Fagron Cleoderm™

Clarifying Cream

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personalizing medicine

Cleoderm™ Clarifying Cream

Cleoderm™ Clarifying Cream is a functional vehicle specially developed for acne or rosacea treatments. Cleoderm was formulated from *Cleome gynandra* leaf extracts with the addition of hyaluronic acid, bisabolol, and biomimetic peptides. This unique combination of ingredients provides anti-inflammatory and humectant properties as well as sebum reduction.

Key points

- Highly spreadable
- Light skin-feel
- Readily absorbed
- Non-comedogenic
- Specially developed for acne treatment and topical products for oily skin

Acne

Acne vulgaris is one of the most prevalent skin disorders worldwide (and the most common skin condition associated with inflammation of pilosebaceous unit). It affects all ethnic and age groups, independent of sex, nationality, or socioeconomic status.[1–4] The incidence in adult women is around 12%, and among adolescents of 12-18 years old, more than 85%.[5,6]

The presence of acne lesions may result in loss of self-confidence, anxiety, or community avoidance.[7] Additionally, it may also affect the sexual quality of life in adult patients.[8]

In addition, relapses are frequent (44%; 39.9% of ≤20-year-olds vs. 53.3% of >20-year-olds) and often associated with impaired quality of life and decrease in productivity or even absenteeism.[9] There is also evidence that acne vulgaris can impact on the difficulties in emotion regulation (DER) scale, notably in the form of anxiety and depression.[10,11]

This occurs because acne lesions can become scarring, which can have an impact on the 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)**.

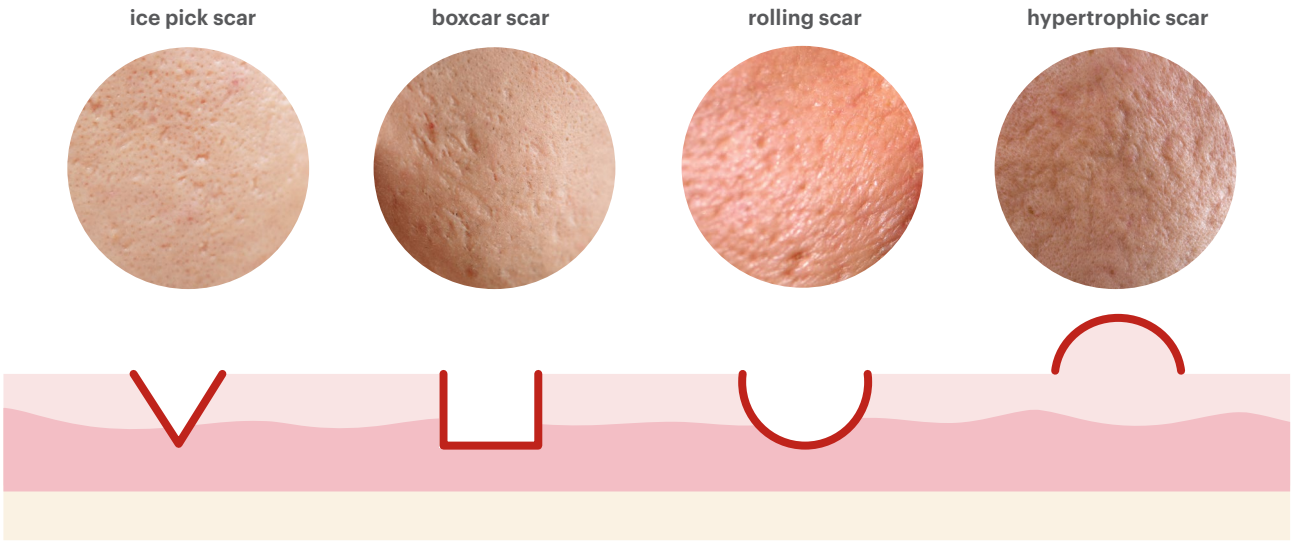


Figure 1. Examples of the different types of scars that can be resulted from acne lesions. Adapted.[12]

Pathogenesis

Acne can be understood as an inflammatory disease that affects the pilosebaceous follicle.[13] The common skin manifestations are comedones, papules, pustules, cysts, nodules and scars.[14]

Although its high prevalence, the multifactorial aetiology 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.[15,16]

The initial process is the formation of micro comedones, which evolve to 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 2)**. These lesions can then be resolved or develop complications, leading to the emergence of scars, either atrophic or hypertrophic.[17]

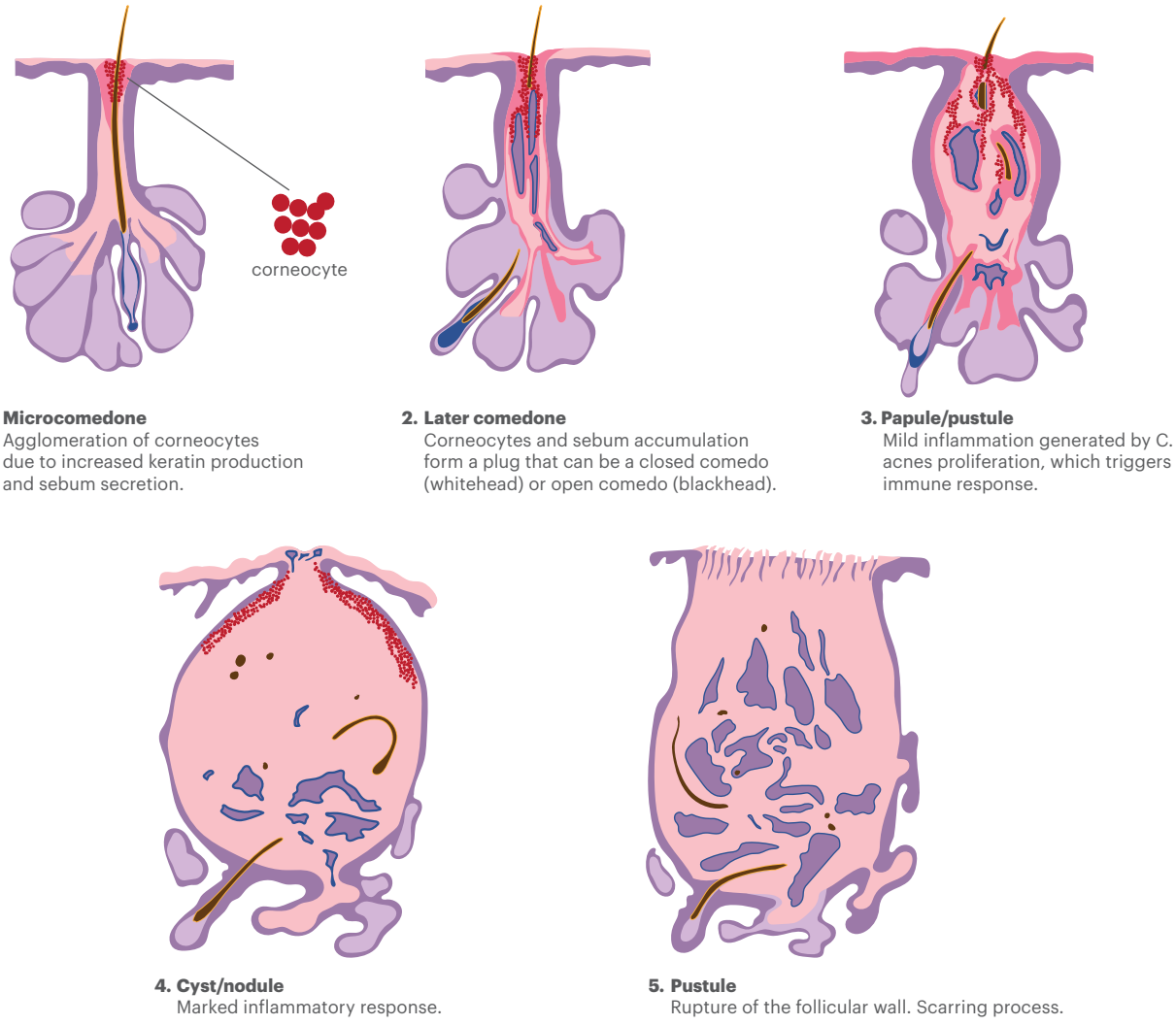


Figure 2. Acne formation process. Adapted.[18,19]

The microbiome balance is important because the skin is also colonized by other microorganisms, such as *Staphylococcus epidermidis* and *Streptococcus pyogenes*. While *S. epidermitis* limits the number of *C. acnes* in the skin (by the release of succinic acid and suppression of IL-6 and TNF-α production), *C. acnes* also limits *S. aureus* and *S. pyogenes* (by the maintenance of acidic pH of the pilosebaceous follicle, through the propionic acid secretion). Thus, the dysbiosis can affect the skin barrier and cause inflammation.[13,20]

The fungus *Malassezia furfur* is also involved in the process, as it has the ability to decompose fatty acids and release irritant chemicals to the skin, in addition to the secretion of allergenic proteins and peptides.[21] However, both organisms exist in a commensal relationship in healthy skin, and in that case the intracate microbiome-microbiome and microbiome-host interactions are more prone to be a causal factor than the simple colonization by one of these organisms.[20]

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 3)**.

- histamine receptor - activated by histamines;[22]
- hormonal DHT receptor - activated by androgens;[23]
- neuromodulator receptor (substance P and corticotrophin-releasing hormone (CRH) receptor) - activated by stress;[24]
- peroxisome proliferator - activated receptors (PPARα, β and γ) – activated by free fatty acids and cholesterol;[25]
- insulin-like growth factor (IGF)-1 receptor - activated by sugar;[26]
- leptin receptor - activated by fat.[27]

The last three are therefore correlated to the diet of the patient. Situations such as peripheral hyperandrogenia (particularly in women) can abnormally activate the androgen receptors.[13]

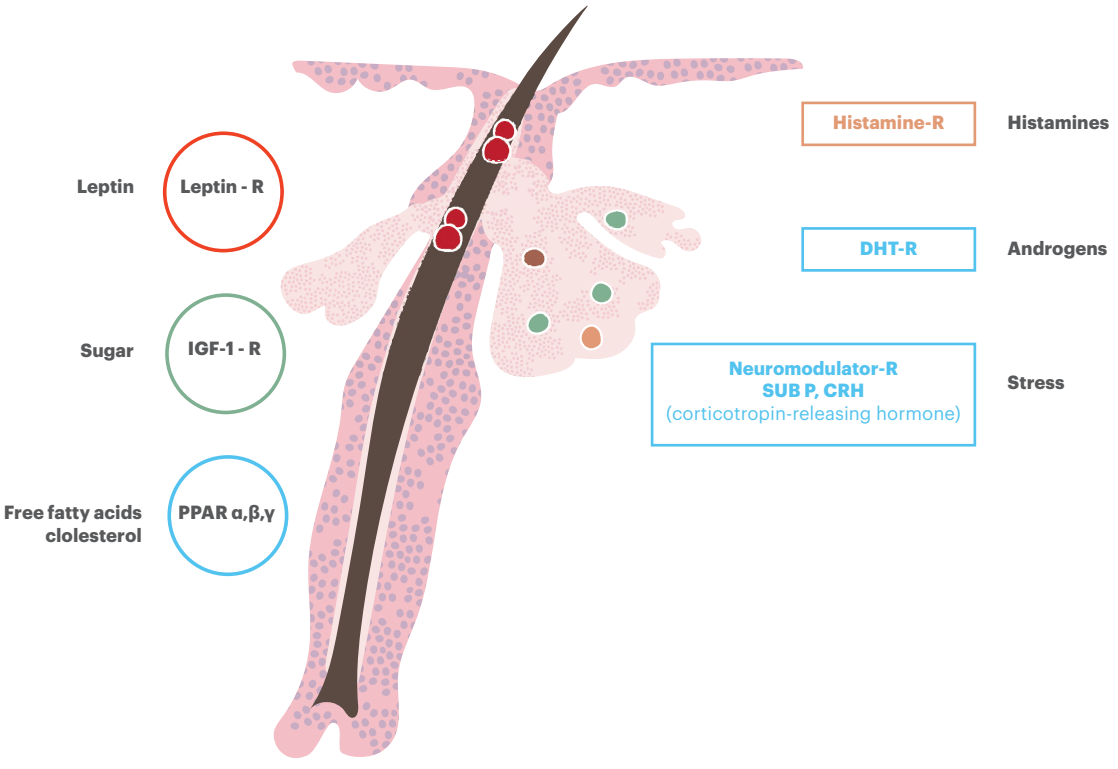


Figure 3. Main receptors involved in sebum production, and their activators. Adapted.[13]

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 also be involved in sebum secretion control.[28]

The immune system can also play a role in acne emergence **(Figure 4)**. *C. acnes* can promote the release of Th17/Th1-related cytokines, specifically IFN-γ and IL-17A.[29] The activation of the innate immunity (via the production of IFN-γ, IL-8, IL-12, TNF-α, IL-1 and MMPs) can result in the hyperkeratinization of the pilosebaceous unit.[13]

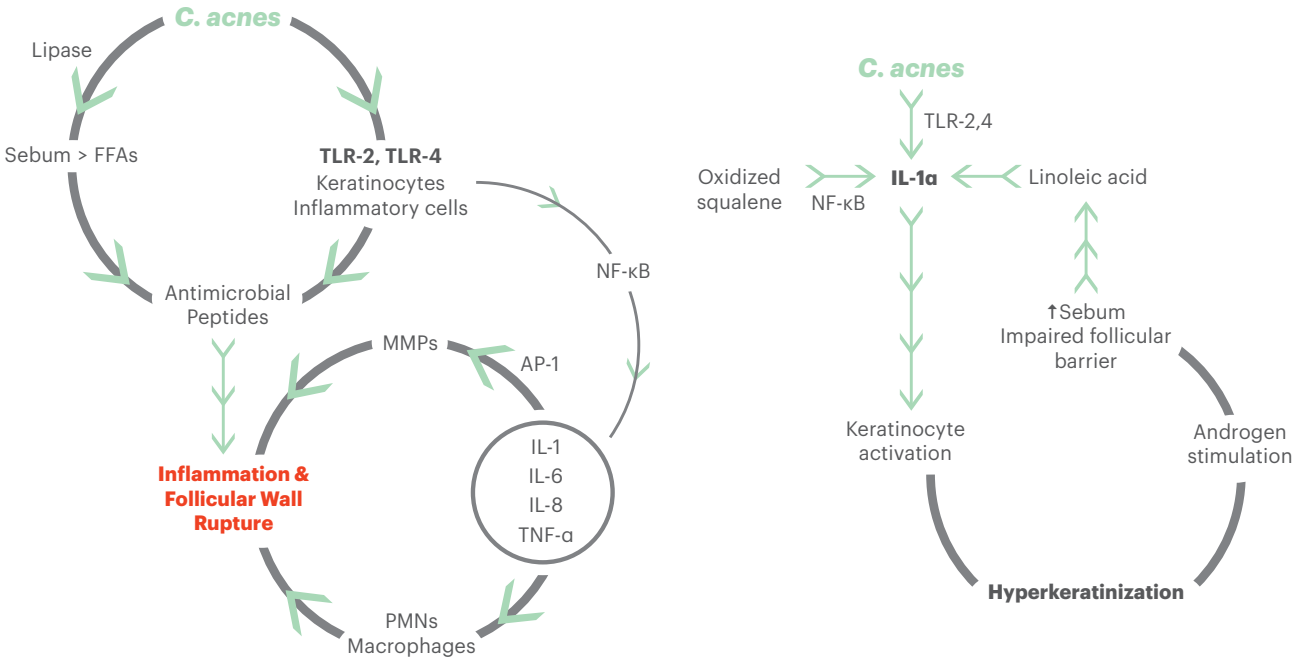


Figure 4. Effect of *C. acnes* in innate immunity and its correlation to acne mechanisms. Adapted.[30]
AP: activator protein, FFA: free fatty acid, IL: interleukin, MMP: matrix metellaproteinases,
NF: nuclear factor, PMNs: polymorphonuclear leukocytes, TLR: toll-like receptor, TNF: tumor necrosis factor.

Finally, the concept of exposome is also being introduced to the acne researches. Exposome can be understood as the sum of internal and external exposures that the person is exposed to from conception until death.[31] In this context, researches have demonstrated that the main internal factors related to the acne are:

- *C. acnes* abnormal proliferation in skin, due to dysbiosis;
- elevated sebum production;
- alteration of follicular epithelium (hyperkeratinization, due to the hyperseborrhoea);
- inflammatory processes, both in innate and acquired immunities.[32,33]

In addition, the external factors that can play a role in both the severity and treatment efficacy of the disease are:[34,35]

- Nutrition (diet)
- Medication
- Stress
- Occupational factors
- Pollutants
- Sun exposure
- Weather factors (such as temperature and humidity)
- Psychosocial and lifestyle parameters.

Cleoderm™ Clarifying Cream

A functional vehicle for acne treatments and topical products for oily skin

Cleoderm™ Clarifying Cream is a functional vehicle with selected ingredients that makes it the ideal choice for compounding topical treatments for acneic or oily 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).

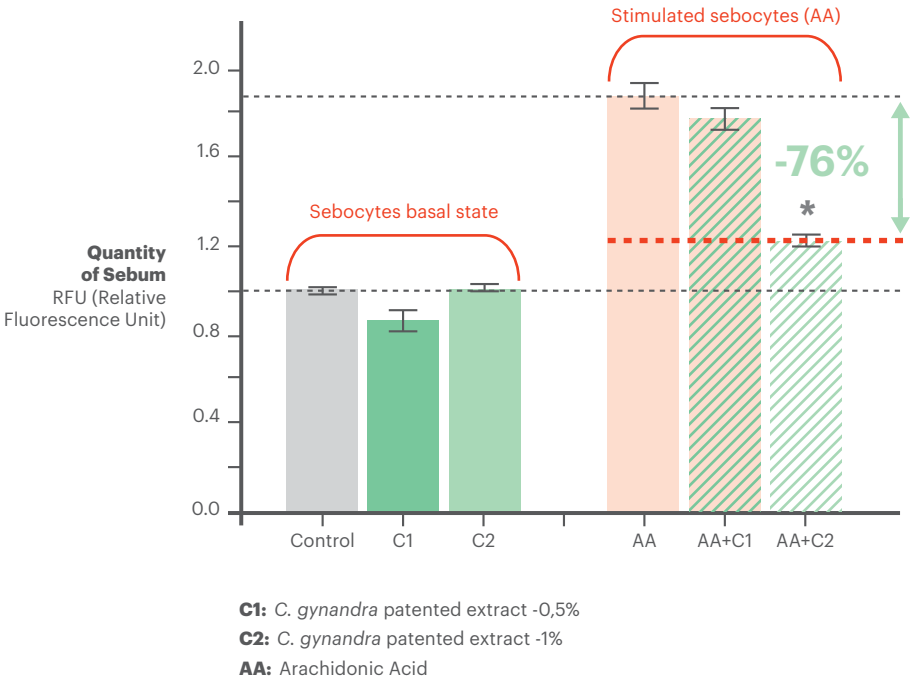
Cleome gynandra L. leaf extract

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

Known by common names such as Gynandropsis, cats whisker, and African spider flower, *C. gynandra* has anti-inflammatory and antioxidant activities[36,37], as well as positive effects on wound repair[38] and skin allergy/ itching.[39]

Cleoderm™ Clarifying Cream uses a patented *C. gynandra* 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 (inhibits *C. acnes*, and suppresses TLR2 , IL-8, and neutrophils).[40–42]

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



C1: *C. gynandra* patented extract -0,5%
C2: *C. gynandra* patented extract -1%
AA: Arachidonic Acid

Figure 5. 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 nonstimulated sebocytes. *p<0.05

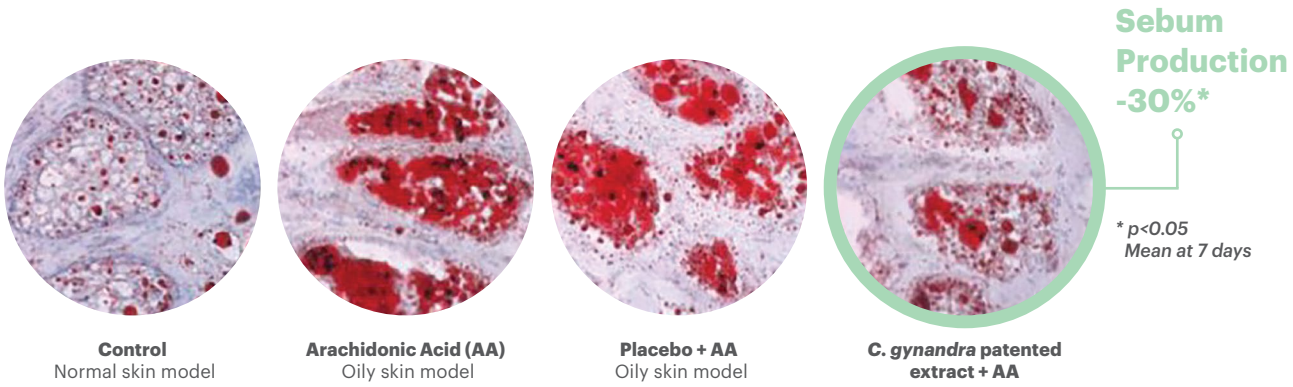


Figure 6. Sebum quantity assessment (Oil-Red-O staining). Explants from human skin, next to the scalp area, treated with arachidonic acid to simulate the inflammatory phase of acne. ***C. gynandra* was able to decrease in up to 30% the quantity of sebum**, after 7 days.

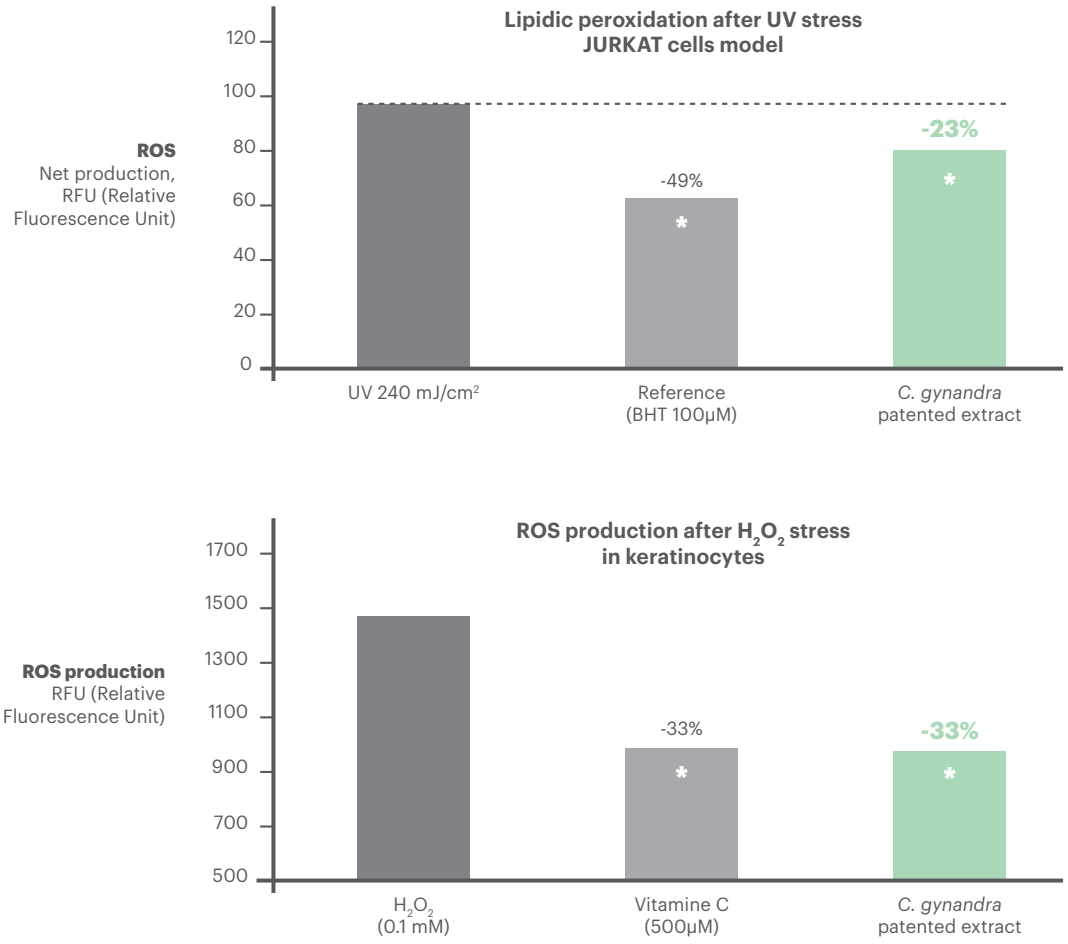


Figure 7. Acne severity is frequently associated with reactive oxygen species (ROS) quantity, and consequently oxidation of squalene. Acneic skins present two times more squalene than health skin; in addition, squalene is highly susceptible to oxidation, and peroxidized squalene is comedogenic and pro-inflammatory. ***C. gynandra* patented extract was able to reduce lipid peroxidation and ROS production**, improving sebum quality. *p<0.05

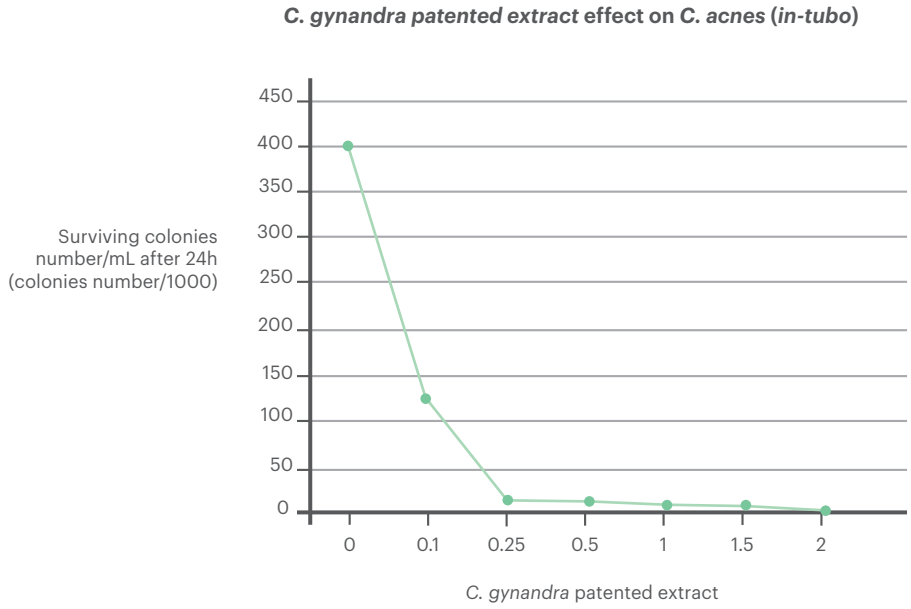


Figure 8. The antimicrobial components of ***C. gynandra*** **patented extract were able to decrease the *C. acnes* population**, helping the skin to protect itself against the bacterial proliferation.

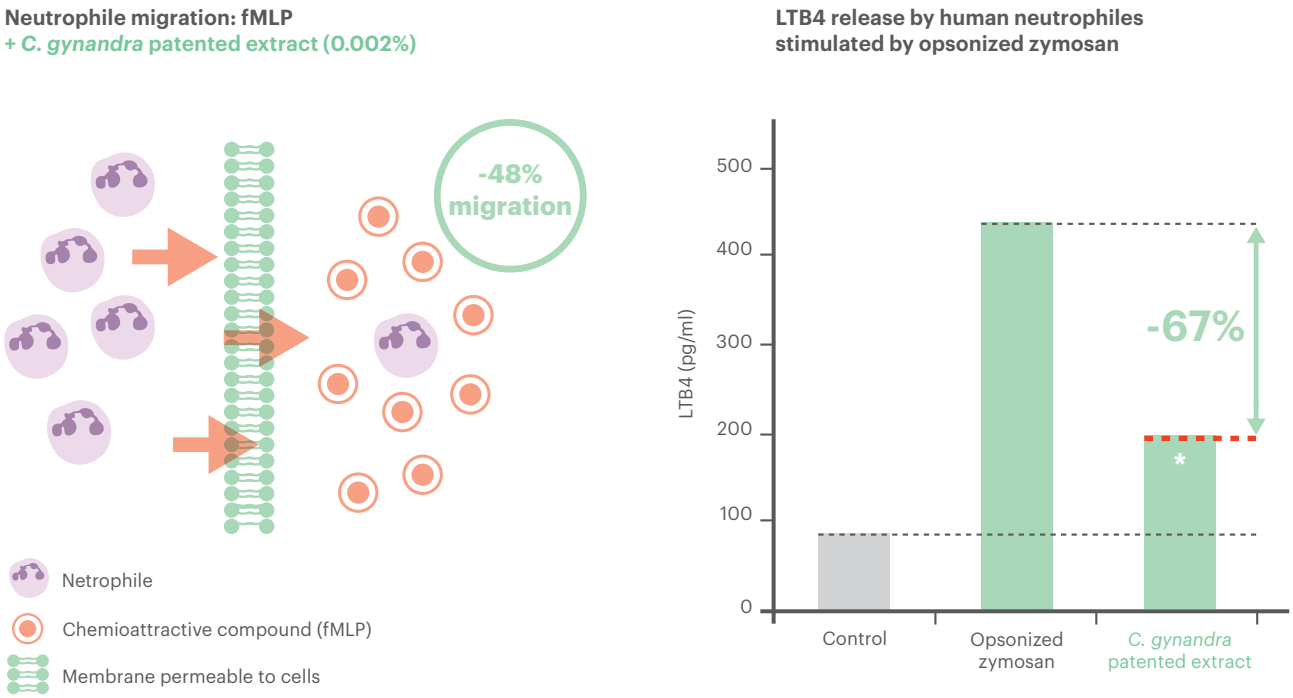


Figure 9. The effects on neutrophil migration can be observed, showing the anti-inflammatory effect of the *C. gynandra* patented extract. Neutrophils produce LTB4, which increase inflammation and sebum production. ***C. gynandra*** **patented extract is able to decrease neutrophil migration in 48%, and LTB4 release in 67%**. LTB4: Leukotriene B4. *p<0.05.

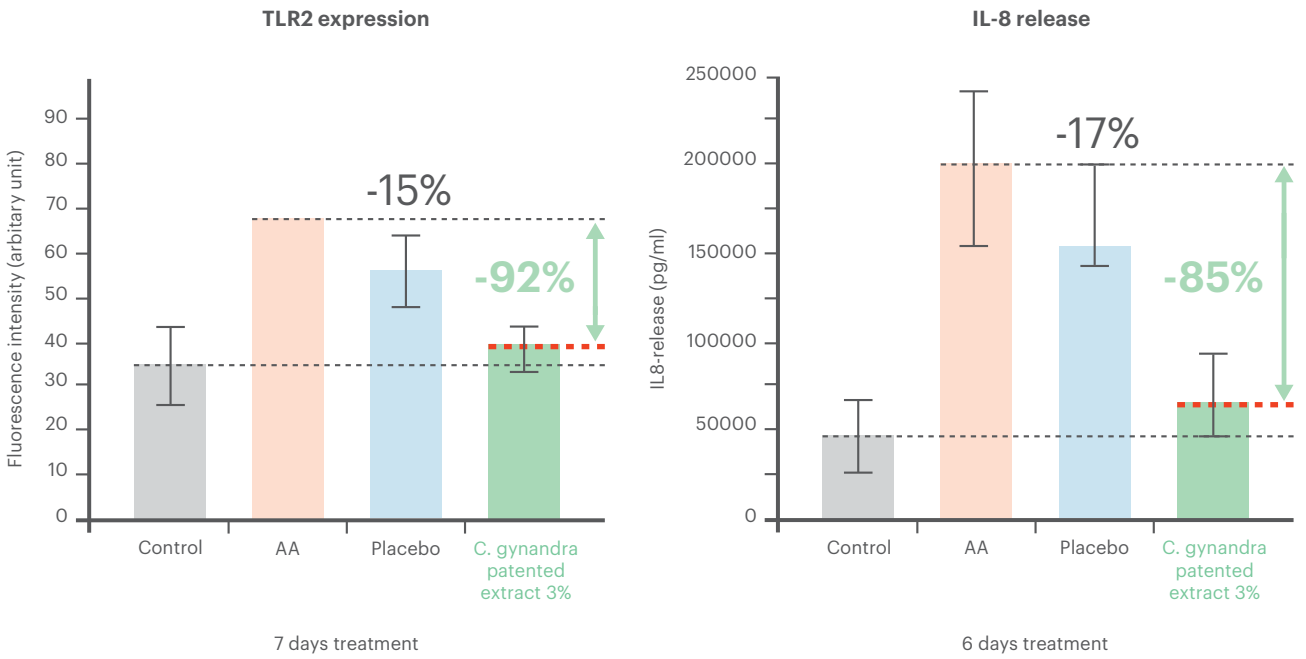


Figure 10. TLR2 is a natural receptor of human immune system which, when activated by *C. acnes*, generates inflammation. Once TLR2 is activated, IL-8 is then released. As one can see, ***C. gynandra* patented extract was capable of decreasing in up to 92% the TLR2 expression, and in up to 85% the IL-8 release**, due to its anti-inflammatory properties. AA: arachidonic acid.

Palmitoyl Tripeptide-8

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

A single group efficacy trial with 50 patients with rosacea showed that the use of a facial lotion containing palmitoyl tripeptide-8 significantly improved redness, flushing, overall appearance, rosacea severity and lesion count – in comparison to the baseline.[43]

Bisabolol

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

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.[44]

In addition to the reduction of proinflammatory markers, bisabolol can also reduce oxidative stress[45] and proved to be safe for topical application on skin.[44]

Due to its anti-inflammatory and antibacterial activities, it can help to treat skin wounds and burns[46,47] as well as act as a penetration enhancer. [48]

Hyaluronic acid

- Improve skin hydration and production of collagen.
- Fight free radicals and maintain skin elasticity.
- Antibacterial and anti-inflammatory properties that help with wound healing.

The current main application of hyaluronic acid in aesthetic dermatology is in fillers and skincare – for the eyes, face, neck, and body, and in anticellulite and antistretch cosmetics. As the molecule does not penetrate deep into the skin, it acts by covering the stratum corneum and then prevents water loss, acting as a moisturizer – and the protective layer also makes skin appear softer and feel smoother to the touch.[49–51]

Hyaluronic acid has shown a range of different activities on the skin: buffering action, due to its excellent viscoelastic properties after water absorption;[52] anti-inflammatory and antibacterial properties;[53,54] antioxidant capacity;[55] and accelerator of the wound healing process.[54,56,57]

Functional oils

Cleoderm™ Clarifying Cream 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[58] and atopic dermatitis.[59]
- ***Simmondsia chinensis* seed oil (jojoba)**
  Simmondsia chinensis seed oil contains up to 50% wax esters, while natural human sebum consist of approximately 26% wax esters, which makes it good option to altered-skin barrier conditions, presenting positive effects on acne[60], wound healing[61], psoriasis and rosacea.[62]
- ***Rosa canina* flower oil (dog rose)**
  Rosa canina is a remarkable source of vitamin C[63] and has documented antioxidant[64], anti-inflammatory[65] and antimicrobial activities[66], as well as clinic evidence of its effects on eczema.[67]
- ***Cocos nucifera* oil (coconut)**
  Cocos nucifera oil contains monolaurin, a molecule with antimicrobial effects.[68] It presents a marked wound healing capacity[69] and anti-inflammatory property.[70]
- ***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.[71,72]
- ***Melaleuca alternifolia* leaf oil (tea tree)**
  Tea tree oil presents a range of positive effects for dermatological purposes, such as antioxidant effect[73], amelioration of acne vulgaris due to anti-inflammatory and antimicrobial effects against *C. acnes*[74,75], improvement of seborrheic dermatitis[76], and increase in wound healing rates.[77]
- ***Rosmarinus officinalis* leaf oil (rosemary)**
  This component has strong antioxidant[78] and anti-inflammatory activities[79,80]. In addition, it has been shown to decrease proliferation of *C. acnes*., as well as suppress the released of chemical inflammatory markers due to its colonization, such as IL-8 and IL-1β.[81]
- ***Vitellaria paradoxa* butter (shea tree)**
  Topical use of shea butter has demonstrated anti-inflammatory and anti-aging properties.[82] It also plays a positive role in wound healing , on wrinkles and on oxidative damage.[83]
- **Tocopheryl acetate (vitamin E acetate)**
  The antioxidant vitamin E has also photoprotective and skin barrier-stabilizing properties.[84] It may also play a role in atopic dermatitis,, psoriasis, skin cancer prevention, wound healing and melasma.[85]

Emulsifier

- Derived from sunflower (*Helianthus annuus*), with low irritation potential.
- Botanical, biodegradable, PEG-free.
- Liquid crystal structure.
- Functional: decreases TEWL (transepidermal water loss), increasing skin hydration and maintaining barrier function.

Thickener

- Acrylamide-free thickener
- Super fresh, soft, velvety feel
- No tacky effect
- Maintain strong viscosity through an extremely wide pH range, and is especially effective at low pH for formulation

Formulas with Cleoderm™

ACNE
Fagron Derma Pack CTNC

Clindamycin hydrochloride	1 g
Tretinoin	15 mg
Nicotinamide	2 g
Cleoderm™	qs 50 g

ACNE
Fagron Derma Pack EBAC

Erythromycin	1.5 g
Benzoyl peroxide hydrous	2.5 g
Azelaic acid	10 g
Cleoderm™	qs 50 g

ACNE
Fagron Derma Pack ETC

Erythromycin	2 g
Tretinoin	15 mg
Cleoderm™	qs 50 g

ACNE
Fagron Derma Pack ABNC

Adapalene	150 mg
Benzoyl peroxide hydrous	1.25 g
Nicotinamide	2 g
Cleoderm™	50 g

ACNE (maintenance phase)
Fagron Derma Pack GS-NAC

Glycolic acid	1.5 g
Salicylic acid	1 g
Nicotinamide	1 g
Fagron aloe vera gel 10x	1.5 g
Cleoderm™	qs 50 g

ACNE (maintenance phase)
Fagron Derma Pack VNC

Vitamin A	200 mg
Nicotinamide	2.5 g
Cleoderm™	qs 50 g

ROSACEA
Fagron Derma Pack PEC

Permethrin	2.5 g
Cleoderm™	qs 50 g

ROSACEA
Fagron Derma Pack INC

Ivermectin	500 mg
Nicotinamide	2 g
Cleoderm™	qs 50 g

ACNE SCARS
Fagron Derma Pack TGC

Tretinoin	12.5 mg
Glycolic acid	6 g
Cleoderm™	50 g

PHOTOAGING
Fagron Derma Pack AHAC

Ascorbic acid	5 g
Glycolic acid	1 g
Azelaic acid	5 g
Lactic acid	2.5 g
Cleoderm™	qs 50 g

SEBORRHEIC DERMATITIS
Fagron Derma Pack KEBC

Ketoconazole	1 g
Nicotinamide	2 g
Betamethasone	25 mg
Tea tree oil	2.5 g
Cleoderm™	qs 50 g

SEBORRHOEIC HYPERKERATOSIS
Fagron Derma Pack TAC

Tazarotene	50 mg
Lactic acid	3 g
Cleoderm™	qs 50 g

HYPERPIGMENTATION
Fagron Derma Pack ANAC

Azelaic acid	7.5 g
Nicotinamide	2.5 g
Alpha bisabolol	500 mg
Tranexamic acid	1 g
Kojic acid	500 mg
Cleoderm™	qs 50 g

Safety

Free from dyes, parabens, mineral oil, sodium lauryl sulfate, propylene glycol, and petrolatum, Cleoderm™ Clarifying Cream is especially suitable for dehydrated and affected skin.

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Cleoderm™ is a cosmetic and it is not intended to diagnose, treat, or cure any disease.

Warnings
For external use only.
In case of contact, rinse eyes thoroughly with water. Stop use and ask a doctor if irritation or rashes appear and lasts. Keep out of reach of children. Do not use on mucosa or open wounds.

If swallowed, get medical help or contact a Poison Control Center immediately. Children under 6 years of age should be supervised when using this product.

Scientific Support
Please contact our scientific experts to get more details about the applications and technical benefits of **Cleoderm™**.

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