

## THE ACNE VULGARIS GEL AND IT'S TREATMENT: A REVIEW

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## ABSTRACT

A prevalent long-term inflammatory disease that affects the pilosebaceous follicles worldwide is acne vulgaris. Its intensity may cause pain, scars, and significant psychological effects, including depression, even though it is not life-threatening. The several causes of acne and the remedies for them are examined in this article. It also covers new dosage formulations, existing drugs, and findings from ongoing clinical studies. Four main aspects contribute to the pathophysiology of acne: inflammation, hyperproliferation of *Propionibacterium acnes* (*P. acnes*), hyperkeratinization of pilosebaceous follicles, and excessive sebum production. Effective diagnosis and treatment of Acne vulgaris relies on accurately identifying acne lesions, including both non-inflammatory (blackheads and whiteheads) and inflammatory (papules, pustules, nodules, and cysts). This review briefly discusses traditional acne treatment approaches, including topical treatments (such antibiotics and retinoids), systemic treatments (including hormone medications, antibiotics, and retinoids), and physical treatments. It also discusses the difficulties caused by *P. acnes*'s resistance to antibiotics that are often found in brand-name drugs, highlighting the need of innovative treatment approaches. Lastly, we look at cutting-edge commercial drugs and new acne therapies that are now undergoing clinical testing.

## 1. INTRODUCTION

People all over the globe suffer from acne, sometimes referred to as The pilosebaceous follicles are impacted by acne vulgaris, a persistent inflammatory skin condition. It is the tenth most prevalent skin condition, affecting an estimated 9.4% of the world's population. About 85% of teenagers suffer from acne, which usually persists until adulthood. About two-thirds of dermatologist visits for acne are made by women.<sup>[1]</sup>

There are two types of acne lesions: inflammatory (papules, pustules, nodules, and cysts) and non-inflammatory (open/black and closed/white comedons). Treatment for these lesions must be continuous and long-term since they might cause pigmentation and skin scarring. The face, neck, chest, and upper back are often affected by acne.<sup>[2]</sup>

Other forms of acne include drug-induced acne (caused by medications such as corticosteroids, isoniazid, lithium, phenytoin, and anabolic steroids), acne in neonates and infants, acne at work, acne fulminans, acne conglobate, acne mechanical, excoriated acne, and chloracne. These variations differ in severity, clinical appearance, and associated symptoms, although sharing clinical and histological traits with acne vulgaris.<sup>[3]</sup>

Acne cannot be completely avoided or cured, but it may be successfully controlled with the right care. Acne has serious financial consequences in addition to its effects on the body and mind. Scientific investigations and conclusions pertaining to treatment regimens have steadily increased as a result of the rising interest in acne research. Both the pathophysiology of acne and the creation of different treatment modalities have been the focus of a great deal of study. The utilisation of combination therapies that address the several pathogenic mechanisms that underlie acne is emphasised by recent developments in acne therapy.<sup>[4]</sup>

The substantial interest and advancement in this topic are shown in the increasing quantity of research publications and scientific findings pertaining to acne therapy. Numerous researches on acne have been carried out, with an emphasis on its pathogenesis and different treatment approaches. The use of combination therapies that address several pathogenic variables causing acne is emphasised by recent developments in acne therapy. Topical applications, innovative therapies, and cutting-edge treatments for efficient acne care are highlighted in the most recent research. These include newly created retinoids with anti-inflammatory qualities and topical retinoids that restore aberrant hyperkeratinisation in the infundibulum.<sup>[5]</sup>

The goal of this article is to present a thorough analysis of the many kinds of acne, their pathophysiology, and the molecular processes connected to them. It also goes into great depth about traditional therapy methods. This review is interesting since it incorporates the results of recent studies and provides a thorough analysis of combination therapy modalities. It also looks at formulations that have been effective and are on the market, as well as dosage forms that are now undergoing different stages of trials. The study also looks at recent advancements and offers a thorough evaluation of possible treatments that are being tested in clinical settings.<sup>[6]</sup>

### 1.1 Factors that contribute to acne pathogens and acne kinds

The conventional aetiology of acne vulgaris involves many significant elements. Genetic predisposition, dietary habits, hormonal imbalances, stress, smoking, environmental variables (such temperature, pollution, humidity, sun exposure, and exposure to mineral oils or halogenated hydrocarbons), and comedogenic medicines (like androgens, halogens, and corticosteroids), bacterial colonisation, and the use of specific cosmetics are some of these. Acne may develop, worsen, or worsen as a result of several conditions. Deformity, emotional anguish, physical agony, and perhaps long-lasting scars are all frequent outcomes of acne vulgaris (AV). Patients may also suffer from feelings of humiliation and worry, which can further exacerbate depression.<sup>[7]</sup>

The aforementioned exposome variables have an impact on the multifactorial aetiology of acne. Excessive sebum production, cut bacterium *acnes* (previously *Propionibacterium acnes*) hyperproliferation and colonisation, aberrant hyperkeratinisation of Acne is caused by four main factors: inflammation, pilosebaceous follicles, and other factors. These contributing factors and the fundamental pathophysiology will be discussed in more detail in the next section.<sup>[8]</sup>

### 1.2 Causes and pathophysiology of acne vulgaris

Acne vulgaris's traditional aetiology is thought to be significantly influenced by a number of contributing variables. Increased sebum production, hormonal factors including androgens, aberrant follicular infundibulum keratinisation, bacterial growth, and the ensuing inflammation are the main causes of chronic acne, as was previously mentioned.<sup>[9]</sup>

#### A. An increase in sebum production

An increase in sebum production inside hair follicles is a major contributing factor to the development of acne. Androgen hormones, are important for promoting sebum production and secretion, according to Gollnick et al. Acne lesions' frequency and severity are clearly correlated with increased sebum production. Thus, while treating individuals with acne vulgaris, this component is essential to take into account.<sup>[10]</sup>

#### B. Anomalies in the pilosebaceous follicles' hyperkeratinization

Single-cell keratinocytes are often released into the follicular lumen by healthy follicles, where they are later removed. Keratinocytes, on the other hand, overproliferated and improperly shed into the lumen in acne sufferers. This causes lipids and monofilaments to accumulate in the pilosebaceous follicles, together with irregularly desquamated corneocytes.<sup>[11]</sup>

#### C. *Propionibacterium acnes* (*P. acnes*) hyperproliferation

*Cutibacterium acnes*, formerly known as *Propionibacterium acnes*, is another cause of acne. It is important to the pathophysiology of inflammatory acne. Because sebaceous follicles produce a lot of sebum, which creates the perfect anaerobic habitat for bacterial development, lipophilic, anaerobic bacterium, flourishes there. In order to help develop comedones and cause irritation on the skin, the bacteria secretes Glycerol and free fatty acids are produced when sebum triglycerides are broken down by the lipase enzyme.<sup>[12]</sup>

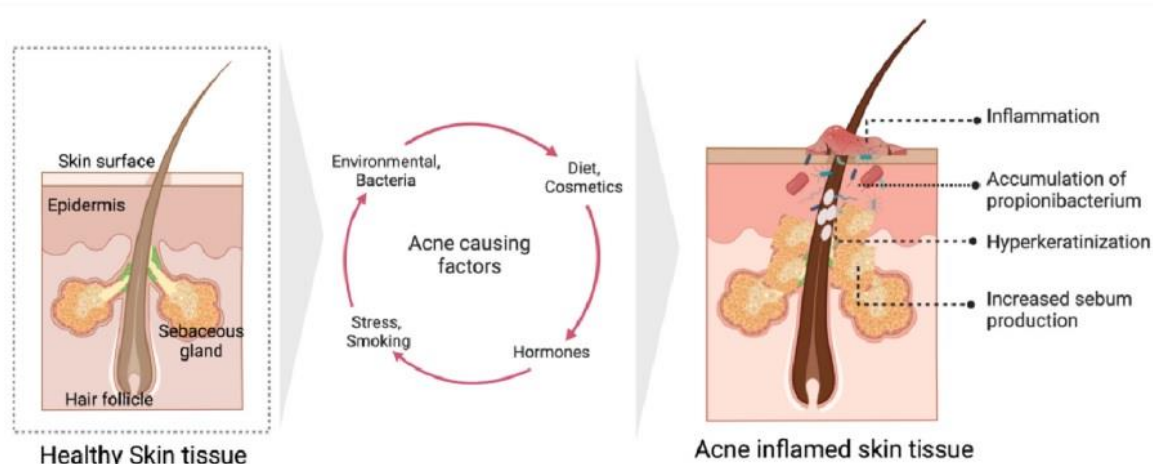
#### D. Inflammation acne

An inflammatory reaction is set off recognises *Cutibacterium acnes*. By producing chemotactic chemicals that attract immune cells including lymphocytes, neutrophils, and macrophages, *Candida acnes* has a potent inflammatory response.<sup>[13]</sup> These disorders have the potential to injure or rupture follicles, which can then discharge lipids, fatty acids and microbes into the dermis. Inflammatory lesions, such as pustules, nodules, cysts, and papules, are the result of this series of events. Conversely, compared to their inflammatory counterparts, Lesions without inflammation are smaller and produce less pus.<sup>[14]</sup>

Reactive oxygen species (ROS), which are produced by neutrophils and harm the follicular epithelium, further aggravate inflammation. Several inflammatory lesions of acne are further fuelled by this injury, which permits follicular contents to be discharged into the dermis.<sup>[15]</sup>

#### E. DNA Methylation

Gene expression can be changed via epigenetic modifications brought on by environmental stress, which are the outcome of the interaction between genetic and environmental variables. The most researched of these alterations is DNA methylation, which has drawn interest in dermatology due to its association with autoimmune, neoplastic, and inflammatory skin conditions. The causes and course of inflammatory skin conditions include psoriasis, atopic dermatitis, and hidradenitis suppurativa, and others have been linked to DNA methylation. Similar to this, epigenetics contributes significantly to the development of acne vulgaris by shedding light on its molecular underpinnings and suggesting possible treatment approaches.<sup>[16]</sup>



**Fig. 1: The Difference Between Healthy and Inflamed Skin Tissue in Acne.**

### 1.3 Types of acne lesions

This group includes acne forms such as conglobate, rosacea, fulminans, cosmetica, mechanica, chloracne, medicamentosa, and excoriée (picker's acne). Acne vulgaris is the most prevalent kind, making up 99% of all acne occurrences. There are two main types of lesions: inflammatory lesions (papules, pustules, nodules, and cysts) and non-inflammatory lesions (open and closed comedones). Open comedones, also referred to as blackheads, and closed comedones, sometimes called whiteheads, are the two different kinds of comedones.<sup>[17]</sup>

**Blackheads:** Blackheads are non-inflammatory acne lesions that develop when an accumulation of Hair follicles are obstructed by oil and dead skin cells. Because the blocked hole stays open, exposing the substance to air, which oxidises and gives it a dark appearance They are referred to as open comedones and are often brown or black. Often present on Blackheads are small acne lesions on the shoulders, back, neck, chest, arms, and face.<sup>[18]</sup>

**Whiteheads:** When oil, bacteria, and dead skin cells clog the pores of the hair follicles, whiteheads tiny, non-inflammatory pimples form. Closed comedones are called whiteheads., as opposed to blackheads, since the pore stays sealed, giving them a white look. Although they can form anywhere on the body, whiteheads most commonly occur in The forehead, chin, and nose are all part of the T-zone.<sup>[19]</sup>

**Papules:** Healthy skin tissue responds to increased androgen activity, excessive oil production, and bacteria by becoming inflamed. It is characterised by discomfort, heat, redness, and swelling. A period of transition between acne lesions that are inflammatory and those that are not is represented by inflammatory lesions such papules. Papules are tiny, pink pimples that are smaller than 5 mm in diameter, free of pus, and frequently show up as a transitional phase of acne development.<sup>[20]</sup>

**Pustules:** Small, inflammatory acne lesions called

pustules appear when pores clog with dead skin cells and excess oil. usually appears as red, inflamed skin with white pimples around it, they are distinguished by a centre region filled with pus or fluid. Numerous body areas, such as Pustules may grow along the hairline and on the shoulders, chest, back, face, neck, pelvic area, and underarms.<sup>[21]</sup>

**Nodules:** A severe kind of inflammatory acne known as acne nodules develops when bacteria, excess oil, and dead skin cells block pores. Despite the fact that this combination often causes whiteheads or blackheads, deeper infections can harm the pores and surrounding tissue by penetrating beneath the skin's surface. Nodules—red, swollen bumps—are the outcome of this. Unlike other forms of acne, acne nodules are more severe, may last for weeks or even months, and are not effectively treated with over-the-counter medications alone. Nodular acne lesions are bigger than papules, measuring more than 5 to 10 mm in diameter, and they frequently appear along the chin or jawline.<sup>[22]</sup>

**Cysts:** Cystic acne, another severe kind of inflammatory acne, develops under the skin due to clogged pores caused by bacteria, dead skin cells, and oil accumulation. Regardless of age, those with oily skin are more likely to experience it. Large, painful, pus-filled red or white lesions are the hallmark of cystic acne, which frequently leaves scars behind. Anywhere on the body, including, these cysts can develop. Inflammatory and non-inflammatory symptoms are often present in people with cystic acne.<sup>[23]</sup>

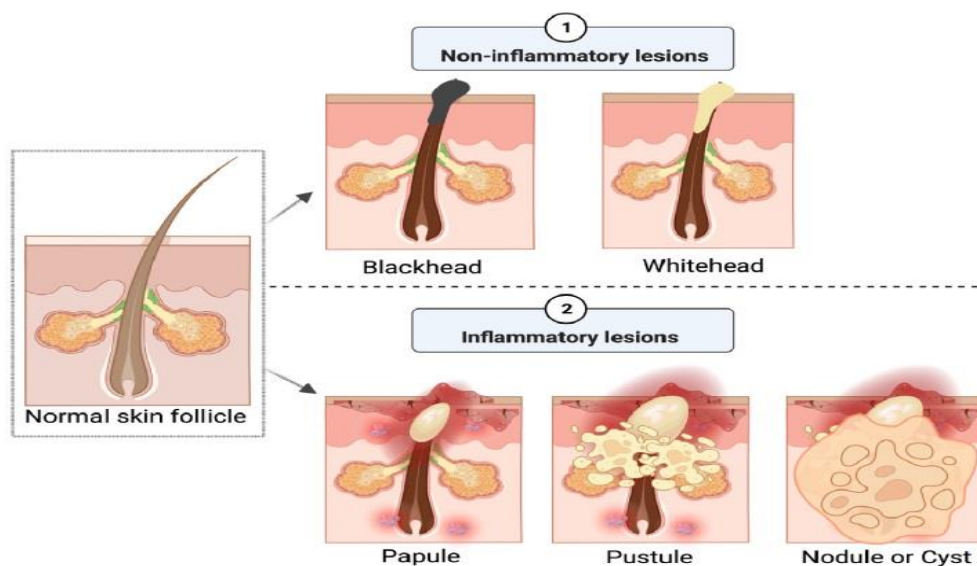


Fig 2. Lesions that are inflammatory and those that are not.

### 1.3.1 The prevalence of acne

Acne vulgaris is the ninth most prevalent skin condition worldwide, with an estimated prevalence of 9.39% across all age categories, according to the Global Burden of Disease Study. About 35% to 100% of people have acne of teenagers at some time, with prevalence rates varying greatly between nations and age groups.<sup>[24]</sup>

Adult acne prevalence was found to be 0.74% in research by Shah et al. on the clinico-epidemiological characteristics of adult acne vulgaris more reporting to medical institutions and more public awareness may be the causes of the rising prevalence of adult acne. Furthermore, it has been proposed that high-glycemic diets are a contributing cause to the increasing incidence of acne.<sup>[25]</sup>

## 2 Acne Treatment

By treating excessive sebum production, aberrant hyperkeratinisation of pilosebaceous follicles, and Cut bacterium *acnes* (formerly *Propionibacterium acnes*) infection, Controlling and eliminating existing lesions is the primary goal of acne vulgaris treatment. Therefore, antibacterial and anti-inflammatory drugs that may be used locally, orally, or systemically are the primary therapy choices.<sup>[26]</sup> Non-pharmacological methods such intralesional corticosteroids, comedone extraction, cryotherapy, optical therapy, and cry slush therapy are also used in addition to pharmaceutical therapies. It has been discovered that combination therapy, which includes both topical and oral medications, is very successful in controlling the pathophysiology of acne.<sup>[27]</sup>

### 2.1 Topical treatments

Applying topical treatments topically to the afflicted region maximises while minimising systemic absorption. There are several topical formulations to choose from, such as lotions, washes, solutions, gels, and creams. Topical medicines are often used to treat acne ranging from moderate to severe. Acne is often treated topically

with antibiotics in addition to retinoids. Skin inflammation is one of the most frequent adverse effects of topical anti-acne drugs. Depending on how severe the illness is, treatment might last anywhere from 6–8 weeks to several years.<sup>[28]</sup>

#### 2.1.1 Retinoids

For inflammatory and non-inflammatory acne, topical retinoid therapy is the most popular first-line treatment. Retinoids may mend the epithelial layer, prevent the formation of new acne lesions, limit comedone development, decrease sebum production, and treat hyperpigmentation and scarring. But this treatment is a long procedure, and it often takes more than three months to see results. Dryness and skin sensitivity are topical retinoids' primary disadvantages. Acne is often treated with retinoids such as tazarotene, adapalene, and retinoic.<sup>[29]</sup>

#### 2.1.2 Antibiotics

Mild to severe inflammatory acne is usually treated with topical antibiotics. By working on These medicines primarily target *P. acnes* to minimise inflammation on the skin's surface. Erythromycin and clindamycin are the two topical antibiotics most often used to treat acne; tetracycline and chloramphenicol, on the other hand, are less effective or have undesirable side effects. Bacterial resistance may be prevented more successfully by employing topical antibiotics with topical retinoids or benzoyl peroxide instead of just antibiotics. Topical antibiotics, when used topically, help acne sufferers by lowering inflammation and *P. acnes* colonisation. The following topical antibiotics are often used to treat acne.<sup>[30]</sup>

#### A. Benzoyl Peroxide

A topical, non-antibiotic disinfectant with antibacterial qualities, benzoyl peroxide (BPO) is often used to treat moderate to severe acne. BPO has a bactericidal effect on *P. acnes* by producing free oxygen, which promotes



the breakdown of bacterial proteins. BPO monotherapy may be used for 6–8 weeks to treat acne patients initially, although topical antibiotics are often used in conjunction with BPO to improve therapeutic effectiveness and lower the likelihood of *P. acnes* resistance. Itching, skin peeling, Redness and discomfort are common side effects of BPO.<sup>[31]</sup>

### B. Salicylic acid

Niacinamide protects the skin against acne by reducing sebum production, a kind of vitamin B3 (nicotinamide), helps cure acne. Niacinamide works well for due of its anti-inflammatory properties, moderate to severe acne. Additionally, it helps heal wrinkles, redness, fine lines, and sun damage. Many skincare products and acne treatments include niacinamide because of its therapeutic advantages.<sup>[32-33]</sup>

### C. Niacinamide

Naturally found in barley and wheat, azelaic acid has keratolytic, antimicrobial, attributes that are both antioxidant and anti-inflammatory. Research has shown that azelaic acid combination treatment works better than azelaic acid alone. Redness, burning, stinging, and even trouble breathing are common side effects. Apart from acne, azelaic acid is also utilised to treat skin conditions including hyperpigmentation and skin whitening.<sup>[34]</sup>

### D. Dapsone

However, its exact mechanism of action for acne treatment is yet unclear, dapsone (diaminodiphenyl sulfone) has antibacterial and anti-inflammatory qualities. According to recent research, dapsone may be effective in treating Its antibacterial, immunomodulatory, and anti-inflammatory qualities can treat moderate to severe acne. Using dapsone gel (5.1%) may reduce acne lesions that are inflammatory or non-inflammatory. It is a more cost-effective choice because of its comparatively cheap price, especially in underdeveloped nations. As a first-line therapy for acne vulgaris, it is not advised.<sup>[35]</sup>

## 2.2 Systemic treatment

Given that both inflammatory and non-inflammatory acne lesions are mostly influenced by the microcomedo, topical retinoids are a first-line treatment option. When patients do not respond oral systemic medicine in response to topical therapies or when acne manifests as nodular or scarring lesions. For acne sufferers to avoid psychological Systemic therapy is necessary for social shame and pain. Oral antibiotics, hormonal medicines, and isotretinoin are the three most used systemic therapies for acne vulgaris.<sup>[36]</sup>

### 2.2.1 Retinoids

The most popular retinoid for treating systemic acne is isotretinoin, which is a derivative of vitamin A. It is still the first-line therapy for severe nodular or inflammatory acne, and for a long time it was the only drug that could successfully suppress acne. Patients with moderate to severe acne who have not responded to previous oral or

topical treatments may also find it beneficial. Regarding severe acne on the face and trunks, acne that leaves scars, and acne that makes people feel distressed, isotretinoin is also considered a first-line therapy.<sup>[37]</sup>

The only drug now available that targets all four of the pathogenic causes of acne is isotretinoin. It functions by de-differentiating the sebaceous glands, reducing sebum production, changing the bacterial ecology on the skin, and preventing *P. acnes* from colonising hair follicles. Additionally, it encourages keratinocyte shedding. The average course of isotretinoin medication lasts 16–24 weeks. Throughout the course of treatment, patients must be continuously monitored due to the possibility of negative consequences.<sup>[38]</sup>

### 2.2.2 Antibiotics

For acne that is moderate to severe, oral antibiotics are frequently administered, especially if the acne is inflammatory, has not responded either covers a substantial area of the body or is similar to earlier topical therapies. Among the often used antibiotics include fluoroquinolones (like levofloxacin), tetracyclines (such doxycycline, minocycline, and lymecycline), erythromycin, clindamycin, azithromycin, roxithromycin, and co-trimoxazole. These antimicrobials function by preventing *P. acnes* from growing and by reducing the inflammatory mediators that the bacteria release.<sup>[39]</sup>

The effectiveness of these antibiotics relies on their capacity to enter the lipid environment of the *P. acnes*-containing dermal pilosebaceous follicles. Tetracyclines' cheap cost, antibacterial, and anti-inflammatory qualities make them popular. Because they are more lipid-soluble, have higher anti-inflammatory effects, and produce less gastrointestinal discomfort, doxycycline and minocycline are favoured over tetracycline for improved penetration into pilosebaceous follicles. Nevertheless, the effectiveness of doxycycline and minocycline over tetracycline is not sufficiently supported by the available data. Interestingly, compared to macrolides, tetracyclines are also linked to decreased rates of *P. acnes* resistance.<sup>[40]</sup>

Not enough research has been done on azithromycin's effectiveness in treating acne. Although *P. acnes* levels are lowered and erythromycin and clindamycin have minor anti-inflammatory benefits, vulgaris has been associated with increasing bacterial resistance, which limits their usefulness. Combinational medicines are currently favoured in order to maximise therapy efficacy and reduce resistance. Treatment with oral antibiotics is usually limited to 12 weeks and is frequently in conjunction using topical medications like retinoids or benzoyl peroxide.<sup>[41]</sup>

### 2.2.3 Hormonal treatment

Hormonal treatment is a popular approach for treating acne in adult females and adolescents, especially since it

may target androgen action on sebaceous glands, which are androgen-dependent. Oral contraceptive tablets, which prevent testosterone from stimulating the formation of sebum, are frequently used as hormonal therapies. These tablets lower the body's levels of physiologically by boosting the production of globulin that binds sex hormones, which generates free, active testosterone.<sup>[42]</sup>

Women's acne may be effectively managed with oral contraceptives, either on their own or in combination with other treatments. However, utilising hormonal anti-androgens to treat acne in females is advised to last at least a year, since the positive benefits of hormone therapy usually become apparent after 3–6 months. By lowering inflammation and treating female acne, the androgen receptor blocker spiro lactone is frequently used in conjunction with oral contraceptives to improve treatment effectiveness.<sup>[43]</sup>

### 3 The advancements and commercial products

The intricacy of acne has recently been better understood scientifically, opening up new research and therapy options. Among these are methods for blocking the mechanisms that lead to the formation of acne. In order to control these pathways, recent research has focused on receptors, proinflammatory mediators such as cytokines and chemokines. Crucial roles in managing acne are also played by elements including follicle-dwelling bacteria, genetic predisposition, the skin microbiome, and nutritional treatment.<sup>[44]</sup>

Using drugs that release nitric oxide (NO), which have strong anti-inflammatory, antibacterial, and antioxidant effects, is one potential strategy. A potent vitamin A derivative, isotretinoin (ISO) is still a very successful medication that can provide long-term acne remission. It is linked to significant adverse effects, though, such as teratogenicity, eye and skin responses, blood parameter alterations, and, in rare instances, acne fulminans. Optimising therapy through dose modifications and combination medicines is crucial to improving patient outcomes and minimising severe negative effects.<sup>[45]</sup>

Over the past 20 years, significant Understanding the fundamental causes of acne has advanced, yet, the development of innovative treatment regimens still faces obstacles. These gaps are being filled by ongoing clinical trials, some of which are included in (from ClinicalTrials.gov). Even though a lot of research has been done on acne treatments, only few of them have made it through clinical testing and are now on the market.<sup>[46]</sup>

Nowadays, most acne treatments are either systemically or topically; relatively few medications combine the two approaches. Table 2 lists a number of commercial treatments that are sold worldwide, illustrating the variety of acne treatment alternatives.<sup>[47]</sup>

### 4 CONCLUSIONS

A frequent inflammatory skin problem is acne that often results in social humiliation and depression, especially in adults. Four major pathogenic elements impact acne development and offer important information to help researchers create efficient treatment plans. These elements are crucial in the development of inflammatory lesions from non-inflammatory ones.

Even though topical, systemic, and physical therapy are well-established methods for treating acne, problems like antibiotic and medication resistance still exist. Additionally, monotherapy techniques have not been enough to control acne completely. To improve the outcomes Dermatologists and other medical professionals that treat acne experts are always investigating new medication options, creative approaches, and combination therapies.

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