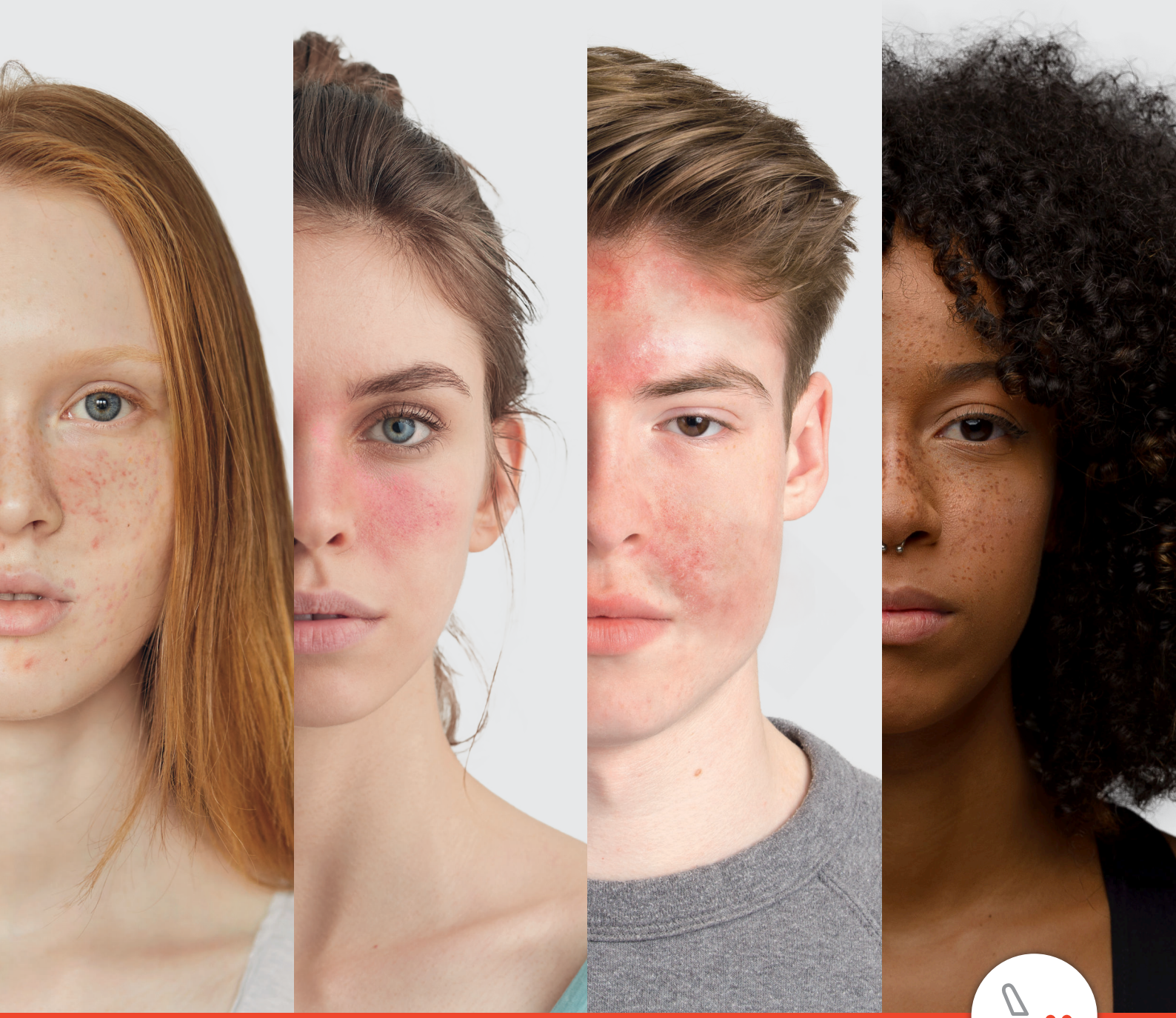

Cleoderm™

Skin Rebalancing Cream

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Fagron
personalizing medicine

Summary

INTRODUCTION

Dermatological skin conditions are a large number of clinical manifestations that can affect between 30% and 70% of the population worldwide,[1] and they can vary greatly in symptoms and severity. In the United States, they can affect one in every three Americans, and in 2013, skin diseases were responsible for $ 75 billion in costs to the healthcare system.[2,3] In Europe, more than 40% of the population has already reported some kind of skin condition.[1]

Some of these conditions can present more or less impact on the quality of life of different individuals, and their knowledge is of high importance to determine the diagnosis, as well as the adequate treatment, both professional and home care.[1] Acne, rosacea, dermatitis, and hyperpigmentation are among the most common ones, and they can affect the patient simultaneously, or as a consequence of each other.[1,2]

Some conditions can have a genetic background, and others can be a result of lifestyle and other external causes, but in any case, adequate treatment is a key to improving the life quality of patients. Most of these conditions respond well to topical treatments, especially personalized ones, and the adequate choice of the vehicle to compound those treatments is paramount to ensure their success.

Cleoderm™ is a topical cream designed to be used as a vehicle for the compounding of personalized dermatological treatments. Its ingredient profile was specifically designed to be gentle on the skin to allow for its use as a vehicle for compounded preparations that may be applied to the face. **Cleoderm™** has a positive role in decreasing sebum production, lipid peroxidation, and reactive oxygen species, as well as inhibition of *Cutibacterium acnes* proliferation, and control of inflammation. The ingredient profile of **Cleoderm™** makes it a good choice as a vehicle for topical use for inflammatory skin conditions, or conditions in which inflammation can worsen its severity.

This brochure describes the four presented skin conditions above and their impact in patient's life quality, and how **Cleoderm™** can play an important role for their personalized treatment.

1. ACNE VULGARIS

Acne vulgaris, also commonly known only as acne, can be understood as an inflammatory disease that affects the pilosebaceous follicles.[4] It is one of the most prevalent skin disorders worldwide (and the most common skin condition associated with the inflammation of the pilosebaceous unit), affecting all ethnic and age groups, regardless of sex, nationality, or socioeconomic status.[5–8] The incidence in adult women is around 12%, and among adolescents of 12 to 18 years old, more than 85%.[9,10] The common skin manifestations are comedones, papules, pustules, cysts, nodules, and scars.[6]

The presence of acne lesions may result in loss of self-confidence, anxiety, or community avoidance,[11] and may also affect the sexual quality of life in adult patients.[12]

In addition, relapses are frequent (44% in the general population: 39.9% of ≤20-year-olds vs. 53.3% of >20-year-olds) and often associated with impaired quality of life and a decrease in productivity or even absenteeism.[13]

There is also evidence that acne can impact the difficulties in emotion regulation (DER) scale, notably in the form of anxiety and depression.[14,15] This occurs because acne lesions can become scarring, which can have an impact on psychological factors.

Acne scars can be divided into three main groups: ice pick scars, rolling scars, and boxcar scars, as well as some less common lesions such as sinus tracts, hypertrophic scars, and keloidal scars (Figure 1).[16]

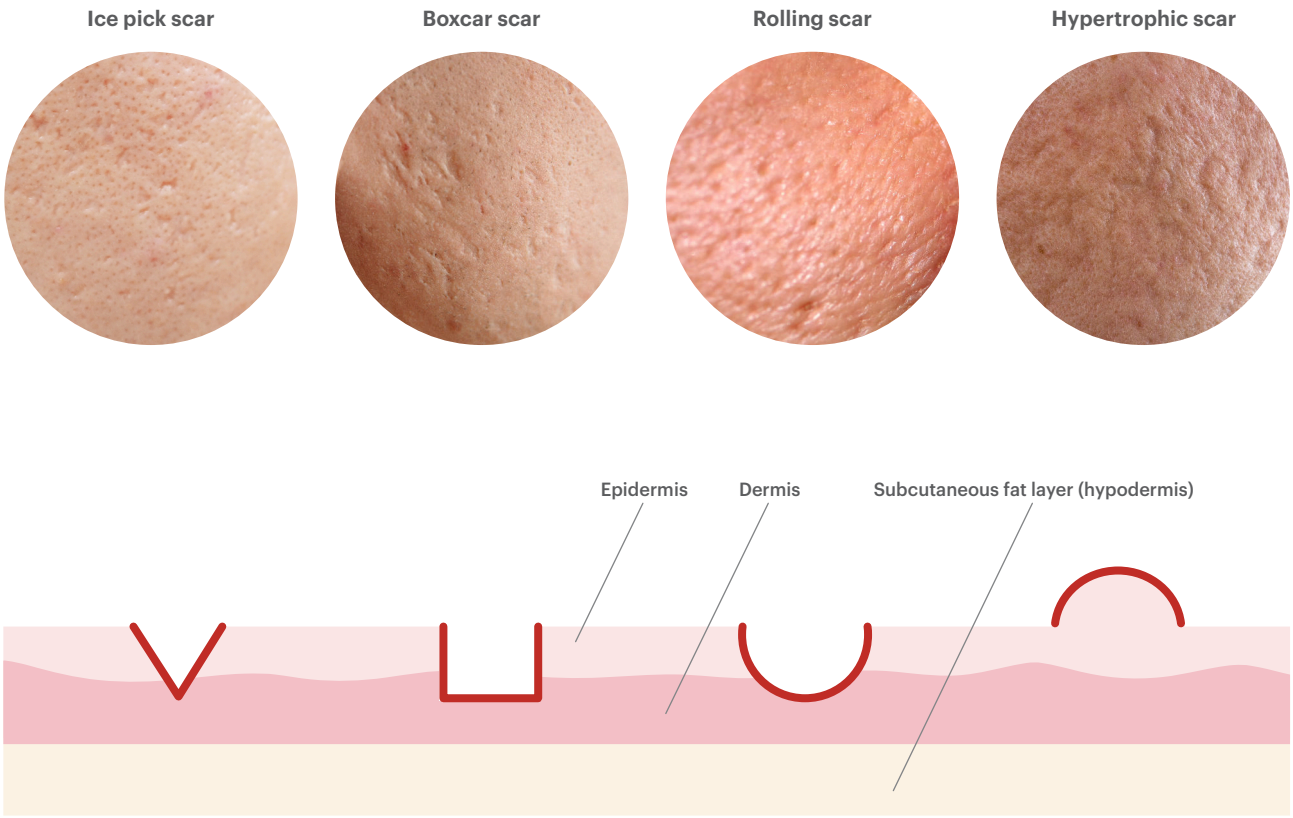
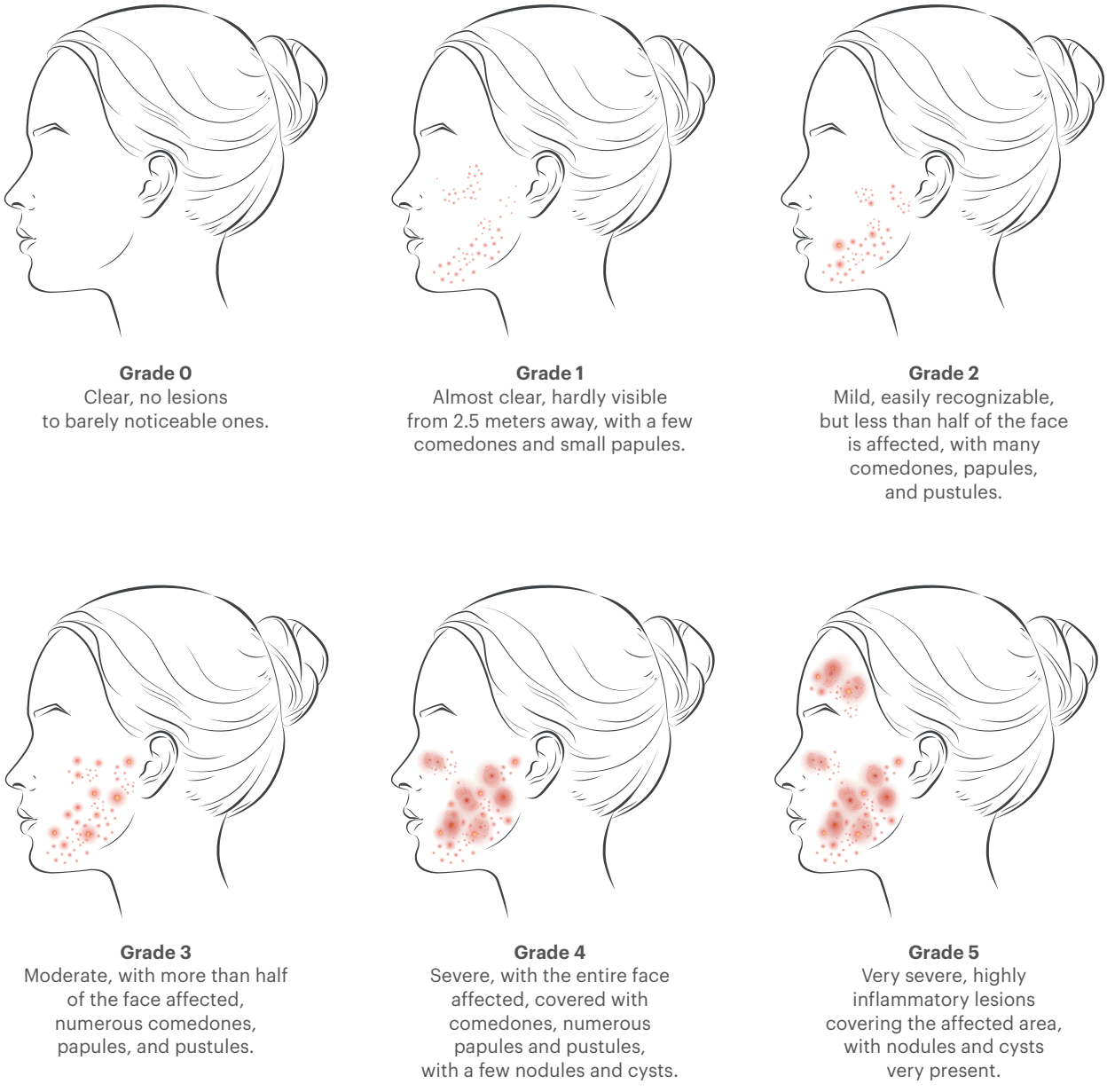


Figure 1. Examples of the different types of scars that can be resulted from acne lesions. Adapted.[16]

1.1 Acne classification

Different scales can be used to grade and classify acne according to its severity. One of the most used systems to make this classification is the Global Acne Severity Scale, which scales facial acne severity from grade 0 to 5, according to the number and type of lesions (Figure 2).[17]

Furthermore, the European Guidelines classify acne in 4 different levels (comedonal, mild to moderate papulo-pustular, severe papulopustular/moderate nodular, and severe nodular/conglobate),[20] and the American Guidelines classify acne in 3 levels (mild, moderate, and severe).[21]



Grade 0
Clear, no lesions to barely noticeable ones.

Grade 1
Almost clear, hardly visible from 2.5 meters away, with a few comedones and small papules.

Grade 2
Mild, easily recognizable, but less than half of the face is affected, with many comedones, papules, and pustules.

Grade 3
Moderate, with more than half of the face affected, numerous comedones, papules, and pustules.

Grade 4
Severe, with the entire face affected, covered with comedones, numerous papules and pustules, with a few nodules and cysts.

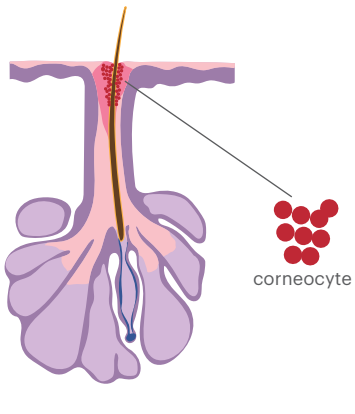
Grade 5
Very severe, highly inflammatory lesions covering the affected area, with nodules and cysts very present.

Figure 2. Acne classification. Adapted.[18,19]

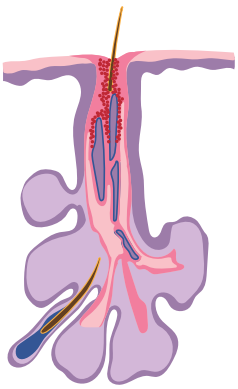
1.2 Acne pathogenesis

Despite its high prevalence, the multifactorial etiology of acne is not yet fully elucidated. The main accepted mechanism involves changes in the pilosebaceous unit through the hyperkeratinization of the pore, overproduction of sebum, and excessive proliferation of *Cutibacterium acnes* (formerly known as *Propionibacterium acnes*, an anaerobic bacteria with philia for lipidic environments) – leading to inflammation of the hair follicle.[22,23]

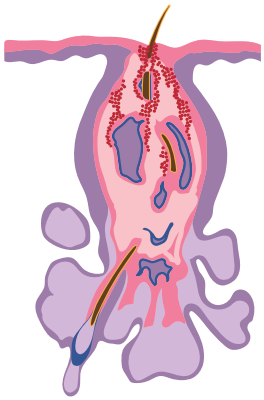
The initial process is the formation of microcomedones, which evolve into macro (visible to the naked eye) comedones (blackheads or whiteheads), and can develop into inflammatory red papules or pustules – usually on the face, neck, chest, and upper back, where the number of sebaceous follicles is higher (Figure 3). These lesions can then be resolved or develop complications, leading to the emergence of scars, either atrophic or hypertrophic.[24]



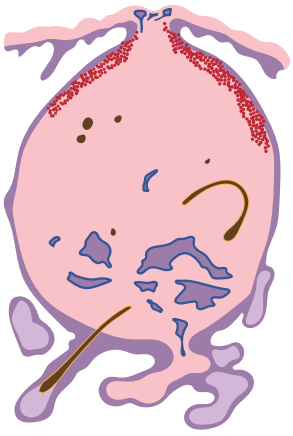
1. **Microcomedone**
   Agglomeration of corneocytes due to increased keratin production and sebum secretion.



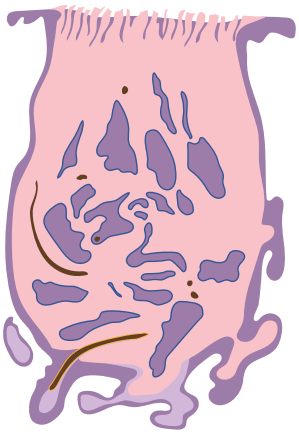
2. **Later comedone**
   Corneocytes and sebum accumulation form a plug that can be a closed comedo (whitehead) or open comedo (blackhead).



3. **Papule/Pustule**
   Mild inflammation generated by *C. acnes* proliferation, triggering an immune response.



4. **Cyst/Nodule**
   Marked inflammatory response.



5. **Pustule**
   Rupture of the follicular wall. Scarring process.

Figure 3. Acne formation process. Adapted.[25,26]

1.2.1 Skin microbiome

The skin microbiome balance is important because this area is colonized by different microorganisms, such as *Staphylococcus epidermidis* and *Streptococcus pyogenes*. While *S. epidermidis* limits the number of *C. acnes* in the skin, *C. acnes* also limits *S. aureus* and *S. pyogenes*. Thus, dysbiosis can affect the skin barrier and cause inflammation.[4,27]

The fungus *Malassezia furfur* is also involved in the process, as it can decompose fatty acids and release irritant chemicals to the skin, in addition to the secretion of allergenic proteins and peptides.[28]

1.2.2 Receptors in the sebaceous glands

Sebum production is highly implicated in acne pathophysiology, and to date, it is known that it can be induced by six receptors expressed in the sebaceous gland (Figure 4):

- Leptin receptor - activated by fat;[29]
- Insulin-like growth factor (IGF)-1 receptor - activated by sugar;[30]
- Peroxisome proliferator-activated receptors (PPARα, β, and γ) – activated by free fatty acids and cholesterol;[31]
- Histamine receptor - activated by histamines;[32]
- Hormonal DHT receptor - activated by androgens;[33]
- Neuromodulator receptor (substance P and corticotrophin-releasing hormone (CRH) receptor) - activated by stress.[34]

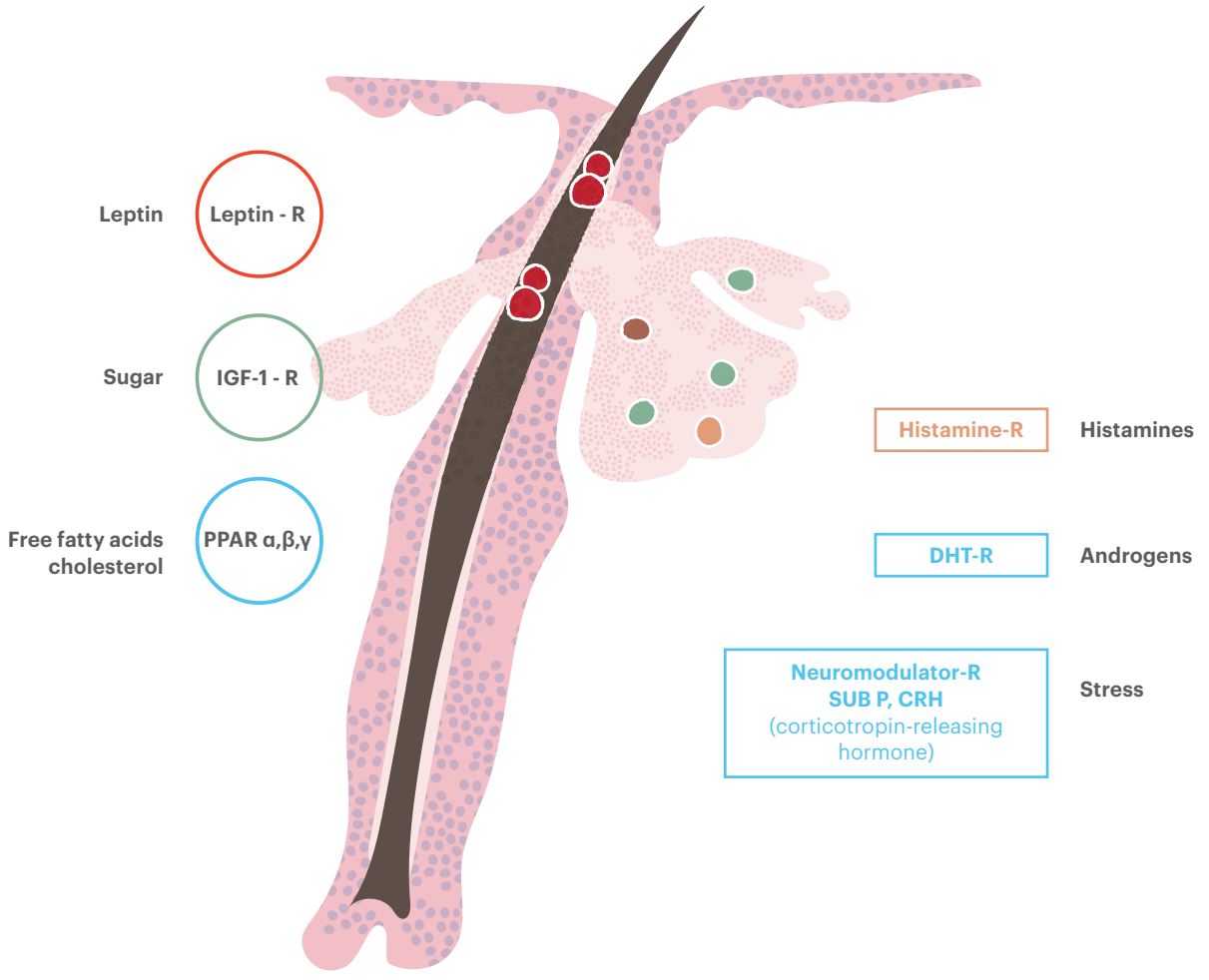


Figure 4. Main receptors involved in sebum production, and their activators. Adapted.[4]

1.2.3 Endocannabinoid and immune systems

Another possible player in the development of acne vulgaris is the endocannabinoid system in the skin, which can be involved in different processes, such as differentiation from epidermal appendages (e.g., sebaceous glands). Additionally, it also appears to be involved in sebum secretion control.[35]

The immune system can also play a role in acne emergence (Figure 5). *C. acnes* can promote the release of cytokines, causing the activation of the innate immunity, which can result in the hyperkeratinization of the pilosebaceous unit. [4,36]

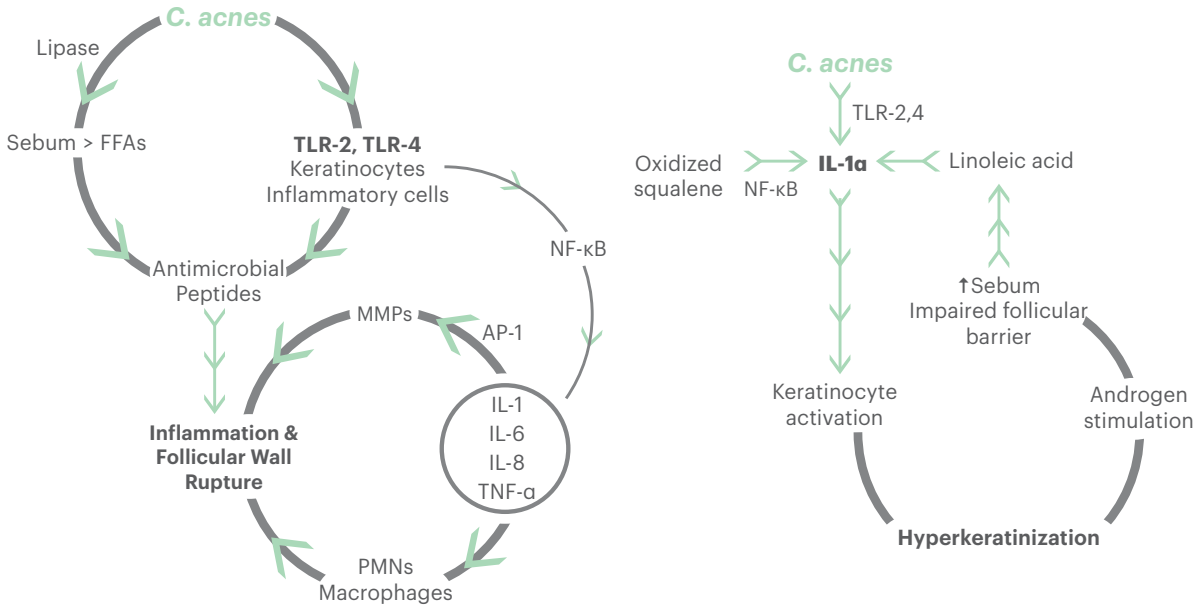


Figure 5. Effect of *C. acnes* in innate immunity and its correlation to acne mechanisms. Adapted.[37] AP: activator protein, FFA: free fatty acid, IL: interleukin, MMP: matrix metalloproteinases, NF: nuclear factor, PMNs: polymorphonuclear leukocytes, TLR: toll-like receptor, TNF: tumor necrosis factor.

1.2.4 Exposome

Exposome can be understood as the sum of internal and external factors that the person is exposed to from conception until death.[38] In this context, the main internal factors related to acne are:

- *C. acnes* abnormal proliferation in the skin, due to dysbiosis;
- Elevated sebum production;
- Alteration of follicular epithelium (hyperkeratinization, due to the hyperseborrhea);
- Inflammatory processes, both in innate and acquired immunities.[39,40]

In addition, the external factors that can play a role in both the severity and treatment efficacy of the disease are:

- **Nutrition (diet)**: mainly dairy products and hyperglycemic carbohydrates;
- **Medication**: hormonal treatments, such as contraceptives, replacement therapies, and anabolic, corticosteroids and immunosuppressants;
- **Occupational factors**: usage of inadequate or aggressive cosmetic products, mechanical stress such as scrubbing and rubbing, affecting the skin microbiome balance, or creating an inflammatory response;
- **Pollutants**: external, such as toxic substances present in the air, or internal, such as tobacco and other drugs exposure, increasing the oxidative damage to the skin;
- **Sun exposure**: ultraviolet radiation triggers inflammatory reactions;
- **Weather factors**: temperature and humidity can trigger the hyperkeratinization of the skin;
- **Psychosocial and lifestyle parameters**: stress, sleep quality, and emotional variations, all inflammatory and oxidative factors.[41,42]

1.3 Differential diagnosis

Although acne diagnosis presents no major difficulties, it is important to evaluate possible overlapping conditions that may occur and can cause some clinical confusion. Some of these conditions may include: rosacea, folliculitis, milia, perioral dermatitis, drug eruptions, verrucas, ulrythema ophryogenes, and steacystoma multiplex.[43,44]

1.4 Acne suggested treatments

The treatment of acne should be based on 3 fronts: the control and healing of existing lesions, preventing scarring, and reducing the duration of the condition. Also, individual patient factors, such as current medication, the severity of the lesions, and endocrine history should be evaluated before the definition of the type of treatment which can be topical or systemic.[39,45]

Topical treatments have the advantage of being applied directly in the affected areas, minimizing systemic side effects. The most common topical treatments for acne include:

- **Retinoids**: topical retinoids have potent anti-inflammatory properties, decreasing sebum production, therefore reducing the formation of lesions and comedones. They can be used as a monotherapy for inflammatory or severe forms of acne, or in combination with other therapies for maintenance treatment. Most used retinoids include tretinoin, adapalene, and tazarotene.[39,45]
- **Antibiotics**: mostly used in severe cases of acne, they present antimicrobial activity against *C. acnes*, reducing the stimulus for inflammation on the skin. The most popular antibiotics used topically for acne treatment are clindamycin, erythromycin, and tetracyclines.[39,44,45]
- **Chemical peels**: acids such as glycolic acid, kojic acid, lactic acid, and salicylic acid, stimulating skin rejuvenation and re-epithelization.[45]
- **Diverse treatments**: other common topical treatments used for acne can be benzoyl peroxide, a comedolytic and antibacterial agent; azelaic acid, with anti-inflammatory, antioxidant, and anti-keratinizing properties; niacinamide, inhibiting sebum production and with anti-inflammatory properties; corticosteroids; dapsone, an antibacterial and anti-inflammatory substance.[45]

In some cases, systemic treatments can be necessary, according to the severity of lesions and inflammation. The most common oral systemic treatments include retinoids such as isotretinoin, antibiotics, and hormone therapies.[45]

2. ROSACEA

Rosacea is a chronic skin inflammation that mainly affects the face. Its clinical manifestations are flushing erythema, telangiectasias, papules, pustules, burning sensation, dryness, edema, and infiltration of the face skin. However, it may also present hyperplasia and hypertrophy of sebaceous glands, with sudden and repeated episodes of vasodilation.[46–51]

Rosacea affects adults between 30 and 50 years, with a higher incidence in women and greater severity in men.[48,49,52] The worldwide distribution of rosacea seems to vary between 2% and 22%.[48] While there is a prevalence related of up to 10% of the general population in countries such as Sweden, individuals with skin phototypes IV to VI (according to the Fitzpatrick classification)[53] seem to be less subjected to the disease, which can be attributed to a difficulty in diagnosing due to the imperception of clinical manifestations, such as flushing and erythema.[46,54,55]

The centrofacial fixed erythema is the most frequent manifestation of rosacea. Initially, there is transient vascular dilation and intermittent erythema insidiously. Subsequently, erythema becomes persistent and bilaterally affects specific skin regions such as zygomatic and malar, nasal, menthol and forehead; and inflammatory papules and pustules appear. Finally, infiltration with edema occurs, and hypertrophy of the sebaceous glands in the nose region (rhinophyma, a late complication of the disease and occurs more commonly in men).

One of the possible explanations is persistent lymphedema and follicular obstruction by sebaceous secretion, which occurs even in the absence of vascular alteration.[48]

2.1 Rosacea classification

Rosacea can be classified according to its primary features, therefore being defined in 4 subtypes (Figure 6) and 1 variant:

- **Subtype 1**: Erythematotelangiectatic (ETR), which is characterized by flushing, erythema, and telangiectasias (common, but not essential);
- **Subtype 2**: Papulopustular (PPR), with persistent erythema and telangiectasias, with the presence of papules and pustules;
- **Subtype 3**: Phymatous, with fibrotic changes and glandular hyperplasia, in combination or not with subtypes 1 and 2;
- **Subtype 4**: Ocular, presenting a watery or bloodshot appearance to the eyes, foreign body sensation and blepharitis, are the most common symptoms, but conjunctivitis, iritis, keratitis, and episcleritis are also described;
- **Variant**: Granulomatous rosacea, characterized by hard, yellow to red cutaneous papules or nodules, normally less inflammatory than papules and pustule.[51,52,56]

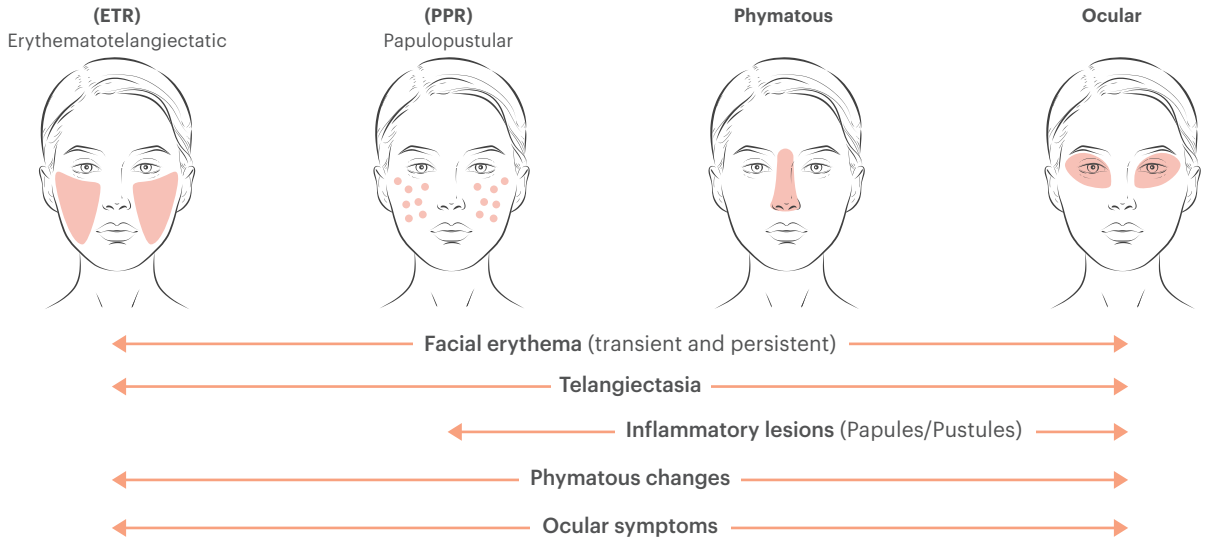


Figure 6. Common clinical presentations of rosacea. Adapted.[50]

2.2 Rosacea pathogenesis

The etiology of rosacea is multifactorial (Figure 7). In addition to genetic predisposition and association with lower phototypes, family history and environmental factors are also involved. Climate change is a provocative or aggravating factor of the disease, such as exposure to cold and warmth, sunlight, the use of cosmetics inappropriately, and emotional aspects. The practice of physical activity and the use of vasodilator drugs, such as antihypertensive drugs, are also considered triggering factors.[46]

Concerning diet, hot beverages such as coffee, alcoholic beverages, and spicy foods, may be implicated in vascular alteration. In this sense, rosacea patients should avoid the consumption of pepper, seafood, teas, coffee, and alcohol.[46,48]

These stimuli induce flushing episodes with damage to the endothelium, leading to angiogenesis and inflammatory changes in the dermis with the production of vasoactive substantiations and worsening of the vascular condition.[48]

Affected skin may have an abnormal response to catecholamines such as epinephrine, norepinephrine, acetylcholine, and histamine.[46] In addition, the type of affected skin (dry and seborrheic skin), abnormalities of the immune system, neurovascular dysregulation, transepidermal water loss (TEWL), and changes in cutaneous pH, when associated with triggering factors, are the main elements involved in the pathophysiology of the disease.[48]

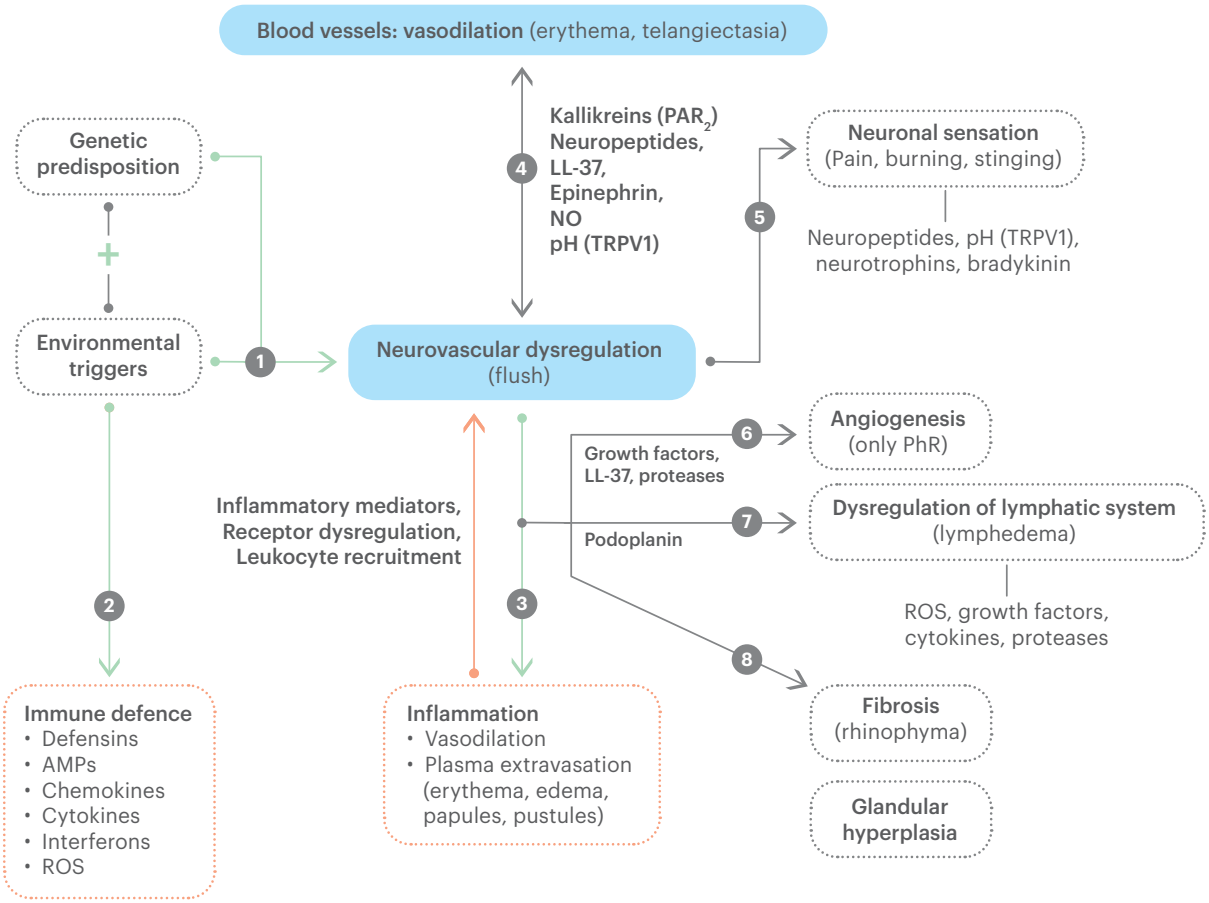


Figure 7. Potential pathophysiological mechanisms of rosacea. Adapted.[52]

Colonization by *Demodex folliculorum*, a commensal mite that parasitizes the hair follicle, produces inflammatory changes leading to the opening of the follicular wall and damage to the cutaneous barrier.[57] Dry or seborrheic skin may have higher levels of infestation of this mite when compared to skins with normal levels of hydration and sebaceous secretion.[58]

Some authors also describe the relationship of rosacea with dyspeptic disorders, more specifically concurrent with the diagnosis of *Helicobacter pylori*.[47,48] Rosacea may also be associated with inflammatory intestinal disease, thyroid disease, and liver disease. In addition, supplementation with vitamins B6 and B12 and treatment with interferon and ribavirin can act as possible triggers.[59]

Studies indicate that patients with papulopustular rosacea may have a disequilibrium in the concentrations of fatty acids present in sebum. Myristic acid may be in higher concentrations, while long-chain saturated fatty acids (behenic, tricosanoic, and lignoceric) and cis-11-eicosanoic monounsaturated acids may be at lower concentrations in the sebum of patients with the classification of rosacea.[60]

As for the immune system, the disregulation of the innate immune response increases the secretion of antimicrobial peptides (AMP) and inflammatory cytokines via activation of toll-like receptors 2 (TLR-2).[48] There is an increase in the production of cathelicidins, which are AMPs found in macrophages and neutrophils. Specifically, cathelicidin LL-37 (Figure 8) is processed by proteases and generates fragments of peptides that cause even more inflammation, erythema, and telangiectasias.[61] Ultraviolet radiation (UVR) and colonization by *Demodex folliculorum* are factors that increase cathelicidin expression.[46]

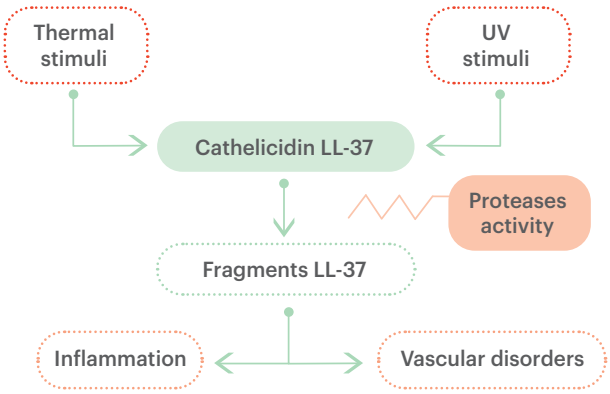


Figure 8. Role of cathelicidin LL-37 in the pathogenesis of rosacea. Adapted.[46]

In rosacea, there is an altered vasoactive response and a neurovascular dysfunction, leading to erythema formation in the face region. Again, the exacerbated production of cathelicidin LL-37, together with predominantly mononuclear inflammatory infiltrate and increased endothelial vascular growth factor (VEGF), are indicated as one of the stimuli for angiogenesis and neovascularization.[52] In addition, local temperature changes lead to exacerbated vasodilation or vasoconstriction reactions.[46]

Damage to the epidermal barrier due to inflammation leads to an increase in TEWL. The pH of the skin surface also changes with these alterations, becoming more alkaline (Figure 9). Therefore, there is a lower tolerance to topical products in the skin of these affected patients, such as soaps, hot water, and topical acids, leading to a burning sensation and itching.[46,62]

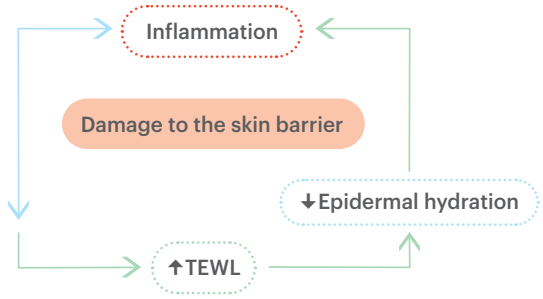


Figure 9. Relationship between skin barrier damage and skin inflammation. The inflammatory process reduces barrier function; together with vasodilation, there is an increase in TEWL with consequent reduction of epidermal hydration levels, constituting another stimulus to inflammation. Adapted.[46]

2.3 Differential diagnosis

Rosacea diagnosis can be sometimes confused with other skin disorders such as acne, or dermatitis. Rosacea differs from Acne vulgaris due to the absence of vascular patterns and the presence of open and closed comedones in the last one. Seborrheic dermatitis involves extra facial regions such as retroauricular and presternal. Also, areas typically not affected by rosacea include the scalp, nasolabial sulcus, and intergluteal sulcus; however, both diseases can coexist. Perioral dermatitis occurs around the lips, sparing the skin/mucosal transition, consisting of papules and pustules on an erythematous base, which may be associated with topical and inhaled corticosteroids and fluoride toothpaste.

For rosacea fulminans, a specific subtype of rosacea, the differential diagnoses include folliculitis and acne caused by Gram-negative bacteria, fungal infections, and mycobacteria.[59] Other differential diagnoses are cutaneous lupus, cutaneous tuberculosis, light polymorphic eruption, Jessner lymphocytic infiltrate, and sarcoidosis.[48]

2.4 Rosacea suggested treatments

Some studies show that inadequate topical products may worsen rosacea, whereas adequate care can help restore the skin barrier, helping to control symptomatology and inflammation.[46]

General care should include cleaning with soap-free agents or products for sensitive skin such as micellar water, mild soaps with pH 5.5, daily moisturizers with ceramides, hyaluronic acid, glycerin, allantoin, or niacinamide – and without alfa-hydroxy acids. Photoprotection with a sun protection factor above 30 and preferably with zinc oxide or titanium dioxide is recommended. Patients should avoid waterproof cosmetics, exfoliating agents, and products containing alcohol, menthol, camphor, sodium lauryl sulfate, and strong fragrances.[63]

Antimicrobials of the tetracycline class and metronidazole are the most used active pharmaceutical ingredients (APIs). Other recommended topical treatments include azelaic acid, brimonidine tartrate, oxymetazoline, and ivermectin.[63–65]

Concerning oral treatments, the common indications are doxycycline, oral isotretinoin, and drugs from the class of tetracyclines (such as tetracycline itself, lymecycline, and minocycline), macrolides (such as azithromycin), and also oral metronidazole, with less scientific evidence.[64,66,67]

For the flushing, treatment with intense pulsed light and intradermal application of botulinum toxin can be used.[68–70]

3. SEBORRHEIC DERMATITIS

Dermatitis is the name given to a group of skin conditions that can cause inflammation, itching, desquamation, and burning sensation in the affected areas. There are several types of dermatitis, and the most common ones are atopic dermatitis, contact dermatitis, and seborrheic dermatitis.[71]

3.1 Dermatitis classification

The dermatitis types can be divided and classified mainly according to their areas of occurrence and according to the cause of the condition:

3.1.1 Atopic dermatitis

Also known as eczema, the atopic dermatitis is a chronic condition that affects mainly the flexural surfaces of the skin but is not limited to them. It is caused by a genetic disturbance in the skin barriers, leading to a dysregulation of the immune system, resulting in itching, scratching and inflammation.[72–74] Atopic dermatitis can have three different clinical phases, starting with the acute phase, characterized by crusting eruptions on the skin; the subacute phase, with dry, scaly, erythematous papules; and the chronic phase, with a dry, scaly, popular form.[74]

3.1.2 Contact dermatitis

Contact dermatitis is the most frequent skin disorder, and it is triggered by the direct contact of the skin with environmental factors, followed by the activation of the immune response, creating a hypersensitivity.[75,76] Contact dermatitis can be divided into irritant and allergic, depending on the type of the activation factor (irritants, such as chemicals, or allergens, such as pollen, among others).[76,77]

3.1.3 Seborrheic dermatitis

Seborrheic dermatitis is a relapsing disease characterized by erythema and scaling of the skin. In some cases, there is associated pruritus, which mainly affects the central region of the face, ears, scalp, and central part of the chest.[78,79] For this reason, this material will be focused on this class of conditions (Figure 10).

It can affect all ages, but it has a bimodal age distribution, with a peak in early childhood (2-12 months) and the second peak in adolescence, after puberty.[78,80] It affects more men than women due to the more significant presence of androgens in that population, increasing the activity of the sebaceous glands.[80]

The prevalence in the general population is 1 to 3%, from which 3 to 5% are in young adults, and 34 to 83% in immunocompromised patients, especially HIV-positive patients.[81] In this population, the condition is more prevalent when the disease progresses with a reduction in the CD4 cell count, evidencing the influence of the immune system in the clinical manifestation.[82] By a mechanism not yet known, it still affects 20 to 60% of patients with Parkinson's disease, often as an early symptom,[83] and seems to be worsened in those treated with levodopa.[84]

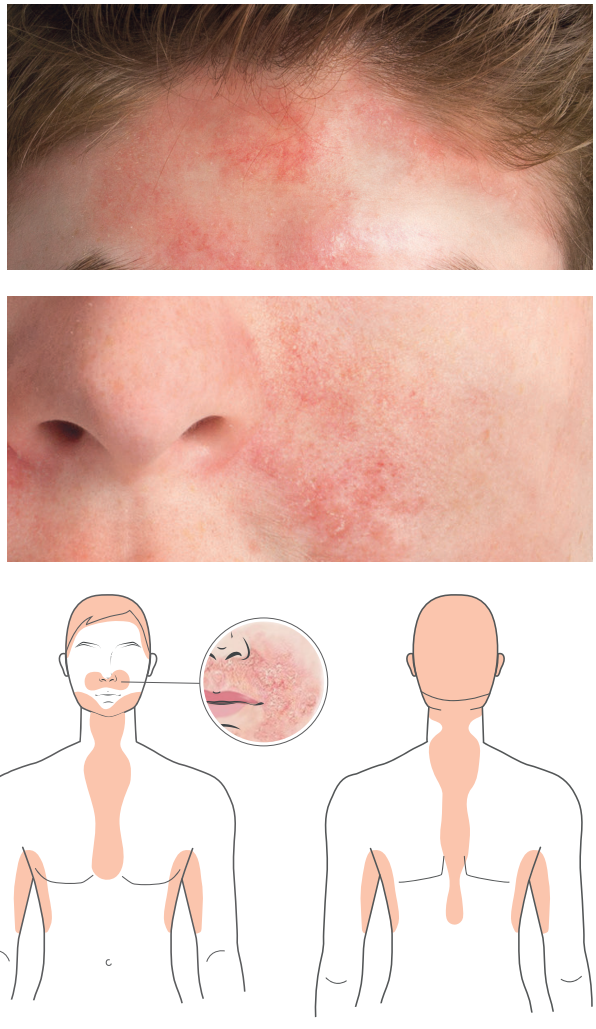


Figure 10. Seborrheic dermatitis affected regions. Adapted.[78]

3.2 Seborrheic dermatitis pathogenesis

The etiology of seborrheic dermatitis is not yet fully understood. However, it is known that several factors influence the disease, such as hormone levels, presence of fungi (*Malassezia* spp)[78] and mites (Demodex),[57] keratinocytes, sebocytes, neurological alterations[83] in addition to the immune response against altered skin lipid composition.[80,81] Even though it is not a disease of the sebaceous glands, it is understood that their presence is necessary since it occurs in areas where there is a more significant predominance of sebocytes (face, scalp, central part of the chest). In addition, the infantile form occurs with decreasing intensity in the first months of life until the first year, when maternal androgen hormones, passed transplacentally, can stimulate gland hypertrophy and gradually decrease.[78]

The following pathophysiological sequence is proposed: after sebaceous secretion, there is local colonization by *Malassezia*. These microorganisms generate oxidative pathways, activating the inflammatory response and releasing cytokines such as IL-1α, IL-1β, IL-2, IL-4, IL-6, IL-8, IL-10, IL-12, and TNF-α. This cascade, in turn, stimulates the proliferation and differentiation of keratinocytes, promoting a change in the skin barrier, which clinically manifests as erythema, pruritus, and desquamation (Figure 11).[80]

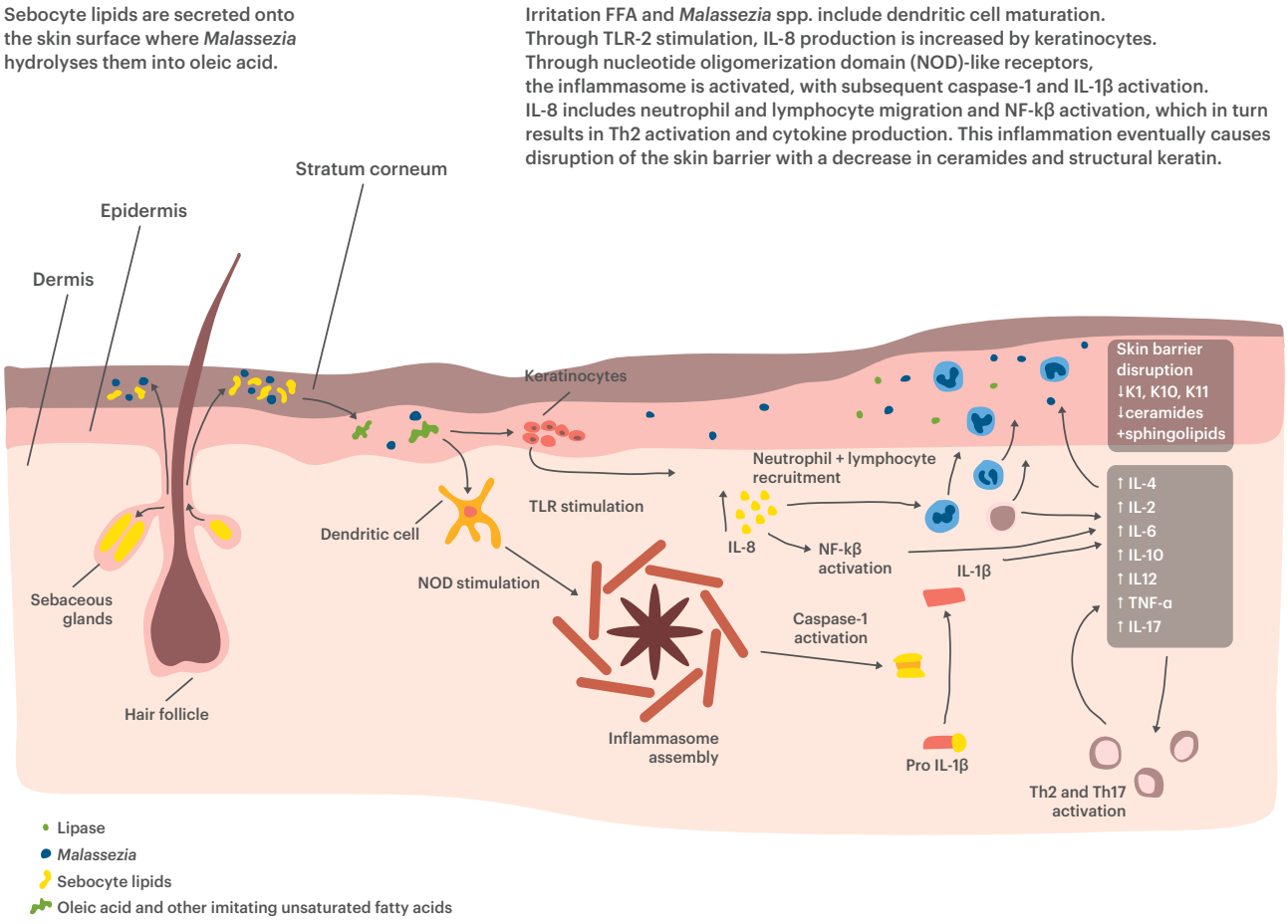


Figure 11. Sequence of the inflammatory cascade in seborrheic dermatitis. Adapted.[80]

3.2.1 Exposome

Exogenous factors that can influence on seborrheic dermatitis are:

- The presence of *Malassezia* and other microbiota;
- Humid climate;
- Poor hygiene;
- Use of some medications such as anticancer and neuropsychiatric medications.[80]

Endogenous factors that can play a role in the development and severity of seborrheic dermatitis include:

- Male gender;
- Increased androgen activity;
- Sebaceous gland activity;
- Lipid composition;
- Immune response.

In children, after the maternal hormones decrease, there is a reduction in the activity of the sebaceous glands until puberty, when they return to activity due to the stimulation of sex hormones. When the production of tallow increases, the then low, however, present population of *Malassezia* has a new food source and proliferates.[85] Males are also more prevalent, as they have higher circulating androgens.[80]

3.3 Differential diagnosis

The diagnosis of seborrheic dermatitis is clinical, based on the location and characteristics of the lesions. A biopsy is usually unnecessary but may be indicated in uncertain cases. In the anatomopathological examination, there is no pathognomonic characteristic of the disease.[84] The primary differential diagnoses are atopic dermatitis, rosacea, psoriasis, candidiasis, tinea, lupus erythematosus, and Langerhans cell histiocytosis.[78]

3.4 Seborrheic dermatitis suggested treatments

Considering the chronic and relapsing characteristics of seborrheic dermatitis, the objective of treatment is the disappearance of clinical manifestations and symptoms, normalizing the structure and function of the skin, and maintaining remission of the disease in the long term.[86] Given the various factors involved in the condition's pathophysiology mentioned above, several treatments are proposed.

Topical antifungal treatment is considered first-line, aiming to control the *Malassezia* population. Topical azole derivatives (cream, gel, shampoo) such as ketoconazole, clotrimazole, miconazole, metronidazole, bifonazole and terbinafine have shown great effectiveness.[87,88] Topical metronidazole, not only because it is antifungal but due to several mechanisms, has also proved to be effective in the treatment of dermatitis.[89]

Topical anti-inflammatories such as fluocinolone, betamethasone valerate, desonide, tacrolimus, and pimecrolimus can also be applied to the skin and scalp.[78] They can be used alone or in combination with antifungals. However, prolonged use is not recommended due to possible adverse effects such as telangiectasias, hypertrichosis, atrophy, and perioral dermatitis.[86]

Keratolytic agents such as salicylic acid, coaltar, and zinc pyrithione have also been used.[78] Benzoyl peroxide is one of the top acne treatments because of its antibacterial and comedolytic properties. However, the same proved to be helpful in the control of dermatitis in the face and trunk.[90,91]

Natural topical treatments can also be applied, such as Aloe vera, which has anti-inflammatory, antibacterial, antifungal, and hypoglycemic properties,[92,93] borage oil (extracted from the *Borago officinalis* plant), an essential oil that contains approximately 25% gamma-linoleic acid,[94] tea tree oil, with action against several types of skin infections, anti-inflammatory, antioxidant, and anti-neoplastic effects.

Topical treatments for seborrheic dermatitis are the first choice. However, severe and recalcitrant cases may require systemic treatments, such as fluconazole, itraconazole, terbinafine, isotretinoin, and even oral corticosteroids.[86]

4. HYPERPIGMENTATION

Hyperpigmentation is a common skin condition that affects many patients, being a frequent complaint in dermatological practice. Hyperpigmentation has many psychological and cultural implications, as it alters the patient's self-image, and can occur at any age, with a similar incidence in men and women.[95,96]

Although all skin types can be affected, individuals with skin phototypes III to VI are more likely to develop hyperpigmentation than those with skin phototypes I and II and have a more severe and persistent condition (Figure 12).[97,98] The prevalence of hyperpigmentation in individuals with high phototypes affected by acne is around 65%.[97] This could be related to the more significant amount of epidermal melanin present in the melanosomes of the epidermis in this population. It has also been proposed that individual differences in the way melanocytes respond to inflammation influence the risk of hyperpigmentation.[99,100]

Figure 12. Hyperpigmentation in Fitzpatrick type IV skin (up) versus VI (down). Note the greater intensity of pigmentation in darker skin.

4.1 Hyperpigmentation classification

4.1.1 Post-inflammatory hyperpigmentation

Post-inflammatory hyperpigmentation is an acquired hyperchromia that occurs due to skin inflammation, characterized by an overproduction of melanin in response to a stimulus that can be endogenous (when it results from inflammatory and autoimmune diseases) or exogenous (when it results from inflammation related to chemical or physical damage).[101] The most common causes of hyperpigmentation include acne vulgaris, eczematous dermatoses, and burns. It can also be caused by psoriasis, lichen planus, drug-induced phototoxicity, and cosmetic procedures. The excess pigment can range from a few inconvenient hyperpigmented macules to large patches of skin.[95]

Post-inflammatory hyperpigmentation can be a result of several mechanisms, such as the direct stimulation of melanocytes by inflammatory mediators (IL-1a, endothelin-1), reactive oxygen species generated by damages to the skin (i.e. UV exposure), or direct damages to the skin.[102]

4.1.2 Melasma

Melasma is a not fully understood hyperpigmentation disorder. It is mainly characterized by asymmetric, brown-colored spots that appear on the face and neck areas, especially when exposed to sunlight.[103,104] This condition affects predominantly women, and it is also more prevalent in high-skin phototypes individuals.[103]

Despite its cause is not well defined, some factors have been associated with the disease, such as hormone production (being a common condition during or after pregnancy), genetic predisposition, sun exposure (UV radiation increases melanocytes activity), and other factors such as some cosmetics composition and the usage of some medicines (i.e. antiepileptic).[103,104]

4.1.3 Solar lentigos

Also known as age spots, lentigines, and liver spots, this hyperpigmentation occurs mostly in areas chronically exposed to sunlight, such as hands, arms, face, and neck.[102,104] Age spots are brown and vary in shape, scale, and color, and their appearance is the result of chronic inflammation of the melanocytes and subsequent change in the genetic expression of both melanocytes and keratinocytes.[102]

4.2 Hyperpigmentation pathogenesis

Physiologically, melanin is mainly found in the basal layer of the epidermis and is not present in the dermis. Epidermal hypermelanosis occurs when the basal layer and the dermo-epidermal junction (DEJ) are preserved, with minimal inflammation and limited hyperpigmentation to the epidermis (Figure 13). Excess melanin is caused by an increase in its production and transfer, resulting from the release and oxidation of arachidonic acid into prostaglandins and leukotrienes or from the effects of other inflammatory mediators on the damaged skin. These inflammatory substances damage both immune cells and melanocytes, which are stimulated to increase melanin synthesis and transfer to surrounding keratinocytes. Hyperpigmentation is rarely restricted to the epidermis.[97,101]

Dermal melanosis, also called pigmentary incontinence, occurs when inflammation leads to a rupture of the basal layer of the epidermis, causing the release of melanin in the papillary dermis. Macrophages in the papillary dermis phagocytize the released melanin and are called melanophages. Melanin can remain in dermal macrophages for years.[99]

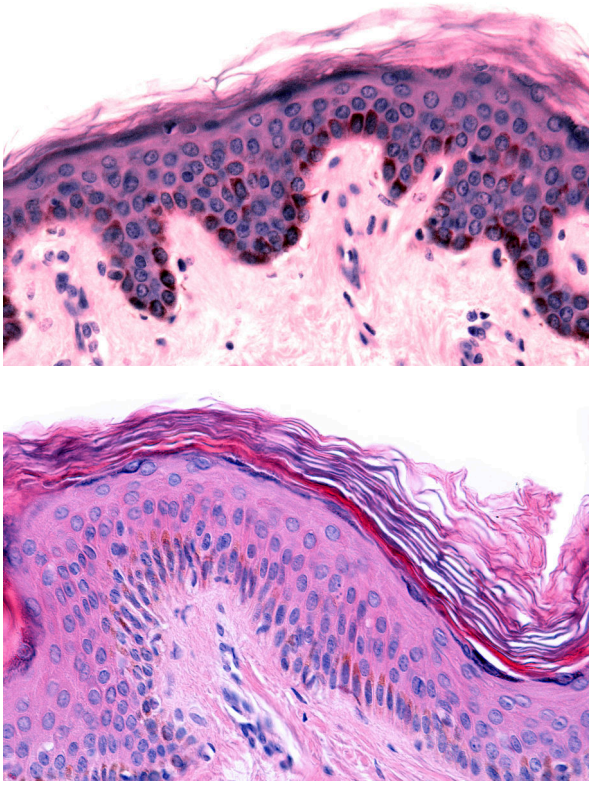


Figure 13. Up: A hystopathology shows hyperpigmentation of the basal layer. Down: A hystopathology shows hyperpigmentation in the deeper layers.

The course and outcome of hyperpigmentation are unpredictable, and post-treatment relapse is prevalent. The clinical manifestations of epidermal melanosis can take months to years to resolve without treatment. Manifestations of dermal melanosis may persist for years and may be permanent. Available interventions for hyperpigmentation primarily reduce epidermal pigment production or distribution. Therefore, in patients with hyperpigmentation in dermal macrophages, the response to treatment tends to be lower. The duration of hyperpigmentation may be longer in individuals with higher phototypes when compared to lower phototypes. Persistent or relapsing inflammation and ultraviolet irradiation can exacerbate the condition.[100]

4.3 Differential diagnosis

The diagnosis of hyperpigmentation relies mainly on the differentiation between its pathogenesis, combined with a clinical evaluation of the patient, allowing for the adequate management of the condition considering its severity, depth, and mechanism.[105]

4.4 Hyperpigmentation suggested treatments

Treatment of hyperpigmentation should be based on interventions to prevent the persistence or exacerbation of inflammation and treatment methods to disperse or destroy melanin at hyperpigmentation. The underlying inflammatory condition must be treated aggressively. The prevention of the involvement of new areas of the skin must be carried out through the treatment of the triggering factor of hyperchromia and the performance of photoprotection. Photoprotection reduces the risk of additional ultraviolet radiation-induced darkening of the affected skin and may allow for the best treatment results. This should be accomplished by using broad-spectrum sunscreens and hats, and sun protection clothing.[95,106]

- **Topical hydroquinone**: hydroquinone suppresses the conversion of dihydroxyphenylalanine (DOPA) to melanin by inhibiting the enzyme tyrosinase, which reduces the formation of melanin in melanosomes. Hydroquinone is less effective for hyperpigmentation, where pigment deposition is primarily in dermal melanophages, as these cells have minimal or absent tyrosinase activity. Other potential mechanisms of hydroquinone activity include inhibition of DNA and RNA synthesis, selective cytotoxicity towards melanocytes, and melanosome destruction.[97,106]

Although hydroquinone is widely used for hyperpigmentation, data on its effectiveness for it are limited. Evidence of efficacy for hyperpigmentation mainly derives from studies of patients with melasma. Prolonged daily use of hydroquinone at 4% or more can trigger inflammatory reactions such as contact dermatitis, and high concentrations of hydroquinone, above 5 to 6%, have been associated with hypopigmentation or persistent depigmentation.[97]

- **Topical retinoids**: retinoids can inhibit melanogenesis by increasing keratinocyte turnover, reducing melanosome transfer, and inhibiting tyrosinase transcription. There are three forms available for topical use: retinoic acid, adapalene, and tazarotene. Studies show that retinoids effectively treat hyperpigmentation alone or in combination with other agents. Irritant contact dermatitis is a common adverse effect of topical retinoids, particularly early in therapy. Therefore, there is a need for greater care for patients with higher skin phototypes because irritation can contribute to the development of additional hyperpigmentation.[106]

- **Triple combination**: the classic triple combination associates hydroquinone, retinoic acid, and a topical corticosteroid. In addition to the direct benefit of hydroquinone as a depigmenting agent, retinoic acid inhibits its oxidation and improves epidermal penetration. In addition to inhibiting melanin synthesis, corticosteroids increase the tolerability of the formula, a common adverse effect.[107]

- **Azelaic acid**: azelaic acid may improve hyperpigmentation by inhibiting tyrosinase and have selective cytotoxic and antiproliferative effects on abnormal melanocytes through inhibiting mitochondrial enzymes and DNA synthesis.[96,97]

- **Kojic acid**: kojic acid is a fungal derivative of certain species of Acetobacter, Aspergillus, and Penicillium. Its depigmenting ability originates from a potent inhibition of tyrosinase by chelation of copper at the enzyme's active site. Studies demonstrate the effectiveness of 2% kojic acid associated with glycolic acid or hydroquinone in the treatment of melasma. However, studies are still needed to determine its role in hyperpigmentation. Its common adverse effect is contact dermatitis.[95,96]

- **Arbutin**: arbutin is a derivative of hydroquinone extracted from the leaves of bearberry, pear, cranberry, or blueberry plants. It promotes depigmentation by inhibiting tyrosinase activity and melanosome maturation without melanotoxic effect. Its effectiveness depends on the concentration, but higher concentrations can lead to paradoxical hyperpigmentation. Synthetic forms of arbutin, alpha-arbutin, and deoxyarbutin, have a more remarkable ability to inhibit tyrosinase than the natural compound. However, clinical studies evaluating arbutin for the treatment of hyperpigmentation in higher skin phototypes are lacking.[95,96]

- **Niacinamide**: niacinamide is derived from vitamin B3 and is a physiologically active agent. *In vitro* studies show that niacinamide significantly decreases the transfer of melanosomes to keratinocytes without inhibiting tyrosinase activity or cell proliferation. It can also interfere with the cell signaling pathway between keratinocytes and melanocytes to reduce melanogenesis. However, studies are needed to determine its safety and efficacy in treating hyperpigmentation.[95]

- **Chemical peels**: a chemical peel is the application of an agent to the surface of the skin, resulting in controlled damage. Superficial chemical peels, which exfoliate part or all of the epidermis, have a whitening effect by promoting the dispersion of melanin in the basal layer. Superficial chemical peels are often used in combination with other therapies in the treatment of hyperpigmentation. The choice of agent used must be made with care to avoid possible irritation, which can worsen hyperpigmentation. In addition, after performing the procedure, the patients should be instructed not to expose themselves to the sun and to use sunscreen to avoid relapses. The most cited peels are salicylic acid 20 to 30%, glycolic acid 50 to 70%, and trichloroacetic acid 15 to 20%.[95,108]

- **Lasers**: due to the broad absorption spectrum of melanin as a chromophore, various lasers have been studied as potential treatments for hyperpigmentation. Different types of lasers, including Q-switched ruby lasers, Q-switched Nd: YAG lasers, and picosecond lasers (short and intense pulse), have been used to treat hyperpigmentation based on small, uncontrolled, and non-standardized studies with small samples. Lasers can be used alone or in combination with topical medications and chemical peels, but they should be used with caution by experienced clinicians as they can cause skin irritation and additional hyperpigmentation. The use of lasers for hyperpigmentation treatment is still a controversial topic without large randomized clinical trials.[106,109]

5. THE ROLE OF DERMOCOSMETIC TREATMENTS

Considering the many possible causes and the chronic aspects of different skin diseases, the focus of treatments is to control existing symptoms and limit the duration of the disorder, avoiding permanent scarring as much as possible, along with other possible complications. To choose the best strategy for treatment, individual patient factors must be taken into consideration, such as medical condition, disease state, the severity of the lesions, patient history, and the preferred type of treatment (oral or topical).[45,86]

When it comes to topical treatments, different preparations can be used such as creams, ointments, solutions, and lotions, among others, but many of these bases formulations contain ingredients that can be irritating or allergenic for sensitive and affected skin, such as petrolatum, mineral oils, lanolin, perfumes, polyethylene glycol, and fatty alcohols.[110]

In addition, the base should be able to promote the adequate percutaneous absorption of different APIs, ensuring the success of dermatological treatments.[111]

The selection of the API for different skin diseases, as well as their dosage, should be based on the severity of each case. Most of these ingredients can be formulated in several forms, but the adequate combination of the API with a suitable cream base can help to decrease possible side effects, increase patient adherence to treatment, and improve the general aspect of the skin.[112]

6. CLEODERM™ SKIN REBALANCING CREAM

A functional vehicle for affected and sensitive skin

Cleoderm™ is a functional vehicle with selected ingredients that make it the ideal choice for compounding topical treatments for affected and sensitive skin. Its main constituents are *Cleome gynandra* L. leaf extract, palmitoyl tripeptide-8, bisabolol, hyaluronic acid, and functional oils (avocado, jojoba, dog rose, coconut, English lavender, tea tree, rosemary, shea tree, and vitamin E acetate). This unique combination of ingredients provides **Cleoderm™** with great anti-inflammatory and humectant properties, as well as sebum production control.

Key points:

- Highly spreadable;
- Light skin feel;
- Readily absorbed;
- Non-comedogenic;
- Dermatologically tested.

Figure 14. Cleoderm™ ingredients.

6.1 Cleoderm™ composition

6.1.1 Cleome gynandra L. leaf extract

Known by common names such as Gynandropsis, cat's whisker, and African spider flower, *C. gynandra* has anti-inflammatory and antioxidant activities[113,114], as well as positive effects on wound repair[115] and skin allergy/itching.[116]

- Rich in rutin and hydroxycinnamic acid;
- Reduces seborrhea by acting on specific lipids associated with acne;
- Improves sebum quality by rebalancing its composition;
- Reduces inflammation.

Cleoderm™ contains a patented *C. gynandra* leaf extract within a specific diluent. The main components of this product are polyphenols, notably rutin and hydroxycinnamic acid. These substances can act synergistically on decreasing sebum secretion and inflammation (through the inhibition of *C. acnes*, and suppression of TLR2, IL-8,and neutrophils).[117-119]

A series of *in vitro* and *ex vivo* tests were conducted with the such component, and the main results are graphicallydescribed here.

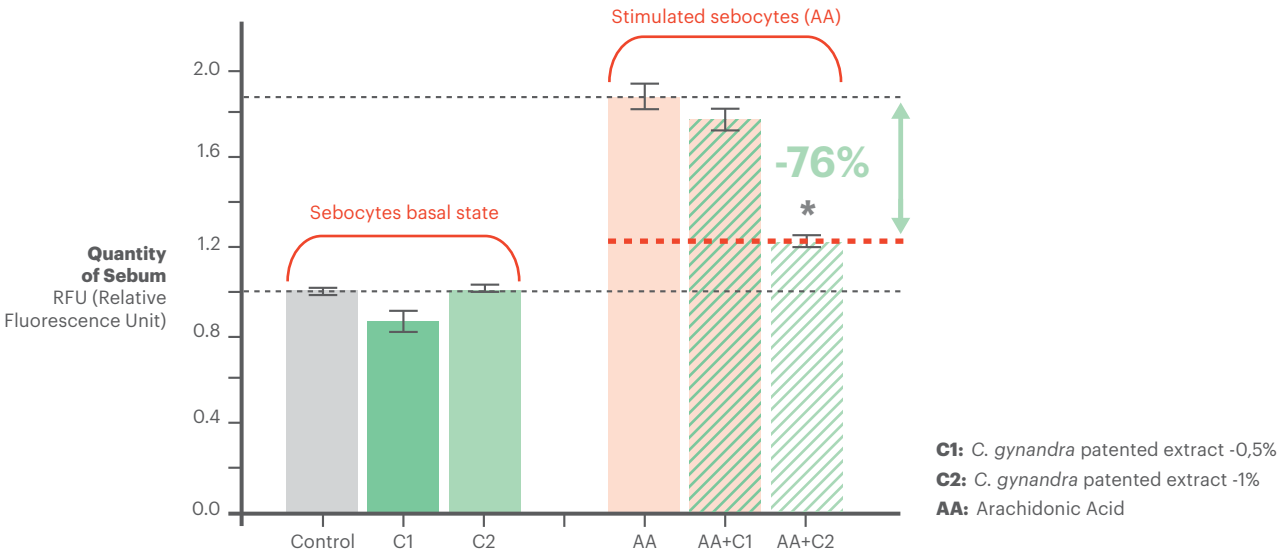


Figure 15. Stimulation of seborrhea with arachidonic acid (AA) inflammatory stress, in human sebocytes model. Lower and higher concentrations of *C. gynandra* extract decreased the quantity of sebum in both stimulated and non-stimulated sebocytes. *p<0.05

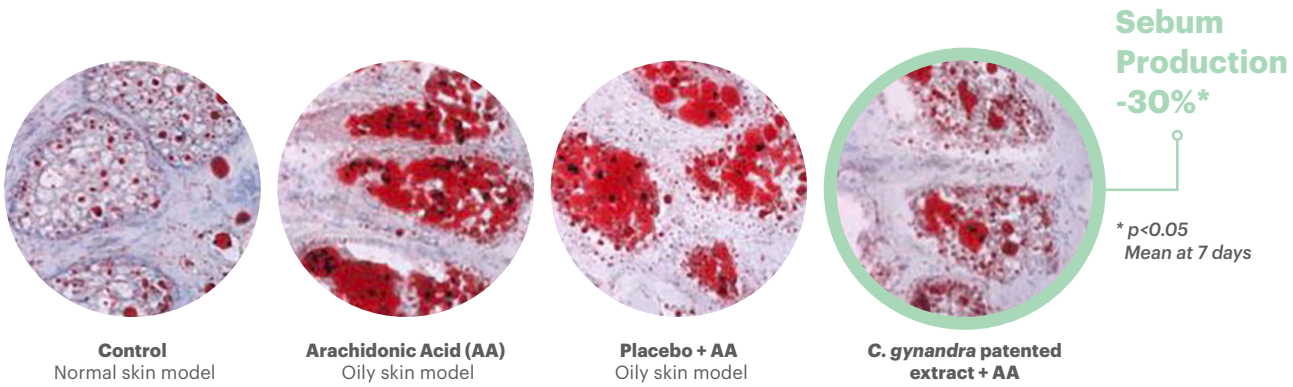


Figure 16. Sebum quantity assessment (Oil-Red-O staining). Explants from human skin, next to the scalp area, treated with arachidonic acid to simulate the inflammatory phase of acne. *C. gynandra* was able to decrease by up to 30% the quantity of sebum after 7 days.

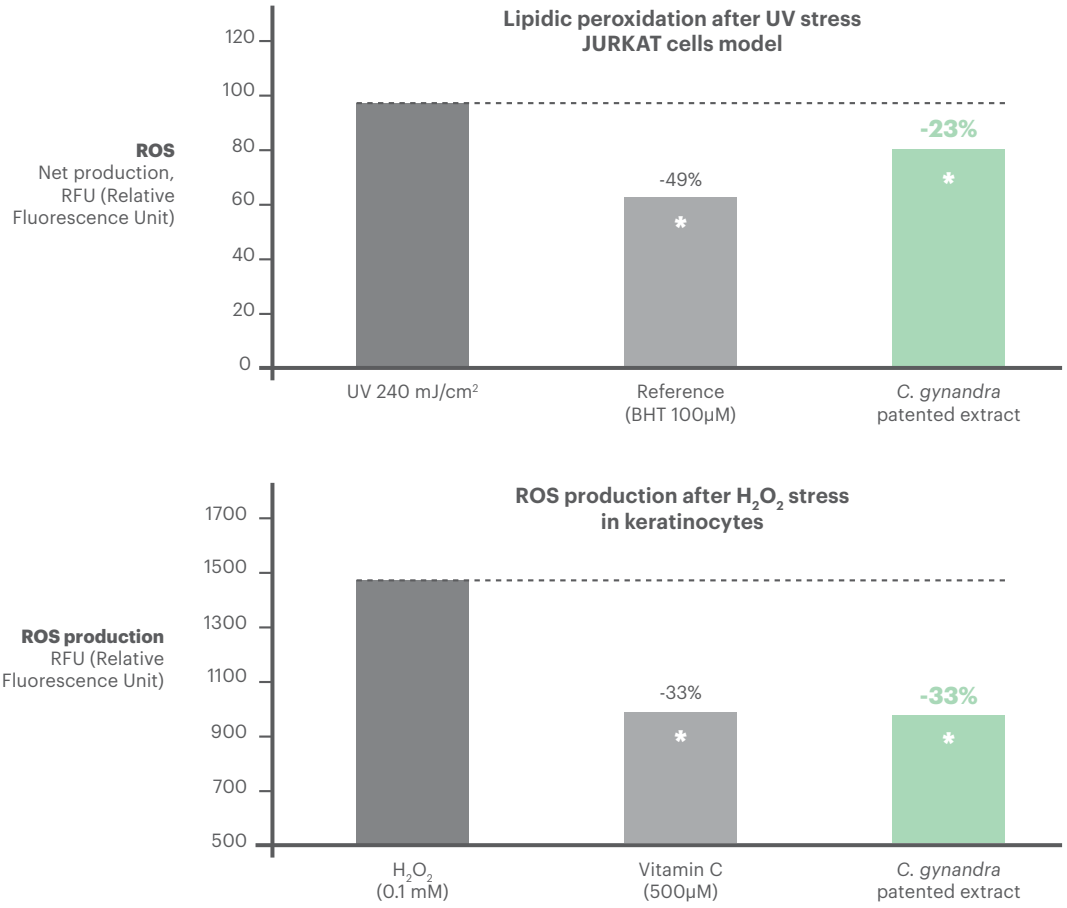


Figure 17. Acne severity is frequently associated with reactive oxygen species (ROS) quantity, and consequently oxidation of squalene. Acneic skins present two times more squalene than healthy skin; in addition, squalene is highly susceptible to oxidation, and peroxidized squalene is comedogenic and pro-inflammatory. *C. gynandra* patented extract was able to reduce lipid peroxidation and ROS production, improving sebum quality. *p<0.05

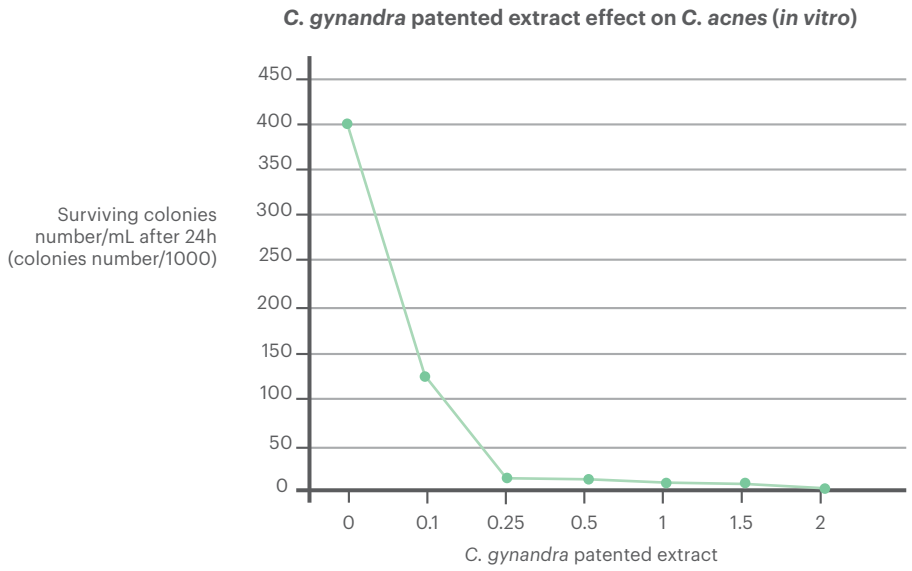


Figure 18. The antimicrobial components of *C. gynandra* patented extract was able to decrease the *C. acnes* population, helping the skin to protect itself against bacterial proliferation.

Figure 19. The effects on neutrophil migration can be observed, showing the anti-inflammatory effect of the *C. gynandra* patented extract. Neutrophils produce LTB4, which increases inflammation and sebum production. *C. gynandra* patented extract was able to decrease neutrophil migration by 48%, and LTB4 release by 67%. LTB4: Leukotriene B4. *p<0.05.

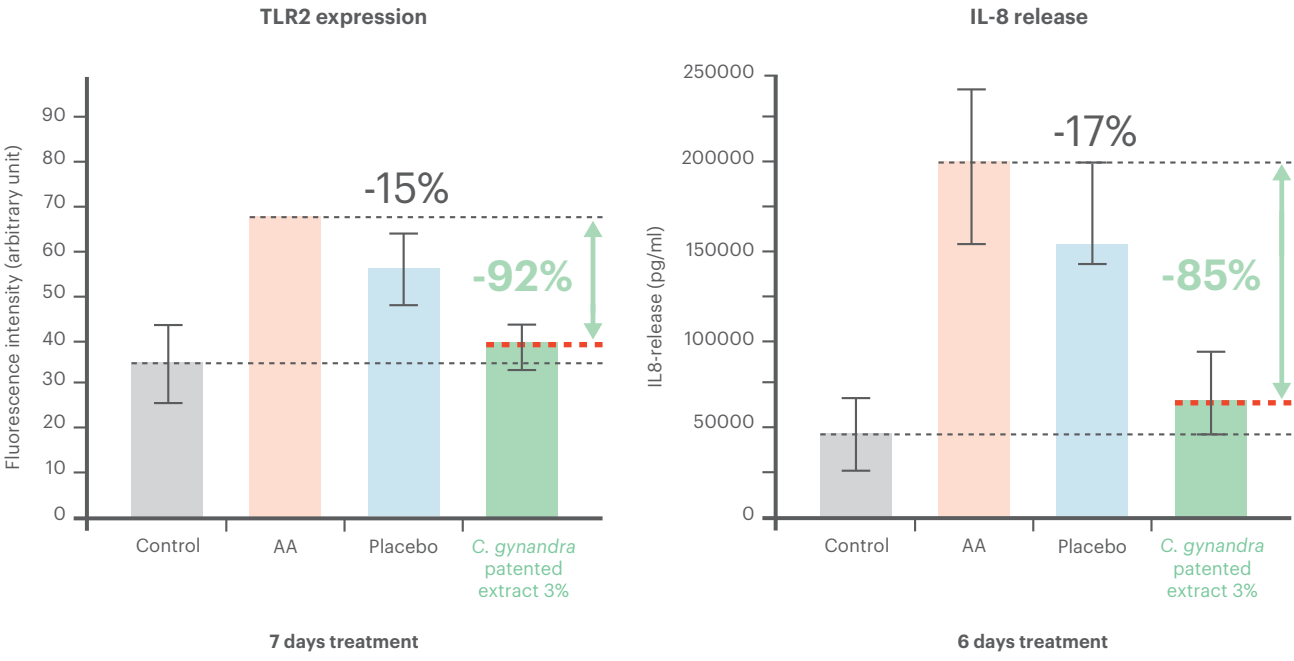


Figure 20. TLR2 is a natural receptor of the human immune system that, when activated by *C. acnes*, generates inflammation. Once TLR2 is activated, IL-8 is then released. As it can be observed, *C. gynandra* patented extract was able to decrease up to 92% of the TLR2 expression, and up to 85% of the IL-8 release, due to its anti-inflammatory properties. AA: arachidonic acid.

6.1.2 Palmitoyl tripeptide-8

- Anti-inflammatory and soothing agent;
- Lipopeptide derived from a neuromediator;
- Prevents and reverses signs of neurogenic inflammation.

6.1.3 Bisabolol

Bisabolol can reduce proinflammatory cytokine production (e.g., TNF-α and IL-6), which can aid in the treatment of inflammatory conditions of the skin, ameliorating its aspect.[120]

- Potent antioxidant and anti-irritant properties;
- Restores suppleness and protects the skin against daily environmental stress;
- Promotes percutaneous absorption of active ingredients (skin-penetration enhancer).

In addition to the reduction of proinflammatory markers, bisabolol can also reduce oxidative stress[121] and proved to be safe for topical application on the skin.[120] Due to its anti-inflammatory and antibacterial activities, it can help to treat skin wounds and burns[122,123] as well as act as a penetration enhancer.[124]

6.1.4 Hyaluronic acid

Hyaluronic acid has shown a range of different activities on the skin: buffering action, due to its excellent viscoelastic properties after water absorption;[125] anti-inflammatory and antibacterial properties;[126,127] antioxidant capacity;[128] and accelerator of the wound healing process.[127,129,130]

- Improves skin hydration and production of collagen;
- Fights free radicals and maintains skin elasticity;
- Antibacterial and anti-inflammatory properties that help with wound healing.

6.1.5 Functional oils

Cleoderm™ has a unique blend of functional oils carefully chosen to optimal effect and sensory experience:

Persea gratissima oil (avocado)

Due to its composition, *Persea gratissima* oil has positive effects on acne[131] and atopic dermatitis.[132]

Simmondsia chinensis seed oil (jojoba)

Simmondsia chinensis seed oil contains up to 50% wax esters, while natural human sebum consists of approximately 26% wax esters, which makes it a good option for altered-skin barrier conditions, presenting positive effects on acne[133], wound healing[134], psoriasis and rosacea.[135]

Rosa canina flower oil (dog rose)

Rosa canina is a remarkable source of vitamin C[136] and has documented antioxidant[137], anti-inflammatory[138], and antimicrobial activities[139], as well as clinic evidence of its effects on eczema.[140]

Cocos nucifera oil (coconut)

Cocos nucifera oil contains monolaurin, a molecule with antimicrobial effects.[141] It presents a marked wound healing capacity[142] and anti-inflammatory properties.[143]

Lavandula angustifolia herb oil (English lavender)

Lavender has long been used in dermatology, for its capacity to relieve symptoms of conditions such as psoriasis, dermatitis, and eczema, as well as inhibition of skin allergies.[144,145]

Melaleuca alternifolia leaf oil (tea tree)

Tea tree oil presents a range of positive effects for dermatological purposes, such as antioxidant effect[146], amelioration of acne vulgaris due to anti-inflammatory and antimicrobial effects against *C. acnes*[147,148], improvement of seborrheic dermatitis[149], and increase in wound healing rates.[150]

Rosmarinus officinalis leaf oil (rosemary)

This component has strong antioxidant[151] and anti-inflammatory activities[152,153]. In addition, it has been shown to decrease the proliferation of *C. acnes*, as well as suppress the release of chemical inflammatory markers due to its colonization, such as IL-8 and IL-1β.[154]

Vitellaria paradoxa butter (shea tree)

The topical use of shea butter has demonstrated anti-inflammatory and anti-aging properties.[155] It also plays a positive role in wound healing, on wrinkles, and on oxidative damage.[156]

Tocopheryl acetate (vitamin E acetate)

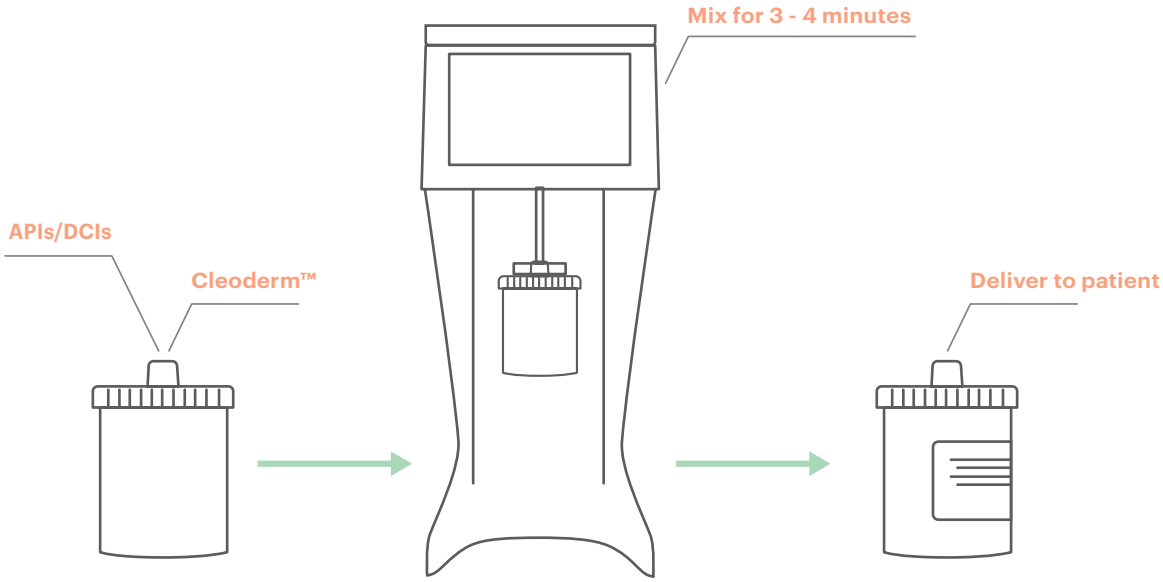
The antioxidant vitamin E has also photoprotective and skin barrier-stabilizing properties.[157] It may also play a role in atopic dermatitis, psoriasis, skin cancer prevention, wound healing, and melasma.[158]

6.2 Compounding with Cleoderm™

Cleoderm™ is an easy-to-compound-with vehicle, compatible with a wide range of APIs and dermaceutical ingredients (DCIs), and different associations. Up to 10% of solvents or levigants can be added to assist the compounding without affecting the final stability of the formulation.

The final product can be compounded by combining the APIs/DCIs, solvents, and **Cleoderm™** in an appropriate size FagronLab™ mixing jar, mixing for 3 to 4 minutes in the respective FagronLab™ EMP mixing machine, at a medium rotation speed. Process through an ointment mill if needed.

For a complete list of APIs, DCIs, and formulations with **Cleoderm™**, please refer to our latest updated Formulary and our Compatibility Table.



6.3 Safety

The safety of **Cleoderm™** was assessed in a clinical evaluation study, for primary and cumulative irritation and sensitization potential, as well as its acnegenic and comedogenic potential[159].

The primary and cumulative irritation and sensitization potential were evaluated in 54 healthy volunteers in a comparative single-blinded study, while the acnegenic and comedogenic potential of the product were assessed in 31 healthy volunteers with combination to oily skin through a non-comparative study. **Cleoderm™** was applied in filter paper discs in both studies. For the evaluation of the irritation and sensitization potential, the investigational product, or a control (0.9% NaCl) was applied to the right or left scapular area of the study subjects. No clinical reactions were observed during the induction or challenge phases, suggesting that **Cleoderm™** presents no irritating or allergenic potential.

Regarding acnegenicity and comedogenicity, no significant increase in the number of acne lesions linked to the application of the product in four areas of the face was reported, indicating that **Cleoderm™** appears not to display acnegenic and comedogenic potential. Furthermore, over 60% of the study subjects exhibited a decrease in the number of acne lesions after product use.

These results show that **Cleoderm™** exhibited no irritating, sensitizing, acnegenic, or comedogenic potential, and the claims dermatologically tested, clinically tested, and non-comedogenic/acnegenic can be supported.

Additionally, **Cleoderm™** is free from dyes, parabens, mineral oil, sodium lauryl sulfate, propylene glycol, and petrolatum.

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