution 10%	Sodium Hydroxide, Water	1.00	several

Production

Mix 1 / Mix 2, add to 1 while stirring / Mix 3, add while stirring / Add 4 while stirring

DEFENSIL®-PLUS 5 (700005.0011 | 0012)

St	Substance	INCI name USA	% [w/w]	Manufacturer
1	Water demin.	Water	91.20	several
2	Carbopol ETD 2020	Acrylates/C10-30 Alkyl Acrylate Crosspolymer	0.40	Lubrizol, US
3	Sisterna SP70-C	Sucrose Stearate	0.50	Sisterna B.V., NL
	Keltrol CG-SFT	Xanthan Gum	0.20	CP Kelco, US
	Euxyl PE 9010	Phenoxyethanol, Ethylhexylglycerin	1.00	Schuelke & Mayr, DE
	Cetiol SN	Cetearyl Isononanoate	2.50	BASF, DE
	DEFENSIL®-PLUS	Octyldodecanol, Ribes Nigrum (Black Currant) Seed Oil, Helianthus Annuus (Sunflower) Seed Oil Unsaponifiables, Cardiospermum Halicacabum Flower/Leaf/Vine Extract, Tocopherol, Helianthus Annuus (Sunflower) Seed Oil, Rosmarinus Officinalis (Rosemary) Leaf Extract	3.00	RAHN AG, CH
	or Myritol 312 (Placebo)	Caprylic / Capric Triglyceride	3.00	BASF, DE
4	NaOH solution 10%	Sodium Hydroxide, Water	1.20	several

Production

Prepare 1 / Add 2 while stirring / Mix 3, add to 1/2 while stirring, homogenise / Add 4, homogenise

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