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# Cleoderm™ Clarifying Cream: A Novel, Topical Vehicle Using Plant-Based Excipients and Actives Targeting Acne and Oily Skin

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## Abstract

Acne vulgaris is the most common skin condition associated with inflammation of the pilosebaceous unit and affects all ethnic and age groups, independent of sex, nationality, or socioeconomic status. Treatment usually includes oral and/or physical and/or topical interventions—the last can be obtained through commercial preparations in fixed doses or as compounded creams/gels, with personalized qualitative and quantitative composition, to be unique to each patient. In this sense, ready-to-use vehicles play an important role as a timesaving strategy and to ensure maximum results from the treatment. In this paper, we present Cleoderm™ Clarifying Cream, a ready-to-use, functional semisolid vehicle for acne treatments and topical products for oily skin, to be used by compounding pharmacies. It contains ingredients that can potentiate the effects of the active ingredients added, and has a light and pleasant skin feel. The current body of evidence shows that Cleoderm™ Clarifying Cream can be an important strategy for compounding personalized acne treatments due to its multiple positive roles on decreasing sebum production, lipid peroxidation, and reactive oxygen species, inhibition of *Cutibacterium acnes* proliferation, and control of inflammation.

## Keywords

Acne Vulgaris, Personalized Medicine, *Cleome gynandra*, Dermatology

## 1. Introduction

Acne vulgaris is one of the most prevalent skin disorders worldwide and the most common skin condition associated with inflammation of the pilosebaceous unit; it affects all ethnic and age groups, independent of sex, nationality, or so-

cioeconomic status [1] [2] [3] [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 can usually affect self-confidence, anxiety, and community avoidance [7]. Additionally, it can also affect the sexual quality of life of adult patients [8].

In addition, relapses are frequent (44%; 39.9% of ≤20-year-old vs. 53.3% of >20-year-old) 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 the difficulties in emotion regulation (DER), notably anxiety and depression [10] [11].

This occurs because acne lesions can become scarring, which can aggravate both the physical aspect of the patient as well as the impact on the psychological factors.

The current body of possible treatments includes oral, physical, and topical strategies. Oral treatments include antibiotics, hormonal agents, or isotretinoin, while physical interventions can be peelings and laser therapy. In addition, topical treatment may include antibiotics, benzoyl peroxide, dapsone, retinoids, or azelaic acid [12]. A recent systematic review and network meta-analysis showed that topical benzoyl peroxide was effective for improving self-reported acne, as well as its combination with adapalene or with clindamycin [13].

Those topical treatments can be obtained through commercial preparations in fixed doses or as compounded creams/gels, with personalized qualitative and quantitative composition, to be unique to each patient. Compounded treatments are an important resource for patient care [14]. However, developing semisolid dosage forms with proven stability, compatibility with a broad range of active pharmaceutical ingredients (APIs), and sensory and functional characteristics adequate to the patients, can be challenging to the compounding pharmacies worldwide. In this sense, ready-to-use vehicles play an important role as a time-saving strategy and to ensure maximum results from the treatment. In this paper, we present Cleoderm™ Clarifying Cream, a ready-to-use, functional semisolid vehicle for acne treatments and topical products for oily skin, to be used by compounding pharmacies. We discuss the rationale behind its composition and its benefits for acneic skin.

## 2. Acne Pathogenesis

To understand the functional aspects of the ready-to-use vehicle Cleoderm™ Clarifying Cream, it is important to understand the multifactorial etiology of acne—although such mechanisms are not yet fully elucidated.

Acne can be understood as an inflammatory disease that affects the pilosebaceous follicle [15]. The common skin manifestations are comedones, papules, pustules, cysts, nodules, and scars [16]. Acne scars can be divided into three main groups: icepick scars, rolling scars, and boxcar scars (**Figure 1**), as well as some less common lesions such as sinus tracts, hypertrophic scars, and keloidal scars.

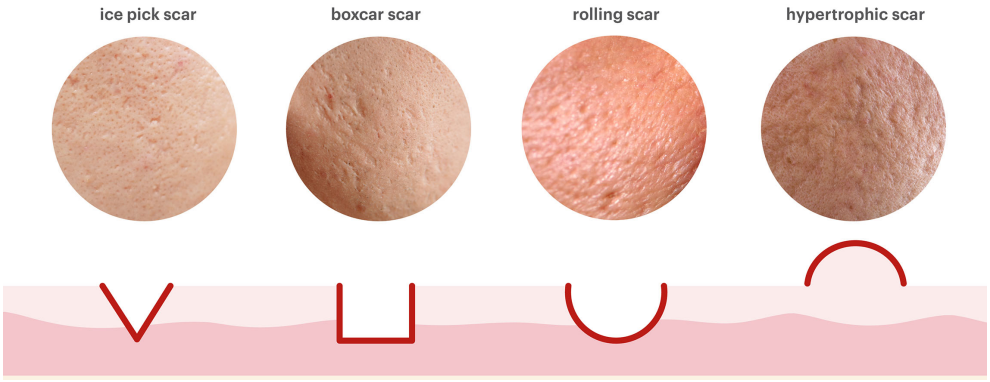


**Figure 1.** Examples of the different types of scars that can be resulted from acne lesions. Adapted from [19].

The main etiological 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 lipophilic bacteria)—this would lead to the inflammatory processes due to the blocking of the hair follicle [17] [18].

It seems that the initial process is the formation of micro comedones, which evolves 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, both atrophic or hypertrophic [20].

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-$\alpha$ 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. dysbiosis can affect the skin barrier and cause inflammation [15] [23].

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 [24]. However, both organisms exist in a commensal relationship in healthy skin, and then the intricated microbiome-microbiome and microbiome-host interactions are more prone to be a causal factor than the simple colonization by one of these organisms [23].

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 [25];
- Hormonal DHT receptor—activated by androgens [26];
- Neuromodulator receptor (substance P and corticotrophin-releasing hormone (CRH) receptor)—activated by stress [27];

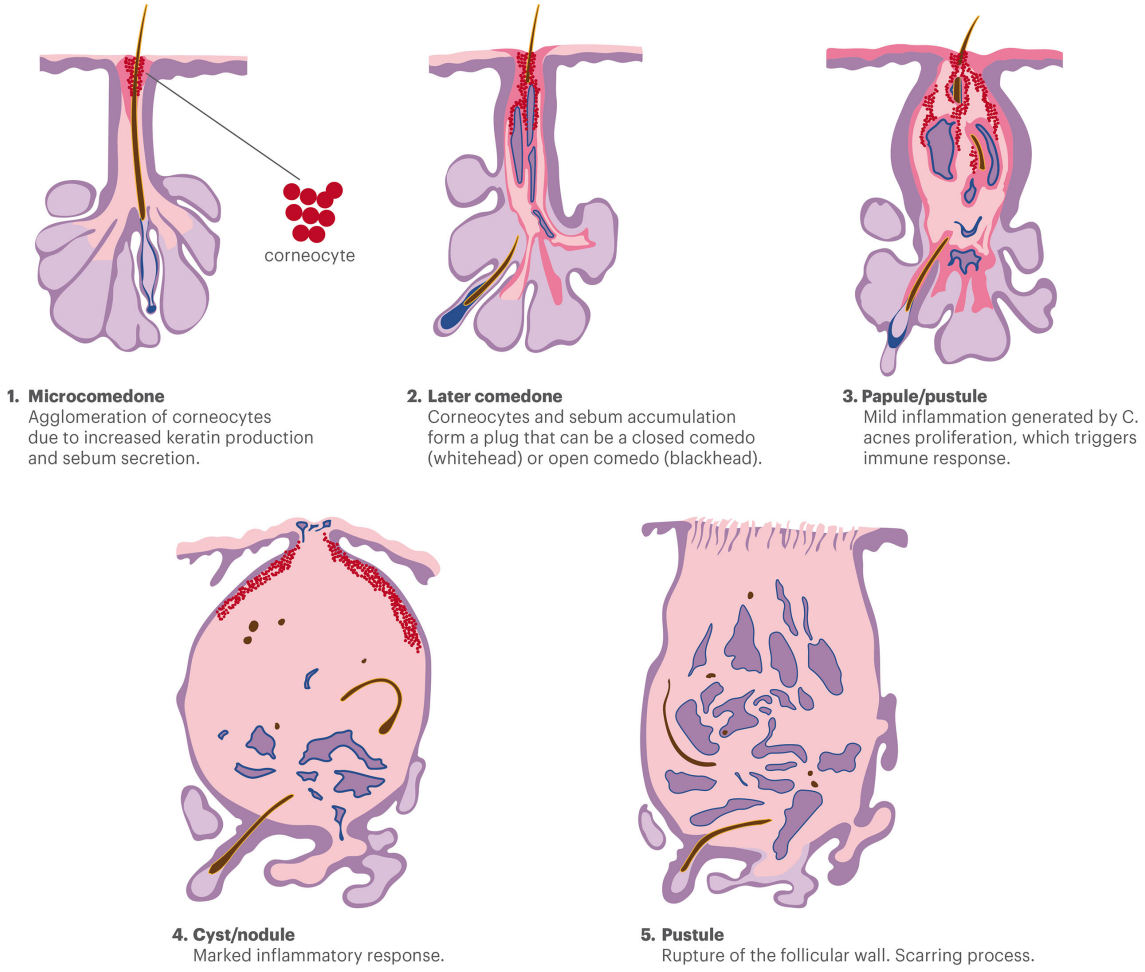


**Figure 2.** Acne formation process. Adapted from [21] [22].

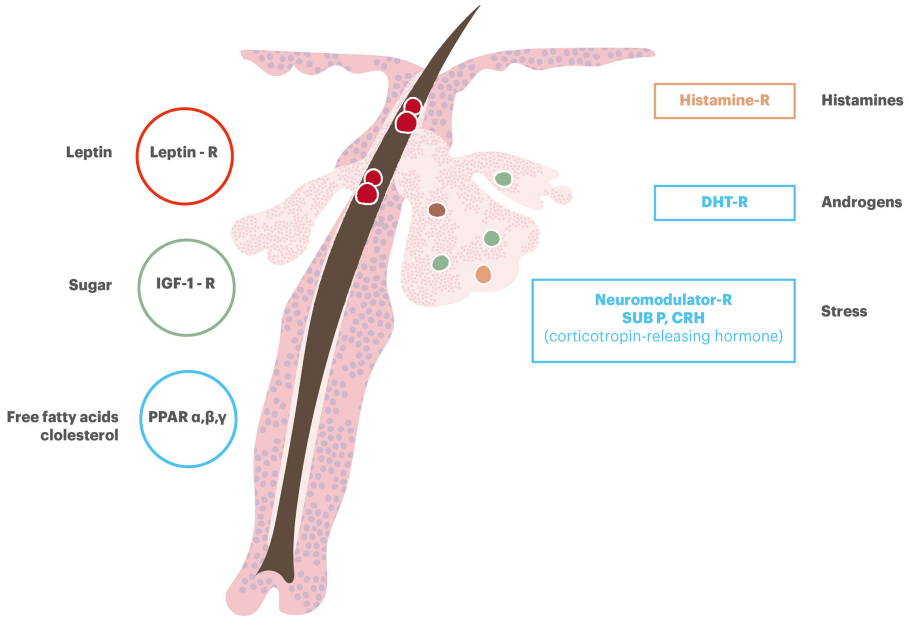


**Figure 3.** Main receptors involved in sebum production, and their activators. Adapted from [15].

- Peroxisome proliferator-activated receptors (PPAR$\alpha$, $\beta$, and $\gamma$)—activated by free fatty acids and cholesterol [28];
- Insulin-like growth factor (IGF)-1 receptor—activated by sugar [29];
- Leptin receptor—activated by fat [30];

The last three are therefore correlated to the diet of the patient. Situations such as peripheral hyperandrogenemia (particularly in women) can abnormally activate the androgens receptors [15].

Another possible player in acne vulgaris development is the endocannabinoid system in the skin, which can be involved in different processes, such as the differentiation of cells of appendages such as the sebaceous gland. Additionally, it also appears to be involved in sebum secretion control [31].

The immune system can also play a role in acne emergence (**Figure 4**). *C. acnes* can promote the release of Th17/Th1-related cytokines, specially IFN-$\gamma$ and IL-17A. [32] The activation of the innate immunity (via the production of IFN-$\gamma$, IL-8, IL-12, TNF, IL-1, and MMPs) can result in the hyperkeratinization of the pilosebaceous unit [15].

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.

Finally, the concept of exposome is also being introduced to acne research. Exposome can be understood as the sum of internal and external exposures that the person is exposed from conception until death [34]. In this context, researchers have demonstrated that the main internal factors related to acne are:

- *C. acnes* abnormal proliferation in the skin, due to dysbiosis;
- Elevated sebum production;

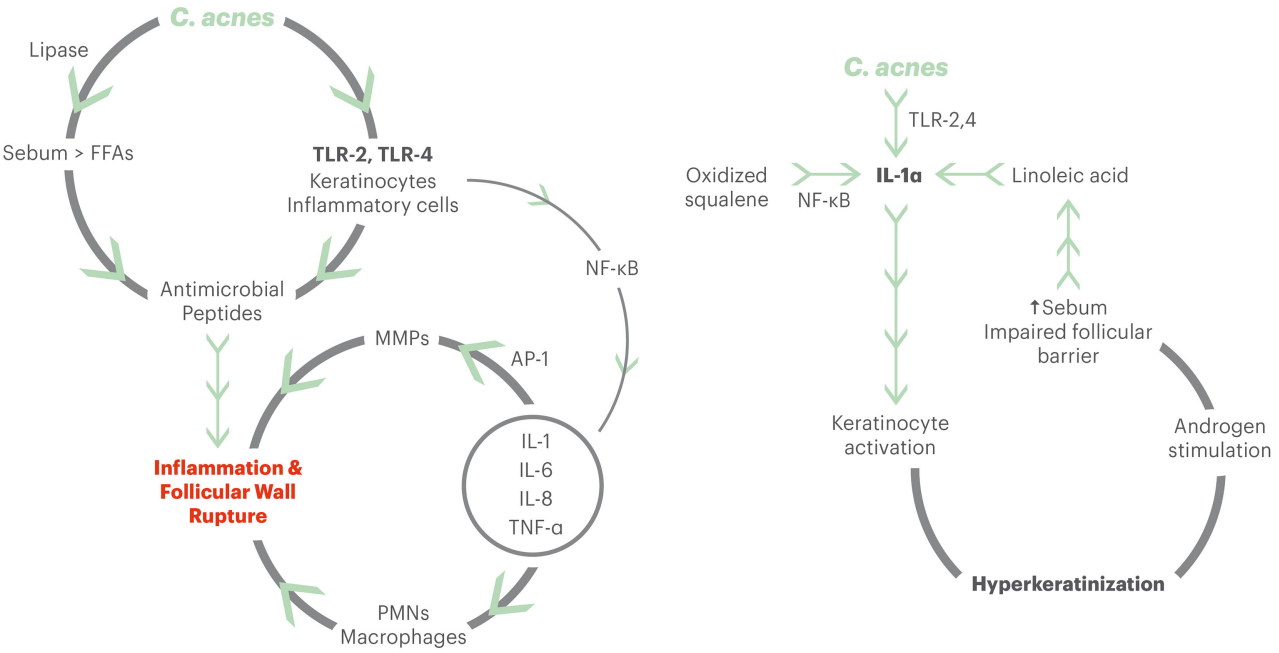


**Figure 4.** Effect of *C. acnes* in innate immunity and its correlation to acne mechanisms. Adapted from [33].

- Alteration of follicular epithelium (hyperkeratinization, due to hyper seborrhea);
- Inflammatory processes, both in innate and acquired immunities [35] [36].

In addition, the external factors that can play a role in both the severity and treatment efficacy of the disease are [37] [38]:

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

## 3. 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 acne topical treatments. Its main constituents are *Cleome gynandra* L. leaf extract, Palmitoyl Tripeptide-8, Bisabolol, Hyaluronic acid, and a blend of 8 functional oils (*Persea gratissima*, *Simmondsia chinensis*, *Rosa canina*, *Cocos nucifera*, *Lavandula angustifolia*, *Melaleuca alternifolia*, *Rosmarinus officinalis*, *Vitellaria paradoxa*, and *Tocopheryl acetate*).

In addition, it is free from dyes, parabens, mineral oil, sodium lauryl sulfate, propylene glycol, and petrolatum.

### 3.1. *Cleome gynandra* L. Leaf Extract

Known by common names such as *Gynandropsis*, cat's whisker, African spider flower, *C. gynandra* is rich in rutin and hydroxycinnamic acid and has anti-inflammatory and antioxidant activities [39] [40], as well as positive effects on wound repair [41] and skin allergy/itching [42].

Cleoderm™ Clarifying Cream uses a patented *C. gynandra* extract within a specific diluent (Pixalia™). 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) [43] [44] [45].

A series of *in vitro* and *ex vivo* tests were conducted with such components, and the main results are graphically described in **Figures 5-10**.

### 3.2. Palmitoyl Tripeptide-8

Peptides have been proving to be useful active ingredients in cosmetics for sensitive skin. Palmitoyl tripeptide-8 (N-(1-oxohexadecyl)-L-histidyl-D-phenylalanyl-L-argininamide) is a synthetic

peptide ester based on an *α*-melanocyte-stimulating hormone (*α*-MSH), originated from pro-opiomelanocortin [47]. It has been previously shown to act as an anti-inflammatory and soothing agent, preventing and reversing 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 [48]. *In vitro*, it has been shown the capacity to inhibit IL-8 production [49], as well as to decrease the number of dilated capillaries and edema [50].

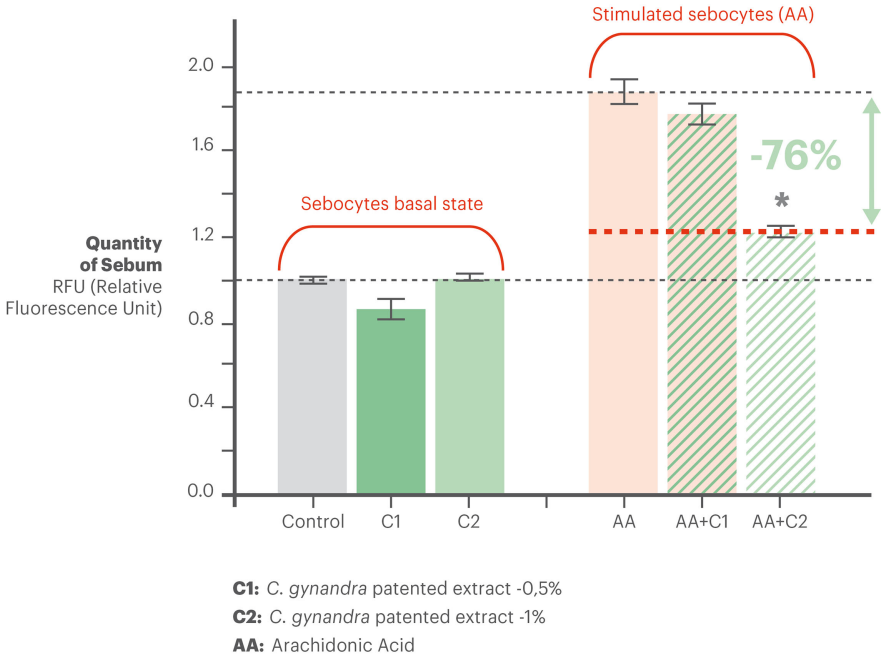


**Figure 5.** Stimulation of seborrhea with arachidonic acid (AA) inflammatory stress, in human sebocytes model. Lower and higher concentrations of *C. gynandra* extract decreased the quantity of sebum in both stimulated and nonstimulated sebocytes. *p < 0.05. Adapted from [46].

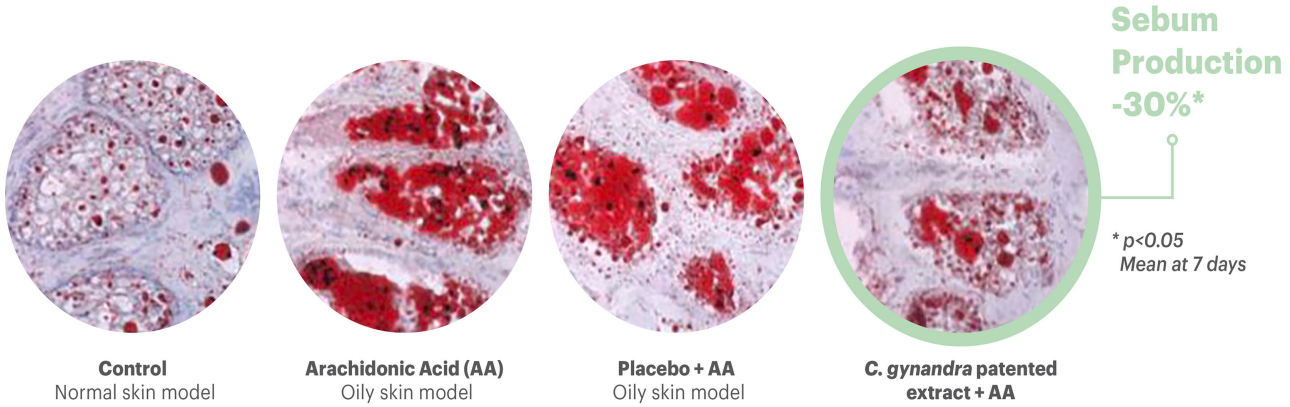


**Figure 6.** Sebum quantity assessment (Oil-Red-O staining). Explants from human skin, next to the scalp area, treated with arachidonic acid to simulate the inflammatory phase of acne. *C. gynandra* was able to decrease in up to 30% the quantity of sebum, after 7 days. Adapted from [46].

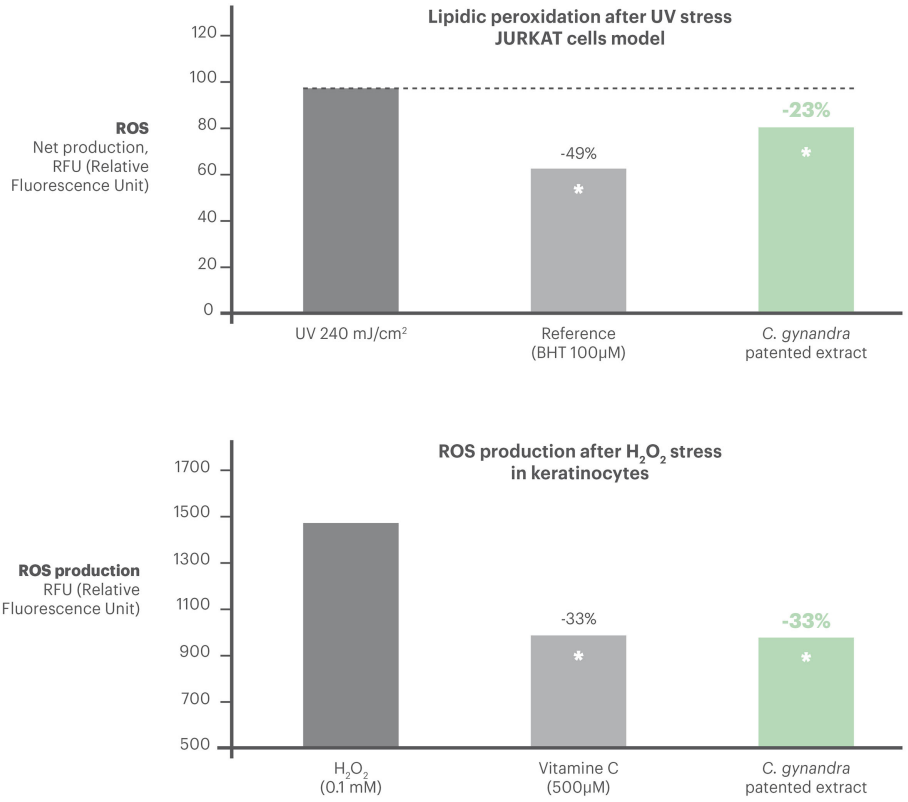


**Figure 7.** Acne severity is frequently associated with reactive oxygen species (ROS) quantity, and consequently oxidation of squalene. Acneic skins present two times more squalene than healthy skin; in addition, squalene is highly susceptible to oxidation, and peroxidized squalene is comedogenic and pro-inflammatory. *C. gynandra* patented extract was able to reduce lipid peroxidation and ROS production, improving sebum quality. *p < 0.05. Adapted from [46].

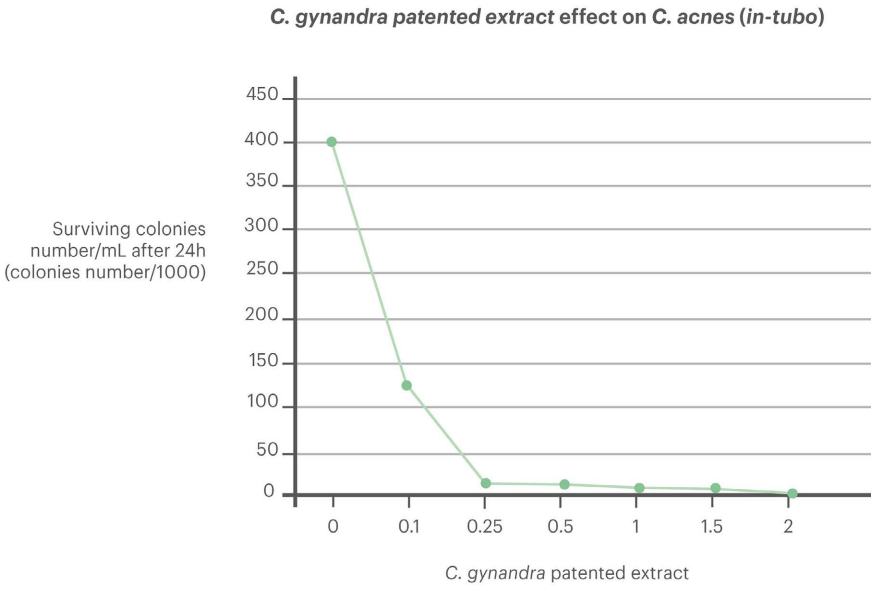


**Figure 8.** Antimicrobial components of *C. gynandra* patented extract was able to decrease the *C. acnes* population, helping the skin to protect itself against bacterial proliferation. Adapted from [46].

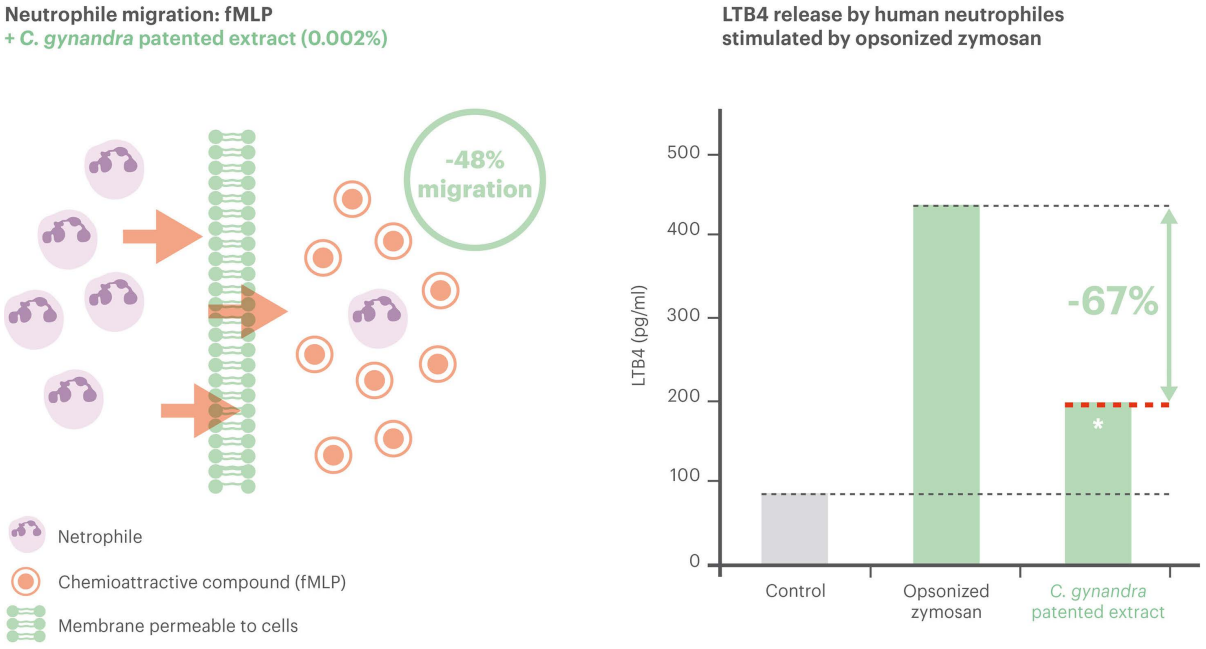


**Figure 9.** The effects on neutrophil migration can be observed, showing the anti-inflammatory effect of the *C. gynandra* patented extract. Neutrophils produce LTB4, which increases inflammation and sebum production. *C. gynandra* patented extract can decrease neutrophil migration by 48%, and LTB4 release by 67%. LTB4: Leukotriene B4. *p < 0.05. Adapted from [46].

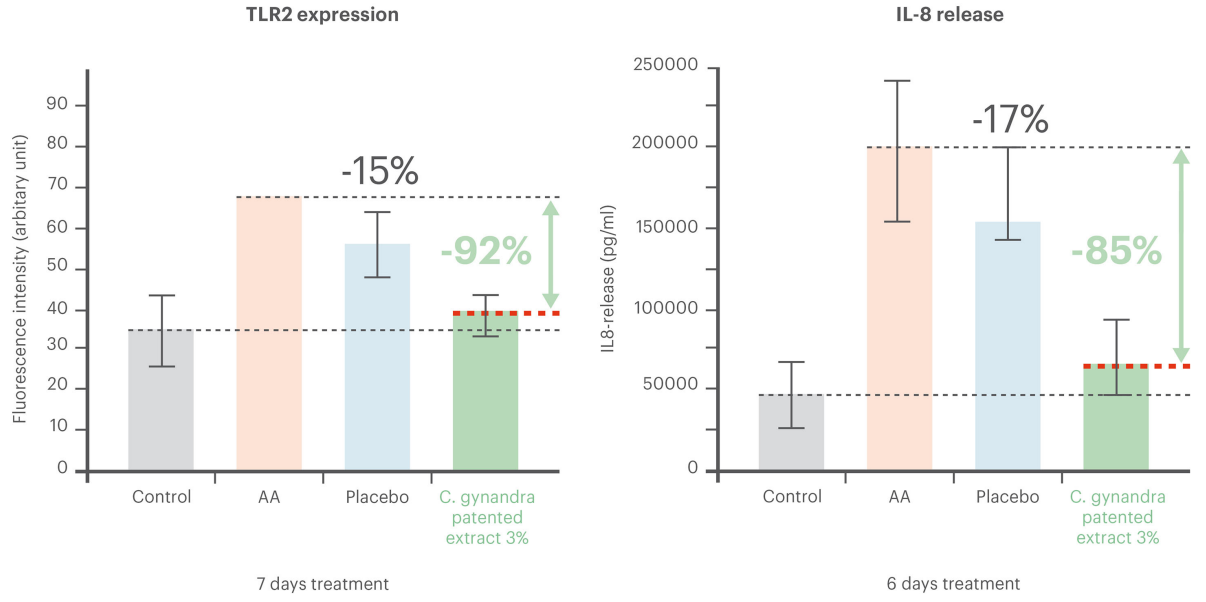


**Figure 10.** TLR2 is a natural receptor of the human immune system which, when activated by *C. acnes*, generates inflammation. Once TLR2 is activated, IL-8 is then released. As one can see, *C. gynandra* patented extract was capable of decreasing in up to 92% the TLR2 expression, and in up to 85% the IL-8 release, due to its anti-inflammatory properties. AA: arachidonic acid. Adapted from [46].

### 3.3. Bisabolol

Bisabolol is potent antioxidant and anti-irritant properties and can reduce proinflammatory cytokine production (e.g., TNF-$\alpha$ and IL-6), which can help in

the treatment of inflammatory conditions of the skin, ameliorating its aspect [51].

In addition to the reduction of proinflammatory markers, bisabolol can also reduce oxidative stress [52] and proved to be safe for topical application on the skin [51].

Due to its anti-inflammatory and antibacterial activities, it can help to treat skin wounds and burns [53] [54], in addition to being a permeation enhancer for the skin penetration of drugs [55].

### 3.4. Hyaluronic Acid

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 anti-stretch 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 [56] [57] [58].

Hyaluronic acid has shown a range of different activities on the skin: buffering action, due to its excellent viscoelastic properties after water absorption [59]; anti-inflammatory and antibacterial properties [60] [61]; antioxidant capacity [62]; and accelerator of the wound healing process [61] [63] [64].

### 3.5. 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 [65] and atopic dermatitis [66].

***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 to altered-skin barrier conditions, presenting positive effects on acne [67], wound healing [68], psoriasis and rosacea [69].

***Rosa canina flower oil* (*dog rose*)**

*Rosa canina* is a remarkable source of vitamin C [70] and has documented antioxidant [71], anti-inflammatory [72], and antimicrobial activities [73], as well as clinic evidence of its effects on eczema [74].

***Cocos nucifera oil* (*coconut*)**

*Cocos nucifera* oil contains monolaurin, a molecule with antimicrobial effects [75]. It presents a marked wound healing capacity [76] and anti-inflammatory property [77].

***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 [78] [79].

***Melaleuca alternifolia leaf oil* (*tea tree*)**

Tea tree oil presents a range of positive effects for dermatological purposes, such as antioxidant effect [80], amelioration of acne vulgaris due to anti-inflammatory and antimicrobial effects against *C. acnes* [81] [82], improvement of seborrheic dermatitis [83], and increase in wound healing rates [84].

***Rosmarinus officinalis leaf oil* (*rosemary*)**

This component has strong antioxidant [85] and anti-inflammatory activities [86] [87]. 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-1$\beta$ [88].

***Vitellaria paradoxa butter* (*shea tree*)**

Topical use of shea butter has demonstrated anti-inflammatory and anti-aging properties [89]. It also plays a positive role in wound healing, wrinkles, and oxidative damage [90].

***Tocopheryl acetate* (*vitamin E acetate*)**

The antioxidant vitamin E has also photoprotective and skin barrier-stabilizing properties [91], being indicated to atopic dermatitis, psoriasis, skin cancer prevention, wound healing, and melasma [92].

### 3.6. Emulsifier and Thickener

Cleoderm™ Clarifying Cream Base utilizes a sunflower-derived oil-in-water emulsifier that is PEG-free, non-ionic, preservative-free, and biodegradable. This plant-based ingredient helps formulation stability and provide emollience to the skin and allows the addition of solvents/excipients and treatment actives while maintaining homogeneity. it also helps to decrease transepidermal water loss (TEWL) and then increases skin hydration and maintenance of barrier function [93].

The acrylamide-free thickener imparts a feathery feel and maintains viscosity through an extremely wide pH range, and is especially effective at low pH for formulations requiring specialized treatment actives [94].

### 3.7. Compatibility with Cosmetic Ingredients

A broad range of active substances have been tested and shown to be compatible in Cleoderm™ Clarifying Cream Base. Compounding pharmacies can use it as a ready-to-use vehicle for multiple formulations. Potential formulations when compounding with Cleoderm™ Clarifying Cream Base are:

- Adapalene (0.1% - 0.3%);
- Alfa-arbutin (0.5% - 2.0%);
- Alpha-bisabolol (0.5% - 2.0%);
- Azelaic acid (1.0% - 25.0%);
- Benzoyl peroxide (2.5% - 10.0%);
- Brimonidine (0.2% - 0.5%);
- Clindamycin (1.0% - 3.0%);
- Cyproterone acetate (0.5% - 2.0%);

- Dapsone (5.0% - 10.0%);
- Ellagic acid (0.25% - 1.0%);
- Enoxolone (0.5% - 1.0%);
- Erythromycin (1.0% - 4.0%);
- Estriol (0.1% - 1.0%);
- Glycolic acid (2.0% - 10.0%);
- Hydroquinone (2.0% - 10.0%);
- Ivermectin (1.0% - 5.0%);
- Kojic acid (1.0% - 4.0%);
- Mandelic acid (2.0% - 10.0%);
- Metronidazole (0.75% - 5.0%);
- Niacinamide (1.0% - 5.0%);
- Progesterone (0.5% - 2.0%);
- Spironolactone (1.0% - 5.0%);
- Tranexamic acid (1.0% - 5.0%);
- Tretinoin (0.01% - 0.1%);
- Vitamin C (5.0% - 20.0%);
- Zinc pyrithione (1.0% - 2.0%);
- Adapalene + benzoyl peroxide (0.1% + 1.0% - 0.3% + 10.0%);
- Azelaic acid + Niacinamide (1.0% + 1.0% - 25.0% + 4.0%);
- Clindamycin + niacinamide + benzoyl peroxide (1.0% + 0.0125% + 4.0% - 1.0% + 0.035% + 4.0%);
- Erythromycin + benzoyl peroxide (1.0% + 3.0% - 5.0% + 7.0%);
- Erythromycin + tretinoin (1.0% + 0.01% - 5.0% + 0.05%);
- Ivermectin + niacinamide + metronidazole (1.0% + 1.0% + 1.0% - 5.0% + 4.0% + 2.0%);
- Metronidazole + niacinamide (1.0% + 1.0% - 2.0% - 4.0%);
- Tretinoin + niacinamide (0.0125% + 4.0% - 0.035% + 6.0%);
- Tretinoin + tranexamic acid + hydroquinone + hydrocortisone (0.0125% + 2.5% + 4.0% + 1.0% - 0.035% + 2.5% + 4.0% + 1.0%).

## 4. Conclusion

The current body of evidence shows that Cleoderm™ Clarifying Cream is an important solution for the production of treatments for acneic and oily skin in the context of personalized medicine. Its compatibility with a broad range of active ingredients, together with its functional ingredients, makes it a prominent vehicle for compounding pharmacies.

## Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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