Brief Overview about Management of Cutibacterium acnes

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Abstract

Background: The skin represents a complex ecosystem. A large and diverse community of microorganisms is present on the body. Depending on the ecological niches, the bacterial distribution can vary .Thus, in a lipidic area, Actinobacteria are more represented, and Cutibacterium acnes can represent until 70% .This anaerobic-aerotolerant Gram-positive bacteria is a skin commensal, and its ecological niche is represented by the sebaceous follicles.C. acnes is able to produce numerous virulence factors. Thus, it produces short-chain fatty acids (leading to a local infammation) which contribute to antibiotic resistance.The mechanisms of antimicrobial resistance of c. acnes in acne mainly involve bioflm formation and genetic mutations in ribosomal RNA (rRNA), leading to higher virulence and transmission of resistant bacterial strains. New treatment approaches targeting c. acnes may include bacteriophages, natural synthetic antimicrobial peptides, probiotics, anti-bioflm agents.

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Keywords: Cutibacterium acnes, Management

Introduction

Acne is a disease affecting mainly the pilosebaceous unit which are hair follicles in the skin that are associated with an oil gland. The clinical features of acne are variable include seborrhea ,non-inflammatory lesions (open and closed comedones), inflammatory lesions (papules ,pustules,nodules and cysts) and various degrees of scars . The distribution of acne lesions depends mainly on the highest density of pilosebaceous units (face, neck, upper chest, shoulders, and back). ***(1).***

Cutibacterium acnes is a dominant cutaneous commensal bacterium both in acne patients and normal individuals. However, it is noteworthy that hypercolonization of C. acnes is not the key factor in acne pathogenesis since acne patients do not harbor more C. acnes in follicles compared with healthy individuals. Instead, the loss of the skin microbial diversity together with the activation of the innate immunity might lead to the chronic inflammatory condition. **(2)**

d- Inflammatory response caused by the immunological activity of c.acnes:

The immune response to C. acnes has a chief role in explanation of acne pathogenesis rather than the damage caused by the bacteria itself. Moreover, c. acnes interacts with markers of the innate immunity,

such as toll-like receptors (TLR),antimicrobial peptides (AMP), inflammatory protease-activated receptors(PAR) and the matrix metalloproteinase (MMP) **(3)**

C. acnes upregulates the secretion of different pro inflammatory cytokines (IL-1a, IL-1b, IL-6, IL-8, IL-12, TNF-α or (granulocyte macrophage colony stimulating factor) by human keratinocytes, sebocytes or macrophages and strongly activates the inflammation of human peripheral neutrophils. Also, it activates TLRs, PARs and antimicrobial peptides (**4)**

i- Toll-like receptors (TLR):

Toll-like receptors (TLR) are transmembrane receptors of the innate immunity system, detecting the invasion by exogenous pathogen. In patients with acne, TLR-2 and TLR-4 are overexpressed in the superficial layers of the epidermis. In vitro, protein extracts of c. acnes stimulate the expression of TLR-2 and TLR-4 by keratinocytes as well as of TLR-2 by macrophages. ***(5)***.

If more cells express TLR-2, acne severity increases as this is leads to more secretion of proinflammatory cytokines, including TNF-α and IL-1,IL-8 and IL-12. This may explained that agents target TLR-2, such as topical retinoids, have been shown to have greater efficacy in patients with more severe acne. Antimicropial peptids like defensins and MMP are also produced in proportion to interaction between c. acnes and TLR-2. ***(6)***,(***7***)

ii-Antimicropialpeptids (AMPs):

They are consisted of cathelicidins and beta-defensins. Human beta-defensin (hBD)-2 is expressed in the pilosebaceous unit and increases in acne lesions as well as is upregulated by C. acnes. Therefore, AMPs may act as a beneficial factor against C.acnes but at the same time, the reaction may stimulate more inflammation in acne **(8).**

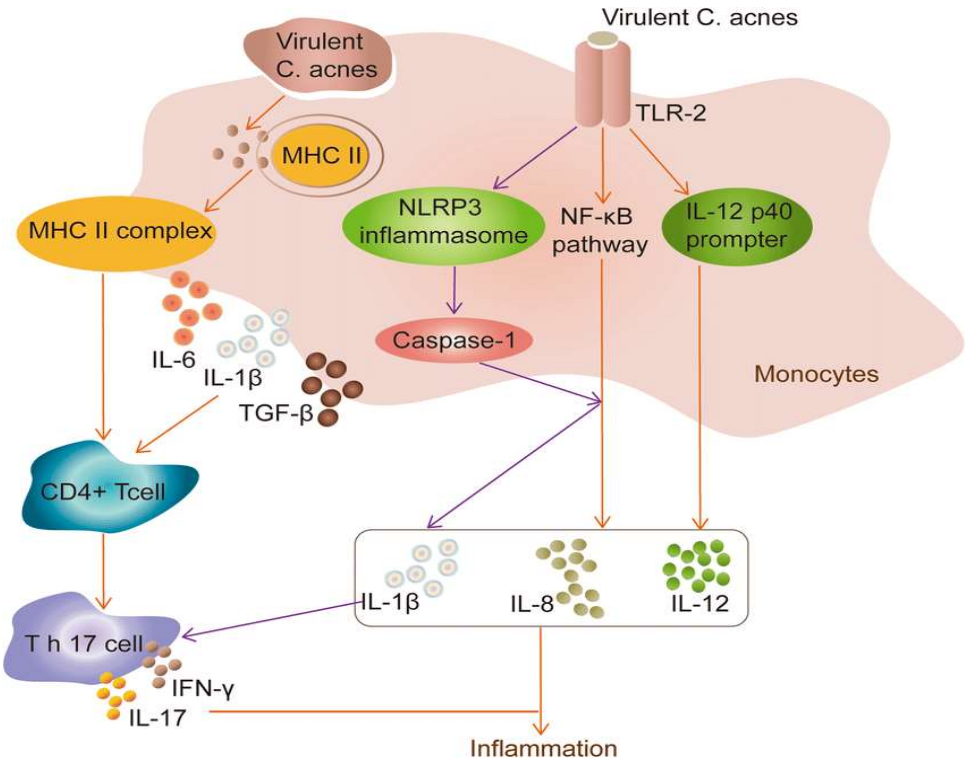

Fig. 1 Inflammatory events in acne vulgaris. C. acnes. **(9)**

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Cutibacterium acnes

The skin represents a complex ecosystem. A large and diverse community of microorganisms is present on the body. Depending on the ecological niches, the bacterial distribution can vary .Thus, in a lipidic area, Actinobacteria are more represented, and Cutibacterium acnes can represent until 70% .This anaerobic-aerotolerant Gram-positive bacteria is a skin commensal, and its ecological niche is represented by the sebaceous follicles**. (12)**

Growth Culture Conditions

Conventional microbial culture of C. acnes from skin samples requires some attention, but in a well-trained microbiology laboratory, it remains easy. Different media can be used, sometimes with supplementation with tween, for example. Schaedler agar, Brucella agar, or chocolate agar plates can be seeded and incubated anaerobically for at least 7–10 days at 37 °C. In acne lesions, different colony aspects can be observed regarding colour and haemolysis. **(10)**

Virulence Factors and antibiotic resistance

1- ***Bioflm***

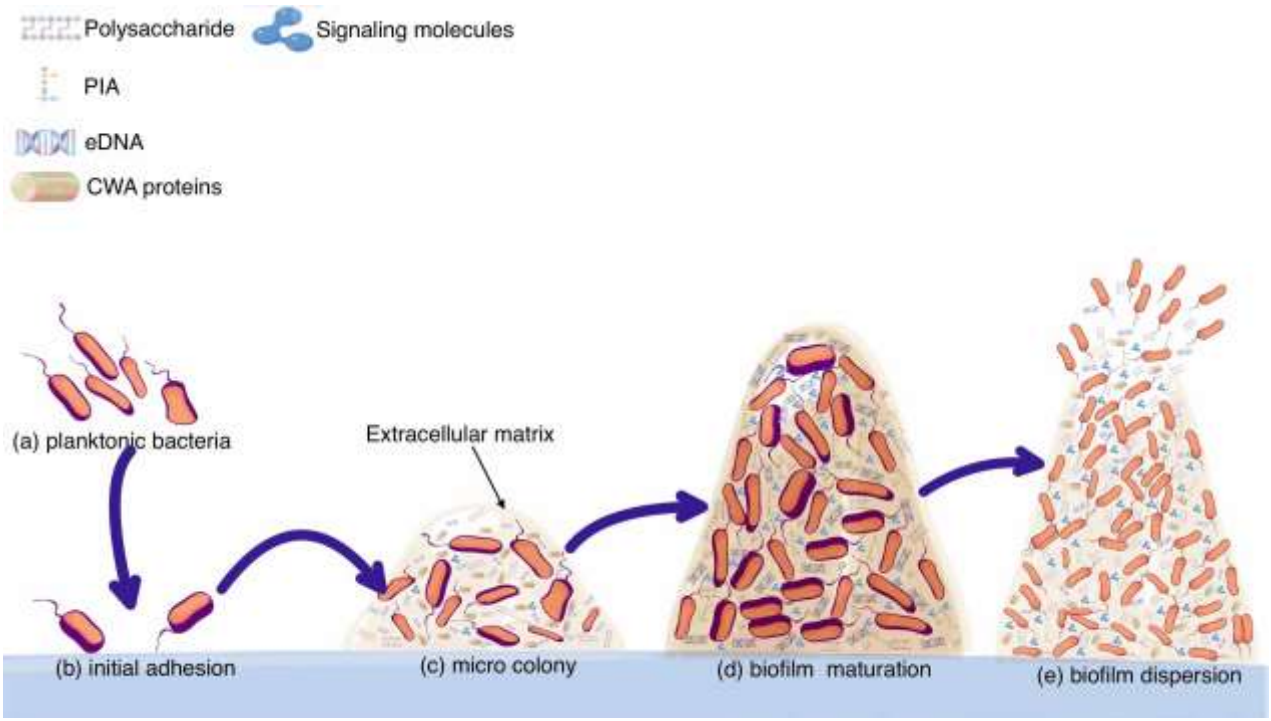
C. acnes bioflms have been found in acne, especially after long-term antimicrobial therapy. Three groups of genes that encode carbohydrate biosynthesis and metabolism, plus various glycosyltransferases, are crucial for bioflm formation. Bioflms facilitate the growth and metabolism of P. acnes, their adhesion to follicular walls, higher virulence, and proinfammatory properties with a greater extracellular lipase activity, as well as antimicrobial resistance. This concept has been furthered by histopathologic study of acne lesions that have a greater degree of follicular colonization and bioflm of c. acnes when compared with controls [31]. The available evidence is mainly derived from in vitro studies, while clinical evidence and interventions targeting c. acnes bioflm in acne treatment are limited. **(11)**

The role of the c. acnes biofilm

1) Bacteria may exist as biofilms in their natural habitat. A biofilm is defined as a microbial aggregate embedded in extracellular matrix which protects cells from harmful conditions in the environment and facilitates escaping from host surveillance mechanisms.

2) It was suggested that P. acnes biofilm may penetrate into the sebum and act like an adhesive, leading to the increased cohesiveness of corneocytes and the formation of microcomedones.

3) A high availability of sebum, a nutritional substrate for P. acnes, may result in an increased proportion of metabolically active bacteria and contribute to a pro-inflammatory phenotype of the P. acnes biofilm. This may explain the acne flares in adolescence when sebum production is dominant**(12)**



Steps of bacterial biofilm formation

From planktonic bacteria to mature biofilms. (A) Planktonic bacteria invade the wound and swim randomly. (B) Planktonic bacteria adhere to the implant surface, which is a reversible process. From forming microcolonies (C) to developing into mature biofilms (D). (E) Biofilm breaks down and bacteria spread outside. ***(*13)**

2-CAMP factors (Christie–Atkins–Munch–Peterson)

The five CAMP factors, encoded by the genome of all C. acnes strains, are membrane pore-forming toxins that act as host tissue degradation enzymes. These secretory proteins are potentially cytotoxic for keratinocytes and macrophages and their activation may result in skin inflammation. Recent in vitro findings indicated that CAMP1 may be involved in C. acnes virulence by interacting directly with TLR2, thus amplifying the inflammatory response ***(6)***

3-Porphyrins

Porphyrins, which exhibit absorbance properties in ultraviolet and visible light, are produced by C. acnes and might contribute to the perifollicular inflammatory reaction during acne development. Indeed, their ability to generate singlet oxygen from oxygen under ultraviolet exposure might enhance the production of cytotoxic substances by oxidation processes, such as squalene peroxide, a proinflammatory lipid.***(6)***

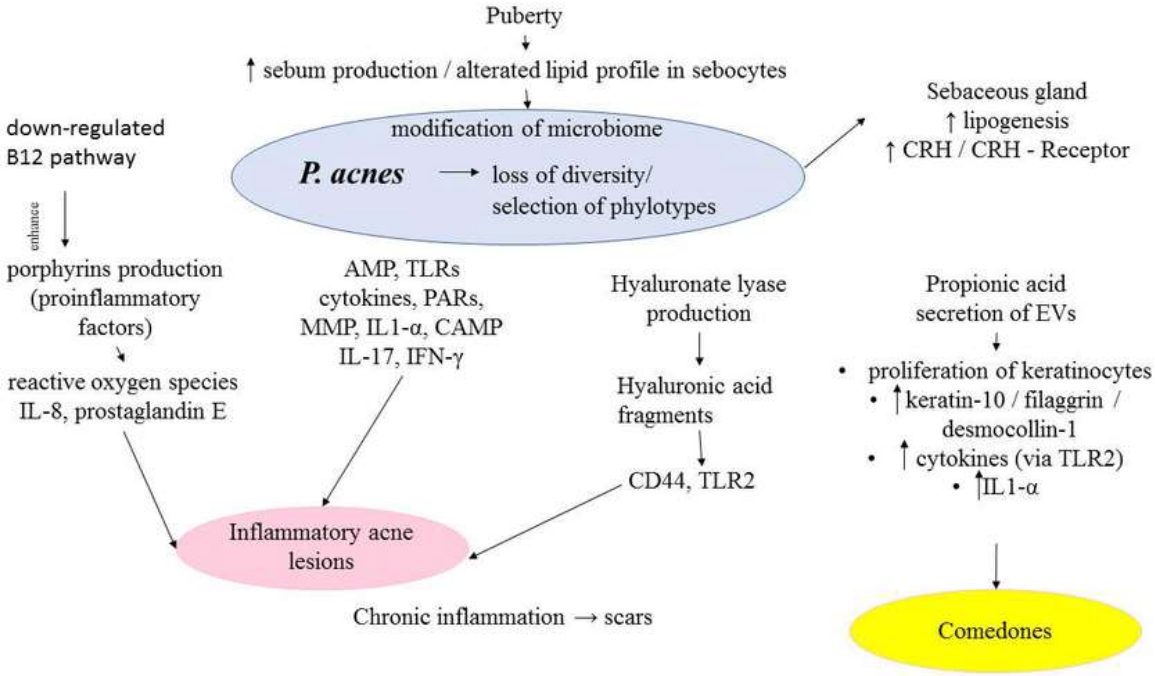
4-Hyaluronate lyase

Recently, the hyaluronate lyase (HYL), has been reported with different gene alleles depending on C. acnes phylotypes. A genotypic and phenotypic investigation, including the generation of a C. acnes hyl knockout mutant, revealed two distinct variants of HYL: one highly active variant (HYL-IB/II), resulting in complete hyaluronic acid degradation and another variant with low activity (HYL-IA), resulting in incomplete hyaluronic acid degradation.***(6)***

Other virulence factors

The acne-associated phylotype IA1 also contains a novel plasmid with a tight adhesion locus and two unique genomic islands, that comprise genes supposed to enhance virulence through increased bacterial adhesion and host immune response.. ***(6)***

Overall, these factors may be important in the emerging association of some C. acnes strains with acne and participate in the modulation of the cutaneous innate immunity and skin inflammation that may influence the severity of inflammatory acne lesions and scars.*(13)*

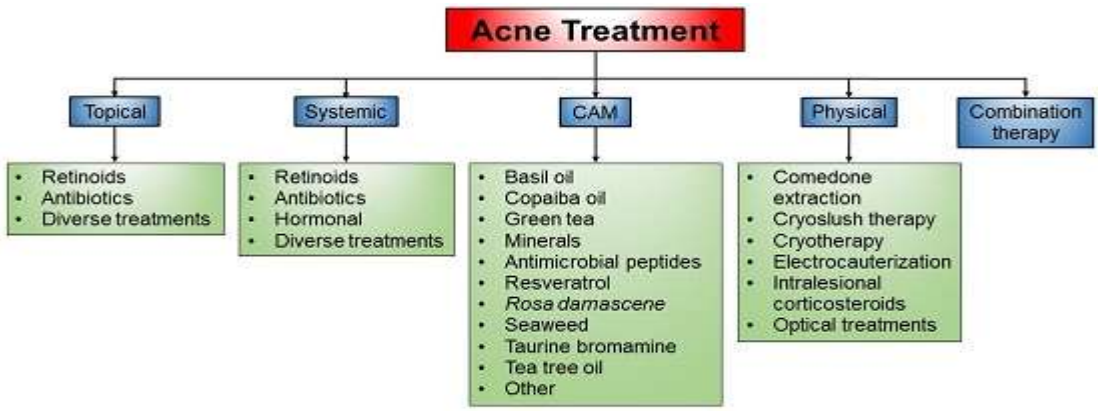


Pathogensis of c.acnes (12)

Management

1	provide the patient with the best appearance
2	minimize scarring and psychological sequelae
3	prevent follicular hyperkeratosis
4	reduce C. acnes
5	inhibit fatty acid production and sebum secretion
6	eliminate comedones

Goals of acne treatment (14)



Topical therapy

Many topical agents are available for the treatment of acne

a- Topical retinoids

A diverse group of vitamin A derivatives that modulate gene expression, are the drugs of choice for the treatment and maintenance therapy of patients with mild-to-moderate acne vulgaris. These agents inhibit keratinocyte proliferation, thereby reducing obstruction of the follicle and preventing the formation of microcomedones. In addition, these agents have an antiinflammatory effect. They are effective for the treatment of comedones, inflammatory papules and pustules. The major side effects are local skin dryness, flaking, erythema, thinning of the stratum corneum, burning sensation and irritation. Some patients may have an exacerbation of acne, so called 'retinoid flare' during the first month of treatment. Topical retinoids are usually applied once daily, preferably at night, due to the photolability and photosensitivity associated with their use.***(14)***

b-Benzoyl peroxide

Is a potent topical antimicrobial with rapid bactericidal action. The bactericidal effect on C. acnes is due to the oxidation of bacterial proteins. Benzoyl peroxide inhibits the lipolysis of sebum triglycerides and decreases the inflammation of acne lesions. In addition, benzoyl peroxide has a modest keratolytic and comedolytic effect. The medication is usually applied once a day. Use of benzoyl peroxide does not induce bacterial resistance and the medication is safe to use during pregnancy or lactation. Benzoyl peroxide can be used as monotherapy or, more commonly, in conjunction with topical retinoids or antibiotic therapy to increase the efficacy of treatment. ***(14)***

c-Topical antibiotics

Have anti-inflammatory properties and, depending on the formulation, are either bactericidal or bacteriostatic. Compared with oral antibiotics, topical antibiotics have the benefit of less systemic toxicity andsystemic side effects. Topical antibiotics should not be used as monotherapy because of the risk of developing bacterial resistance. Combining topical antibiotics with topical retinoids or benzoyl peroxide will improve the therapeutic outcome and will reduce the emergence of antibiotic-resistant strains of C. acnes.***(14)***

d- Dapsone

Is a sulfone antibiotic with anti-inflammatory and antibacterial properties. The medication exerts its antibiotic effect by inhibiting bacterial DNA synthesis. Dapsone is available in 5% and 7.5% gel formulations and is effective as an adjunct treatment for acne vulgaris. The medication is often used in individuals with sensitive skin and in women with acne***.(13)***

e-Azelaic acid

Is a naturally occurring, saturated, straightchained acid that has antibacterial, anti-inflammatory, antikeratinizing, comedolytic, tyrosinase-inhibiting and antioxidant properties. Topical azelaic acid (e.g. 15% or 20% gel) has been used with success for the treatment of acne vulgaris and post-inflammatory hyperpigmentation. The medication has a favourable safety profile and is safe during pregnancy or lactation. Side effects are mild and consist mainly of local erythema, dryness, burning, stinging, pruritus, dysesthesia and hypopigmentation in dark-skinned individuals. No bacterial resistance to azelaic acid has been reported ***(14)***

g-salicylic acid

Salicylic acid (SA) is a typical peeling agent.It is a beta- hydroxy acid extracted from natural botanical sources and can also be artficially synthesized. Variation of SA concentration from 0.5% to 30%, even 50%,changes its affect from cleaning and anti- inflammation to chemical peeling. The safety and tolerance of SA have been demonstrated, and thus, it is widely used in dermatology.Antiinflammatory activity is another important property of SA, relieving facial erythema. Nevertheless, the specific mechanisms and signalling pathways used of SA remain unclear. Accordingly, we initially explored the mechanisms by which SA antagonizes acne in human SEB- 1 sebocytes. This experimentation provided novel basis for the therapeutic rationale involved in the SA treatment for acne vulgaris in human SEB- 1 sebocytes. **(15)**

3)Systemic therapy

a- Oral antibiotics

are an important therapy for acne unresponsive to topical therapy and the more inflammatory types of acne lesions, including pustules, nodular lesions and abscesses. These agents administered systemically produce a significant reduction in C. acnes. In addition, oral antibiotics have intrinsic antiinflammatory properties, exerting their action through the inhibition of neutrophil chemotaxis and the alteration of macrophage and cytokine production.Tetracyclines (doxycycline, minocycline, sarecycline) are preferred because of greater efficacy and better tolerability. In general, tetracyclines should be taken on an empty stomach as the absorption of tetracyclines is inhibited by food. The recommended dose of doxycycline and minocycline is 50 or 100 mg daily or twice daily. ***(14)***

Unclear situations and open questions regarding antibiotic resistance

in acne Antibiotic prescription is the daily decision, and antimicrobial resistance has been recognized as a major global public health concern. Various antimicrobial programmes have been initiated to address this issue in different aspects. The antibiotic resistance in acne treatment has been known for more than 30 years. There are a number of discussions, with many respective measures and efforts being undertaken; however, many open questions remain**. (16)**

b-Oral isotretinoin

(13-cis-retinoic acid) decreases sebum production, follicular keratinization and intrafollicular concentration of C. acnes. In addition, oral isotretinoin has a direct anti-inflammatory effect. It is the drug of choice for severe, extensive, nodular acne vulgaris but is also often used in moderate cases where scarring is evident, acne-related psychosocial distress is significant or other treatment modalities have

failed. Oral isotretinoin shows superior efficacy in the management of severe acne. The considerable benefits must be weighed against their potential risks. (***14)***

Mechanisms of action

Retinoids influence the proliferation and differentiation of cells and therefore reverse the abnormal desquamation by affecting the follicular epithelial turnover. This leads to an expulsion of mature comedones (open and closed type) and suppression of microcomedone formation). The change of the microclimate in the pilosebaceous follicle by prevention of hypercornification promotes an inhospitable aerobic environment for c. acnes and is likely to enhance the penetration of other topical drugs. It can be assumed that an indirect immunomodulatory effect takes place by changing the follicular environment**. (17)**

Role of isotreitinion against c.acne

Prospective study with microbiolgical correlation was done on 50 patients with estimation of lipase enzyme activity produced by c.acnes before and after course of oral isotritinoin. Screening of enzyme production showed that all of the isolates possessed lipase activity before treatment, while, 44(98%) isolates were negative for lipase activity and only, 1(2%) of isolates was exhibiting lipase activity, after treatment. These results indicated that lipase was the common virulence factor which is produced by C. acnes isolated from acne lesions. **(18)**

c-hormonal therapy(contraceptive pills)

For women in post-menarche with acne, hormonal therapy is a therapeutic option. The use of oestrogens in the form of oral contraceptives in the treatment of acne is based on the ability of oestrogen to suppress the stimulatory effect of androgens on pilosebaceous units leading to decreased size and function of sebaceous glands with a resultant reduction in sebum production and keratinous material accumulation. The use of oral contraceptives should be considered in women in post-menarche typically over the age of 15 years with moderate-to-severe, recalcitrant, pustulocystic or nodulocystic acne who do not respond or are intolerant to conventional therapy.***(14)***

d-N Acetyl Cysteine

The effectiveness of oral and topical NAC has been assessed in a few studies and the medication has been shown to help improving inflammatory acne lesions by reducing ROS, inhibiting leukotrienes and prostaglandin, stabilizing membranes, and inhibiting lipidperoxidation.21 Given the studies conducted on the applications and effectiveness of NAC on acne and its complications, including excoriated acne, as well as its functional mechanisms and potential anti-fibrotic effects, which may be able to moderate another side-effect of acne, namely scarring, the present review study was carried out on the applications of NAC in treating acne and its side-effects**.(19)**

An analysis of the data from 99 patients in a double-blind study demonstrated that 5% acetylcysteine topical gel is significantly superior to placebo (P = .04) in reducing comedo counts. Comparable results were obtained in both sexes. This study indicates that acetylcysteine is an effective therapeutic option for the treatment of mild to moderate acne **(20)**

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