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Review Article

Review on Pathophysiology and Modern Treatment of Acne Vulgaris

Shaikh Taiba Zaki*, Gavhane Anjali, Tolsarwad Ganesh

Swami Vivekanand College of Pharmacy, Udgir

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ABSTRACT

Acne vulgaris is a prevalent chronic inflammatory disorder of the pilosebaceous unit, primarily influenced by hormonal stimulation of sebum production, abnormal keratinocyte proliferation, Cutibacterium acnes dysbiosis, and activation of innate immune pathways. Conventional therapies such as topical retinoids, benzoyl peroxide, antibiotics, hormonal agents, and systemic isotretinoin remain effective; however, their long-term use is often limited by antibiotic resistance, adverse effects, and poor patient adherence. Recent advancements in acne management have introduced novel, targeted approaches, including narrow spectrum antibiotics like sarecycline, sub-microbial tetracycline dosing, nanotechnology-based drug delivery, and sebaceous targeting light and laser modalities (1726-nm lasers). In addition, innovations in microbiome directed therapies, including extracellular vesicle based immunomodulation, show safer and more precise alternatives aimed at restoring microbial balance rather than eradicating C. acnes together, these emerging treatment strategies represent a shift toward personalized, mechanism based dermatologic therapy, with the potential to enhance efficacy, reduce safety concerns, improve adherence, and better address quality of life impacts in patients affected by acne vulgaris.

INTRODUCTION

Acne vulgaris is one of the most prevalent long-lasting inflammatory skin disorders globally. It primarily impacts teenagers and young adults, affecting the hair follicle and oil gland units in the skin. It may persist or even start in later stages of life. This condition is marked by the presence of papules, pustules, nodules, and cysts, and it can also place serious psychological and social

challenges on those who experience it. The development of acne is now recognized as a complex inflammatory condition influenced by hormonal factors, microbes, and innate immune responses, resulting from a sophisticated interplay of hormonal shifts, genetic factors, environmental influences, and disruptions in the microbiome over several years. In recent years, acne treatment has expanded to include a broader range of advanced options, from new topical products to laser

***Corresponding Author:** Shaikh Taiba Zaki

Address: Swami Vivekanand College of Pharmacy, Udgir

Email ✉: taibazaki2@gmail.com

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treatments. This review offers a detailed examination of the underlying pathological mechanisms of acne vulgaris and explores both

traditional and cutting-edge treatment methods, with an emphasis on their effectiveness, safety, and potential future research avenues. [1,2,3].

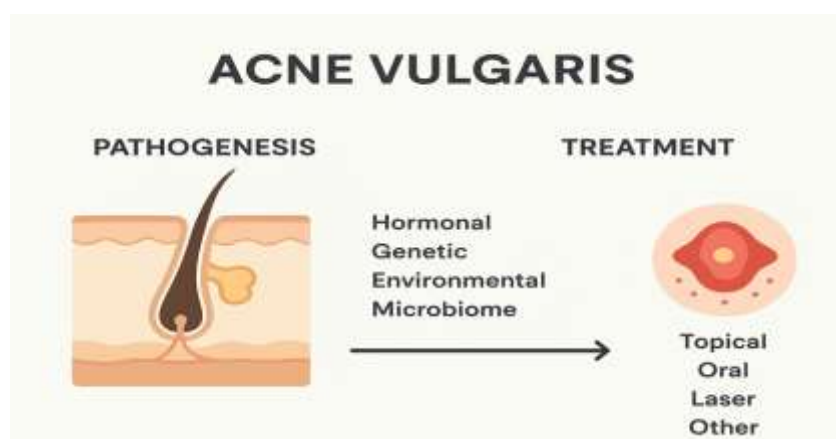


FIG NO 1: Pathogenesis and Treatment Overview Of Acne Vulgaris

(2) LITERATURE REVIEW:

1. Prevalence and Burden of Acne Vulgaris

Dreno and Poli (2017) noted that acne stands out as one of the widespread long-term inflammatory skin conditions, especially prevalent in teenagers. Tanghetti (2020) emphasized its significant psychological effects, such as anxiety, social isolation, and diminished quality of life [1,2].

2. Pathophysiological Complexity Involving Microbial Dysbiosis

Cavallo and colleagues (2022) showed that biofilms of *Cutibacterium acnes* play a role in ongoing inflammation and can make treatments less effective. Additionally, a study by Rozas and others (2021) indicated that specific phylotypes of *C. acnes* are important for keeping the skin balanced, suggesting that acne arises from an imbalance in the skin's microbiome instead of solely due to infection [8,9,38].

3. Inflammatory Pathways and NLRP3 Inflammasome Activation

Research by Spittaels et al. (2021) indicated that porphyrins from *C. acnes* strains linked to acne activate NLRP3 inflammasome activity, causing the secretion of IL-1 β and additional cytokines. This supports the notion that acne is an immune-mediated inflammatory condition and not merely a bacterial infection [10].

4. Clinical Effectiveness of Traditional Therapies

Zaenglein and colleagues (2016) identified topical retinoids as the primary treatment because of their ability to reduce comedones and inflammation. Williams and Layton (2014) confirmed that adapalene is not only effective but also gentler on the skin than traditional retinoids, endorsing its application for mild to moderate acne. [3,15].

5. Antibiotic Stewardship and Narrow-Spectrum Antibiotics

Dreno and colleagues (2017) indicated that extended use of broad-spectrum antibiotics for treating acne elevates antimicrobial resistance, necessitating improved management practices. Moore and Charles (2017) revealed that the narrow-spectrum antibiotic sarecycline

specifically targets the acne-related Cutibacterium acnes while leaving the gut bacteria unaffected. Moreover, Moore and others (2017) indicated notable clinical advancements in inflammatory lesions when using sarecycline. Deeks (2019) validated that it has a reduced chance of causing systemic side effects compared to traditional tetracyclines. Collectively, these results endorse a limited use of antibiotics, avoidance of single-agent therapy, and a preference for targeted treatments [4,5,6,7].

6. Advancements in Laser and Light-Based Treatments

Gold and colleagues (2022) noted that lasers with a wavelength of 1726 nanometers effectively decrease inflammatory lesions by specifically focusing on sebaceous glands. A study conducted by Spathis and others (2020) validated that light therapy enhances the condition of ongoing acne and its resultant scars, providing a non-medicinal option for stubborn instances. [22,23,24].

7. Emerging Nanotechnology & Microbiome-Based Therapies

Spada and colleagues (2018) showed better effectiveness with fixed-dose combination treatments that utilize nanoparticles for improved delivery. Cavallo and others (2023) indicated that extracellular vesicles derived from non-harmful Cutibacterium acnes strains can influence inflammation, highlighting possible future applications for personalized treatments based on the microbiome [14,21,31].

(3) AIM&OBJECTIVES

AIM:

- Review on pathology and advanced treatment of acne vulgaris

OBJECTIVES:

- To understand the pathophysiology of acne vulgaris, including the roles of hormones, sebum production, follicular hyperkeratinization, Cutibacterium acnes, and inflammation.
- To review traditional treatment approaches such as topical agents, systemic therapies, and hormonal treatments used in acne management.
- To explore advanced and emerging therapeutic innovations, including narrow-spectrum antibiotics, laser/light-based technologies, nanotechnology-driven formulations, and microbiome-based therapies.
- To evaluate and compare the efficacy, safety, and challenges of conventional and advanced treatments, emphasizing patient adherence and future directions in acne care.

(4) MATERIAL AND METHOD

(4.1) PATHOPHYSIOLOGY OF ACNE VULGARIS:

Understanding the mechanisms by which various factors interact with the pilosebaceous unit is essential for developing effective treatments for acne vulgaris [3,33].



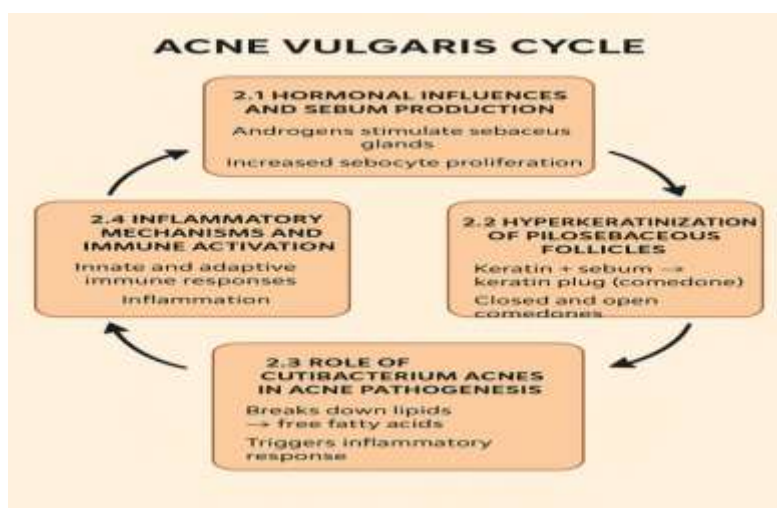


FIG NO 2: Acne vulgaris pathogenesis cycle

(4.1.1) HORMONAL INFLUENCES AND SEBUM PRODUCTION:

A key element in the development of acne is the rise in sebum generation. Hormones like androgens, especially testosterone and Insulin-like Growth Factor-1 (IGF-1), are crucial in promoting the sebaceous glands to produce more sebum than normal. The effects of these hormones are significant, as they not only aid in the initial

development of acne lesions but also shape the conditions for other harmful factors to operate. An overproduction of sebum leads to a lipid-heavy environment that encourages the growth of bacteria that naturally reside on the skin, paving the way for later inflammatory reactions. The connection between hormonal spikes, particularly during puberty, and heightened sebum production emphasizes the relationship between hormonal changes and skin issues [33].

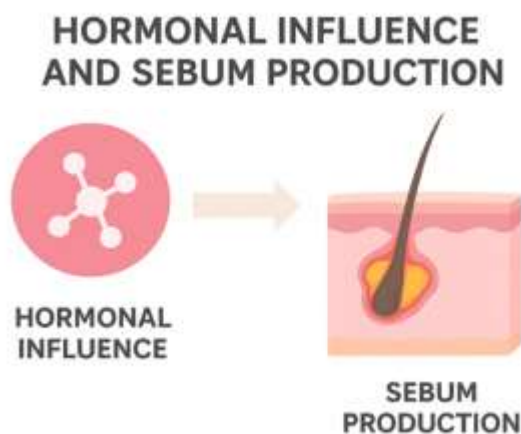


FIG NO 3: Hormonal regulation of sebum production in acne vulgaris

(4.1.2) HYPERKERATINIZATION OF PILOSEBACEOUS FOLLICLES:

Keratinocytes detach from the typical follicular skin layer in a regulated way. Conversely, hyperkeratinization takes place when

keratinocytes grow excessively and do not shed properly in individuals with acne. This unusual turnover of keratinocytes leads to the formation of microcomedones, which can develop into visible open (blackhead) or closed (whitehead) comedones. The blocking effect is worsened by

the buildup of sebum and cellular waste inside these follicles, creating a breeding ground for bacteria [3].

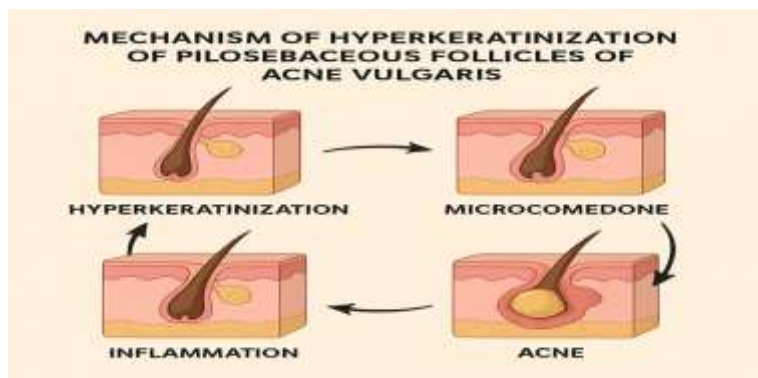


FIG NO 4: Pathophysiological Mechanism of Follicular Hyperkeratinization in Acne Vulgaris

(4.1.3) ROLE OF CUTIBACTERIUM ACNES IN ACNE PATHOGENESIS:

Cutibacterium acnes, which was previously known as Propionibacterium acnes, plays a significant role in the onset of acne. While it is a frequently found commensal organism in the skin's microbiome, specific phylotypes, particularly SLST H1, are closely linked to inflammatory acne. Research has shown that C. acnes produces

lipases, proteases, CAMP, and proteins that help develop biofilms and activate the host's immune system. By releasing lipolytic enzymes, this bacterium degrades triglycerides present in sebum into pro-inflammatory free fatty acids, which leads to inflammation in the area. Additionally, its capability to form biofilms not only shields it from antimicrobial treatments but also enables it to remain within the pilosebaceous unit, causing ongoing inflammation. [8,9,31,36].

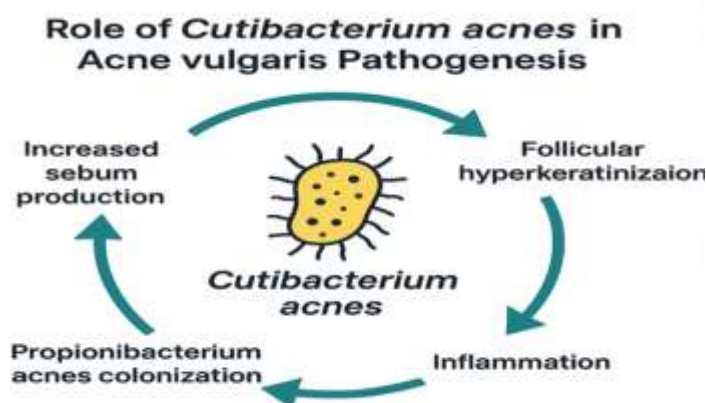


FIG NO 5: Role of Cutibacterium acnes in Acne Vulgaris Pathogenesis

(4.1.4) INFLAMMATORY MECHANISMS AND IMMUNE ACTIVATION:

The inflammation seen in acne vulgaris is multi-layered and involves activation of both the innate

and adaptive immune systems. When acnes proliferates within the follicle, it stimulates the expression of Toll-like receptors (TLR) such as TLR2 and TLR4 on keratinocytes and immune cells. This interaction leads to the activation of

intracellular signaling pathways, notably the NF- κ B, MAPK, and NLRP3 inflammasome, resulting in the secretion of a cascade of proinflammatory cytokines (including IL-1 α , IL-1 β , IL-6, CXCL8/IL-8, and TNF- α). The inflammatory milieu further damages the follicular wall,

facilitating the progression of micro comedones into more advanced lesions such as papules, pustules, nodules, and cysts. The persistence of this inflammatory cycle contributes significantly to both tissue damage and scarring in patients with chronic acne [10,34,35,37].

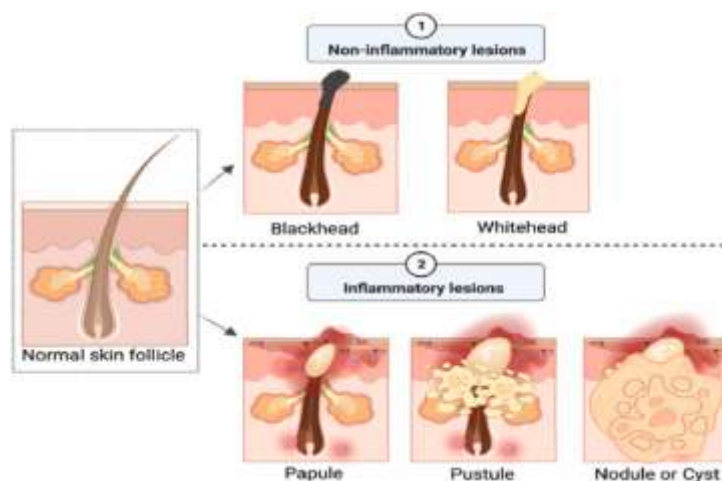


FIG NO 6: Classification of Acne Lesions into Non-Inflammatory and Inflammatory Types

(4.2.1) ADDITIONAL CONTRIBUTING FACTORS

Beyond the core pathogenic pillars of sebum production, hyperkeratinization, microbial activation, and inflammation, acne vulgaris is influenced by several additional factors: [3,33]

- **Genetics:** Family history and genetic predispositions significantly influence sebum production, inflammatory responses, and keratinocyte behaviour.[33].
- **Environmental Stressors:** Pollution, ultraviolet radiation, and exposure to certain chemicals can exacerbate the inflammatory response in acne [12].
- **Diet and Lifestyle:** High glycemic diets and stress are increasingly recognized as modulators of both sebum production and inflammatory cascades [33].
- **Commensal Interactions:** The dynamic interplay between. acnes and other skin microbiota, such as *Staphylococcus*

epidermidis, can affect the overall microbial balance, potentially tipping the scale toward pathogenicity [11,13,27,32].

(4.3) TRADITIONAL TREATMENT MODALITIES:

Traditionally, a variety of topical, systemic, and physical treatments have been used to treat acne vulgaris to stop one or more of the fundamental pathogenic processes [3].

(4.3.1) TOPICAL THERAPEUTICS

Topical treatments have long served as the frontline therapy for mild to moderate acne due to their direct application to affected areas, which minimizes systemic absorption and allows for targeted action [3,15].

(4.3.2) RETINOIDS

Topical retinoids including tretinoin, adapalene, and tazarotene are cornerstone therapies in acne

management. They function primarily by normalizing follicular keratinization, reducing the formation of microcomedones, and providing anti-inflammatory benefits. For example, tretinoin, a derivative of vitamin A, works by promoting cellular turnover, thereby mitigating pore blockage and reducing sebum accumulation. Adapalene, known for its enhanced tolerability, offers a balance between efficacy and minimal irritation, making it suitable for first-line treatment in many cases. Tazarotene, a more novel retinoid, is particularly effective when used in cases unresponsive to first-line agents, albeit with a slightly higher risk for local irritation [3,15,16].

(4.3.3) TOPICAL ANTIBIOTICS AND COMBINATIONAL APPROACHES

Acne populations on the skin's surface are reduced and inflammation is reduced with the help of topical antibiotics like erythromycin and clindamycin. However, the long-term use of these drugs as a single therapy is restricted by resistance, particularly with erythromycin (up to 60% resistance in some strains). Antibiotic-benzoyl peroxide (BPO) or retinoids in combination with antibiotics can improve treatment efficacy and lower the risk of antibiotic resistance. Because it produces free oxygen radicals, benzoyl peroxide can kill bacteria on its own, making it a useful addition to topical regimens [3,7,14].

(4.3.4) ADJUNCTIVE TOPICAL AGENTS

In addition to retinoids and antibiotics, various other topical agents contribute to acne management:

- **Salicylic Acid:**

It is a beta-hydroxy acid that helps unclog pores, exfoliates the skin, and reduces inflammation. Salicylic acid (SA) is a common topical acne

treatment that works best for comedonal acne because of its keratolytic and comedolytic properties. It belongs to the beta-hydroxy acids (BHAs) and is oil-soluble, allowing it to penetrate deeply into lipid-rich follicular pores [3]

- **Mechanism of Action [3,14]**

- a. Keratolytic Effect**

- Promotes exfoliation of the stratum corneum.
- Breaks down desmosomes between keratinocytes → prevents clogging of pores.

- b. Comedolytic Action**

- Helps dissolve and remove:
 - Blackheads (open comedones)
 - Whiteheads (closed comedones)

- c. Anti-inflammatory Properties**

- Reduces inflammatory mediators in the pilosebaceous unit.
- Helps calm redness and swelling around inflamed lesions.

- d. Reduces Sebum Accumulation**

- Its lipophilic nature allows penetration into sebaceous follicles.
- Helps reduce oil build-up and congestion.

How to Use (General Routine) [3,14]

- Cleanser with 0.5–2% SA once daily
- If leave-on serum → apply after face wash
- Moisturize
- Sunscreen in the daytime



- **Niacinamide:**

A form of vitamin B3 that inhibits inflammation and regulates sebum production Properties. Vitamin B3 comes in the amide form as nicotinamide. It is widely used in dermatology for its resulting in its efficacy as a treatment for acne vulgaris [3].

- **Uses in Acne Vulgaris [3]**

a. Reduces Inflammatory Acne

- Decreases redness, swelling, and papules/pustules.
- Effective as an anti-inflammatory agent similar to topical antibiotics.

b. Controls Sebum Production

- Helps reduce oiliness, shine, and pore clogging.

c. Prevents Post-Inflammatory Hyperpigmentation (PIH)

- Minimizes dark spots that occur after acne heals.

d. Improves Skin Barrier

- Strengthens the skin, reducing irritation from acne medications like retinoids or benzoyl peroxide.

- **Mechanism of Action in Acne [3]**

a. Anti-inflammatory Pathway

- Inhibits pro-inflammatory cytokines: IL-1, IL-6, TNF- α
- Reduces inflammatory lesions and redness.

b. Sebum Regulation

- Modulates sebaceous gland activity → decreases excess sebum.

c. Antibacterial Enhancement

- Enhances skin immunity, indirectly reducing *Cuti bacterium acnes* activity.

d. Reduces Pigmentation

- Blocks melanosome transfer → lowers risk of PIH after acne.

e. Improves Skin Barrier

- Boosts ceramide production → less irritation, reduced acne flare-ups.

- **Azelaic Acid:**

With antibacterial, anti-inflammatory, and anti-keratolytic effects, azelaic acid is useful particularly in patients with post-inflammatory hyperpigmentation [3]

- **Mechanism of Action [3,38]**

Azelaic acid improves acne through multiple pathways:

a. Anti-keratinizing (↓ Hyperkeratinization)

- Normalizes keratinocyte differentiation in the follicular epithelium Prevents comedone formation

b. Antibacterial

- *Cuti bacterium acnes* and *Staphylococcus epidermidis* growth.
- Reduces free fatty acids in sebum.

c. Anti-inflammatory

- Reduces reactive oxygen species (ROS).



- Suppresses pro-inflammatory mediators (IL-1 β , TNF- α).
- Helps reduce redness and swelling.

d. Anti-tyrosinase

- Inhibits tyrosinase → useful for post-inflammatory hyperpigmentation (PIH)

• Indications [3]

- Mild to moderate acne vulgaris
- Comedonal acne
- Inflammatory acne
- Acne with post-inflammatory hyperpigmentation
- Safe for sensitive skin, pregnancy, and long-term use

• How to Use [3]

- Apply twice daily (morning & night).
- Start with once daily if irritation occurs.
- Apply to clean, dry skin.
- Use for 8–12 weeks for visible improvement.

• Safe to combine with:

- Benzoyl peroxide
- Niacinamide
- Adapalene
- Salicylic acid (alternate days)

• Benefits [3]

- Non-comedogenic

- Brightens acne scars
- Minimal risk of bacterial resistance
- Safe for prolonged use
- Suitable for all skin types and skin tones

• Dapsone Gel:

Dapsone gel is a topical sulfone-based anti-inflammatory medication used primarily for inflammatory acne, particularly papules and pustules. It is known to reduce both inflammatory and noninflammatory lesions and has a side effect profile. It is available in gel forms with 5% and 7.5% [26,28].

• Mechanism of Action [26,28]

Dapsone works through multiple pathways:

a. Anti-inflammatory

- Inhibits neutrophil activity
- Reduces oxidative stress
- Blocks myeloperoxidase activity
- Decreases inflammatory cytokines (IL-8, TNF- α) → Helps reduce redness, swelling, and painful inflammatory lesions.

b. Antibacterial

Although not a strong antibacterial agent against *Cutibacterium acnes*, it has some inhibitory effect and helps prevent lesions from progressing.

c. Keratolytic (Mild)

Improves follicular turnover slightly, preventing clogging and development of new lesion

• Indications [26,28]



Dapsone gel is used for:

- Mild to moderate inflammatory acne
- Papules and pustules
- Acne in sensitive skin
- Acne in adult females
- Patients unable to tolerate retinoids or benzoyl peroxide

Safe in patients with G6PD deficiency only when used topically (does NOT cause hemolysis like oral dapsone).

- **How to Use [26,28]**

- Apply a thin layer once daily (7.5% gel) or twice daily (5% gel).
- Use on clean, dry skin.
- Improvements usually seen in 2–4 weeks, with full results at 12 weeks.
- Can be safely combined with:

- Retinoids
- Salicylic acid
- Azelaic acid
- Niacinamide

- **Benefits [26,28]**

- Well tolerated
- Minimal irritation
- Suitable for sensitive or dry skin
- Good option for women with persistent adult acne

- Effective even when other topical agents fail
- Low risk of bacterial resistance

- **Side Effects [26,28]**

Usually mild:

- Dryness
- Redness
- Oiliness (rare paradoxical effect)
- Slight peeling
- Temporary orange-yellow discoloration when used with benzoyl peroxide

(9) SYSTEMIC THERAPEUTICS:

For moderate to severe acne, particularly in cases unresponsive to topical treatment, systemic therapies are indicated [29].

(9.1) ORAL ANTIBIOTICS AND RESISTANCE CONCERNS

Systemic antibiotics like macrolides and tetracyclines (like doxycycline and minocycline) are frequently used to reduce acnes populations and reduce the inflammatory burden. Modern formulations such as sub-microbial dosing or extended-release versions are designed to target inflammatory drivers while minimizing the disruption of the gut microbiome [7,17]. Because they deliver targeted antimicrobial action against acnes while maintaining the heterogeneous balance of gut flora, narrow-spectrum antibiotics like sarecycline have emerged as a promising alternative [4,5,6].

(9.2) HORMONAL TREATMENTS:



Anti-androgens like spironolactone and oral contraceptives address the androgen-driven hypersecretion of sebum in women, thereby reducing the incidence of acne lesions. Such treatments are particularly beneficial in adult female patients with acne and often serve as adjuncts to other therapeutic modalities [16,3]

(9.3) ISOTRETINOIN AND ITS MULTIFACETED IMPACT:

Isotretinoin is still the only primary systemic medication that directly addresses all four main causes of acne: keratinocyte proliferation, inflammation, microbial colonization, and sebum production. Because of its profound and lasting effects, it is now used to treat severe nodulocystic acne. However, the risk of significant side effects like teratogenicity, mucocutaneous dryness, and possible psychological effects that necessitate careful patient monitoring and counselling limits its use [18,19].

(10) MODERN TREATMENT APPROACHES AND EMERGING THERAPIES:

With the development of cutting-edge therapeutic approaches, the acne management landscape has significantly changed over the past few years. In addition to enhancing efficacy and tolerability, these innovations aim to more precisely and precisely address the underlying pathogenic mechanisms [20,21].

(10.1) NOVEL ANTIBIOTIC STRATEGIES AND DOSING INNOVATIONS:

The development of antibiotics with a narrow spectrum, like sarecycline, which specifically target inflammatory strains while minimizing collateral damage to the gut microbiome, is one recent innovation. Additionally, sub-microbial tetracycline dosing strategies, like those of

minocycline and doxycycline, are intended to modulate inflammatory pathways without putting a lot of pressure on the antibacterial bacteria, which could result in resistance. These methods reframe the use of antibiotics as targeted immunomodulatory agents rather than broad-spectrum antimicrobial compounds in the treatment of acne [4,5,6,7,17].

(10.2) ADVANCED LASER AND LIGHT-BASED MODALITIES

Advanced laser therapies have gained traction as a non-pharmacological means to treat acne, particularly in patients non-responsive to conventional treatments. The use of 1726 nm lasers, such as those found in devices like AviClear and Accure, which directly target sebaceous glands, effectively reduces sebum production and aids in the resolution of acne lesions, are examples of recent advancements. Clinical data indicate that approximately 40% of patients with moderate to severe acne achieve clear or nearly clear skin for up to six months post-treatment, and 80–90% experience a reduction of at least 50% in inflammatory lesions. These therapies also show promising results in improving post-acne scarring, bridging the gap between medical treatment and aesthetic dermatology.

Advanced laser and light-based treatments for acne vulgaris work mainly by targeting sebaceous glands and the bacteria *Cutibacterium acnes* with specific wavelengths of light and laser energy. The therapeutic process involves selective photothermolysis, bacterial destruction, inflammation reduction, and stimulation of tissue remodeling [22,23,24]

(10.2.1) Diagrammatic Process Description:

Light/Laser Exposure:



Skin is exposed to specific light or laser wavelengths such as 1450 nm diode laser, 1927 nm fractional thulium laser, 595 nm pulsed dye laser (PDL), blue light (415 nm), or red light.

Targeting Sebaceous Glands & Bacteria:

- Laser energy penetrates the skin to selectively heat sebaceous glands, reducing sebum production.
- Blue light activates bacterial porphyrins in acne, producing reactive oxygen species that kill bacteria.

Inflammation Reduction Tissue Repair & Remodelling

- Pulsed dye lasers target blood vessels, reducing redness and inflammation in lesions.
- Red light penetrates deeper, modulating inflammatory mediators and promoting healing.
- Fractional lasers create controlled microthermal zones, stimulating collagen and elastin production.
- These processes lead to wound healing and reduction of acne scars over time[22,24,35]

(10.3) EMERGING TOPICAL AGENTS AND NANOTECHNOLOGY-DRIVEN FORMULATIONS:

The upcoming generation of topical treatments makes use of cutting-edge formulation methods and novel active ingredients. One of the most effective single-agent topical treatments for acne has emerged as a fixed-dose combination therapy with clindamycin, adapalene, and benzoyl peroxide. Nanotechnology has also been incorporated into novel formulations to enhance drug delivery and lessen irritation. For instance, formulations that make use of nanoparticle-based systems and microemulsions have been developed

with the goal of maximizing the active agent's penetration into the pilosebaceous unit and minimizing adverse effects. The use of a topical treatment made from *Spongilla lacustris* extract, which is being made into a once-weekly mask with dual anti-inflammatory and antimicrobial properties, is another promising development. Positive outcomes from early trials may pave the way for a new class of natural, patient-friendly treatments [20,21,25].

(10.4) MICROBIOME-BASED AND EXTRACELLULAR VESICLE THERAPEUTICS:

Utilizing the skin microbiome for therapeutic purposes has been the subject of recent research. It has been demonstrated that extracellular vesicle (EVs) derived from specific acne phylotypes, particularly those associated with healthy skin (SLST H1), protect against inflammation and dysbiosis. These EVs facilitate interkingdom communication with the human host and may help restore microbial balance, thereby offering a natural alternative for the treatment of acne. Although research into this strategy is still in its infancy, it holds a lot of promise for patients looking for alternatives to antimicrobial and anti-inflammatory medications [27,30,31].

(11) COMPARATIVE CLINICAL OUTCOMES AND EFFICACY ANALYSIS:

Long-term clinical experiences with acne treatments have shown that an individualized approach is necessary for best results. Dermatologists now have access to a more diverse arsenal thanks to the ever-changing landscape of both conventional and cutting-edge treatments [3,20].

(12) EFFICACY AND SAFETY PROFILES:

Studies evaluating advanced therapies have provided compelling data regarding their efficacy. For example, clinical trials of advanced laser treatments have reported that a significant proportion of patients achieve clear or nearly clear skin after treatment [22,23,24].

In a similar vein, when compared to monotherapies, fixed-dose combination topical treatments have demonstrated higher adherence rates and improved clinical outcomes [20,21].

Contrarily, traditional systemic antibiotics have been shown to be effective, but concerns about antibiotic resistance and gut microbiome disruption necessitate cautious, short-term use. Isotretinoin is still the gold standard for severe cases because it targets multiple pathogenic mechanisms. However, its potential side effects necessitate careful monitoring [7,17,18,19].

(13) PATIENT ADHERENCE AND QUALITY OF LIFE CONSIDERATIONS:

Treatment compliance is a critical determinant of long-term success in acne management. Adherence is influenced by a number of factors, including the severity of side effects, frequency of dosing, and complexity of the treatment. By simultaneously targeting multiple pathogenic factors and reducing the burden of using numerous products separately, combination regimens typically improve patient adherence [20,26]. Furthermore, advanced treatments particularly those with improved tolerability, such as narrow-spectrum antibiotics and novel laser modalities have been associated with enhanced quality of life, reduced scarring, and better cosmetic outcomes. These benefits are integral to addressing not only the physical but also the psychological and social impacts of acne vulgaris [2,4,5,22].

(14) CHALLENGES AND FUTURE DIRECTIONS IN ACNE MANAGEMENT

Despite significant advances over the past decades, several challenges remain in the management of acne vulgaris [28].

- **Antibiotic Resistance:** Long-term treatment options are limited by the rise of antibiotic resistance, particularly with conventional antibiotics like erythromycin. Antibiotic stewardship must be prioritized in future strategies, as must the investigation of non-antibiotic alternatives [7,17].
- **Patient compliance:** Acne is a chronic condition that necessitates long-term treatment plans. Complex regimens, frequent dosing, and adverse effects contribute to reduced adherence. Innovative drug delivery systems, including nanotechnology-based formulations, promise enhanced compliance [25,26].
- **Side Effects of Systemic Therapies:** Systemic therapies have serious side effects like teratogenicity and mucocutaneous dryness, despite the fact that isotretinoin is extremely effective. Safer dosing strategies and combination therapies to reduce these risks are the focus of ongoing research [18,19].
- **Heterogeneity of Acne:** From mild comedonal acne to severe nodulocystic lesions, acne vulgaris can take many different forms. Individualized treatment plans that take into account an individual's pathophysiology, genetics, and lifestyle factors are necessary due to the disease's heterogeneity [3,33].
- **Advancements in Microbiome Research:** Emerging modalities that leverage the skin microbiome and extracellular vesicles are still in their infancy. Further research is needed to



validate their long-term efficacy and safety, and to understand the complex interrelationships between skin bacteria and host immunity [27,30,31].

Future directions are likely to include:

- **Integrated Treatment Regimens:** Combining physical treatments (like lasers) with tailored pharmacological regimens to optimize outcomes [22,24].
- **Personalized Medicine Approaches:** Genomic and microbiomics profiling to predict treatment response and customize therapy [30,31].
- **Expanded Use of Non-Invasive Modalities:** Development of safe, effective, and patient friendly techniques, including light-based therapies and novel topical formulations [22,25].
- **Enhanced Delivery Systems:** Nanoparticle-mediated drug delivery systems aimed at maximizing therapeutic concentrations in the pilosebaceous unit while minimizing systemic exposure [25].

(15) RESULT AND DISCUSSION

(15.1) RESULTS

This evaluation examined the underlying causes and modern treatment options for acne vulgaris, incorporating insights from 38 research articles. The findings indicate that acne is a complex inflammatory condition, mainly influenced by:

- Excessive sebum production influenced by hormones (testosterone, IGF-1)
- Follicular hyperkeratinization leading to comedogenesis

- Cutibacterium acnes dysbiosis and its virulence factors
- Activation of inflammatory pathways, particularly TLR-2/TLR-4, NF- κ B, MAPK, and NLRP3 inflammasome

Conventional treatments, both topical and systemic, such as retinoids, benzoyl peroxide, antibiotics, hormonal medications, and isotretinoin, demonstrate notable clinical advantages in addressing one or several harmful factors. Nonetheless, their application is frequently constrained due to side effects, resistance from bacteria, and low compliance from patients.

Emerging therapies such as:

- Narrow-spectrum antibiotics (sarecycline)
- Laser and light technologies (1726-nm sebaceous-targeting laser)
- Nanotechnology-mediated drug delivery systems

demonstrated enhanced safety, accuracy, and sustained management, mainly by lowering inflammation, decreasing reliance on antibiotics, and enhancing sebum control. Research indicated a 40–90% decrease in lesions following advanced laser therapies and better adherence to fixed-dose topical regimens using nanotechnology.

(15.2) DISCUSSION

The assessment shows a significant change in how acne is treated, moving from basic antimicrobial treatments to specific interventions that focus on the underlying processes of the disease. In the past, acne was mainly viewed as a bacterial issue; however, new research clearly identifies it as a complicated inflammatory condition influenced



by hormonal, microbial, and immune system factors.

(15.2.1) Relevance of Pathophysiology to Treatment Outcomes:

Increased oil production, influenced by androgens, is a primary factor; therefore, hormonal treatments (oral contraceptives, spironolactone) offer long-lasting advantages, especially for women. The thickening of hair follicles, which leads to comedones, supports the initial recommendation of topical retinoids, now enhanced by newer options that are more tolerable. The imbalance of *C. acnes* and the resistance resulting from biofilms clarify why using antibiotics alone does not succeed, highlighting the necessity for combination therapies and careful use of antibiotics. The discovery of NLRP3-inflammasome activation provides insight into ongoing inflammation, even without an excess of bacteria. This supports the increasing application of non-antibacterial, anti-inflammatory options like azelaic acid, dapson gel, and narrow-spectrum antibiotics.

(15.2.2) Clinical Impact of Advanced Modalities

Emerging technologies such as 1726-nm lasers provide a breakthrough in non-pharmacological sebum suppression, offering long-term improvement comparable to oral isotretinoin but without systemic toxicity. Similarly, nanoparticle-based retinoids and antibiotic formulations increase penetration into the pilosebaceous unit and reduce irritation, critically improving patient compliance.

(15.2.3) Future Perspective

Microbiome-directed therapies such as extracellular vesicle (EV)-based skin modulation

introduce an innovative concept: restoring bacterial balance instead of eradicating *C. acnes*. These approaches align with precision medicine and may revolutionize acne therapy by minimizing side effects and resistance.

(15.2.4) Conclusion of Discussion

The combination of pathology-guided traditional treatments and emerging targeted, technology-driven therapies represents the future of acne management. Personalized care that considers hormonal profile, skin microbiome, inflammatory pathways, and lifestyle can significantly enhance therapeutic success and quality of life.

16) CONCLUSION AND SUMMARY

Acne vulgaris is a multifactorial condition marked by elevated sebum production, abnormal keratinocyte proliferation, *Cutibacterium acnes* colonization, and an intricate inflammatory cascade. Traditional therapies including topical retinoids, antibiotics, and systemic treatments such as isotretinoin have long been effective in managing acne, yet they are associated with significant limitations such as antibiotic resistance, adverse effects, and compliance issues.

Recent advances in acne treatment have broadened therapeutic options considerably. Innovations such as narrow-spectrum antibiotics (sarecycline), sub-microbial dosing strategies, and advanced laser therapies represent significant breakthroughs in the field. Topical formulations driven by nanotechnology and microbiome-based strategies involving extracellular vesicles are two promising new approaches to acne management. Not only do these cutting-edge treatments have the potential to increase patient compliance and safety, but they also target the underlying pathogenic mechanisms with greater precision. In a nutshell, an integrated strategy that fuses tried-



and-true treatments with cutting-edge therapeutic innovations is where acne management's future lies. Dermatologists can better individualize treatment plans, reduce scarring and psychological distress, and ultimately improve the quality of life for patients with acne vulgaris by addressing the multiple dimensions of acne pathology, which include hormonal influences and microbial dysbiosis, inflammation, and genetic predispositions.

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