



Review Article

## Topical Therapy in Acne. What's New?

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### ABSTRACT

Acne is a chronic inflammatory disease with a complex pathogenesis. The latest insights into a diverse array of pathogenic factors in acne have paved the way for the development of new molecules for acne treatment. These new agents focus on different targets intricately linked to acne pathogenesis. This review focuses on the latest topical treatments for acne that have received approval, as well as those that are currently undergoing clinical trials. Among the new drugs, trifarotene, a fourth-generation retinoid, which is available in India, has the advantage of superior tolerability compared to existing topical retinoids. Similarly, the first topical antiandrogen, Clascoterone, marks a significant breakthrough by specifically targeting hormonal factors contributing to acne. The development and availability of newer formulations of old molecules such as tazarotene, tretinoin, and new fixed drug combinations with better safety and efficacy, is a welcome addition in the topical anti-acne basket for a dermatologist. Numerous clinical trials are exploring novel anti-acne agents which target insulin-like growth factor 1, peroxisome proliferator-activated receptor modulators, and melanocortin receptor 5. Furthermore, other agents, such as antimicrobial peptides, bacteriophages, and cannabinoids, are also in the trial phase for acne therapy. All these new additions can help update the treatment algorithms of acne management with less dependence on systemic therapy and oral antibiotics.

**Keywords:** Clascoterone, Melanocortin receptor 5, Peroxisome proliferator-activated receptor, Topical anti-acne, Trifarotene

### INTRODUCTION

Acne is a chronic inflammatory disease of the pilosebaceous unit which affects 90% of individuals sometime in their life, predominantly affecting adolescents and young adults. The complex etiology involves hyperkeratinization of the follicle, bacterial colonization by *Cutibacterium acnes*, and an increase in sebum production driven by androgens, all of which culminate in inflammation.<sup>[1]</sup> In addition, there is an interplay of other contributory factors, including genetics, diet, oxidative stress, hormones, neuropeptides, microbiome, and innate and acquired immunity.<sup>[1]</sup> The latest advances in understanding of acne pathophysiology have paved the way for novel approaches in acne management. This review article brings attention to the latest additions in topical acne therapies. The authors aim to explore innovative topical anti-acne therapies currently implemented in clinical practice with special emphasis on novel molecules and formulations, while also exploring future possibilities for acne treatment that are on the horizon.

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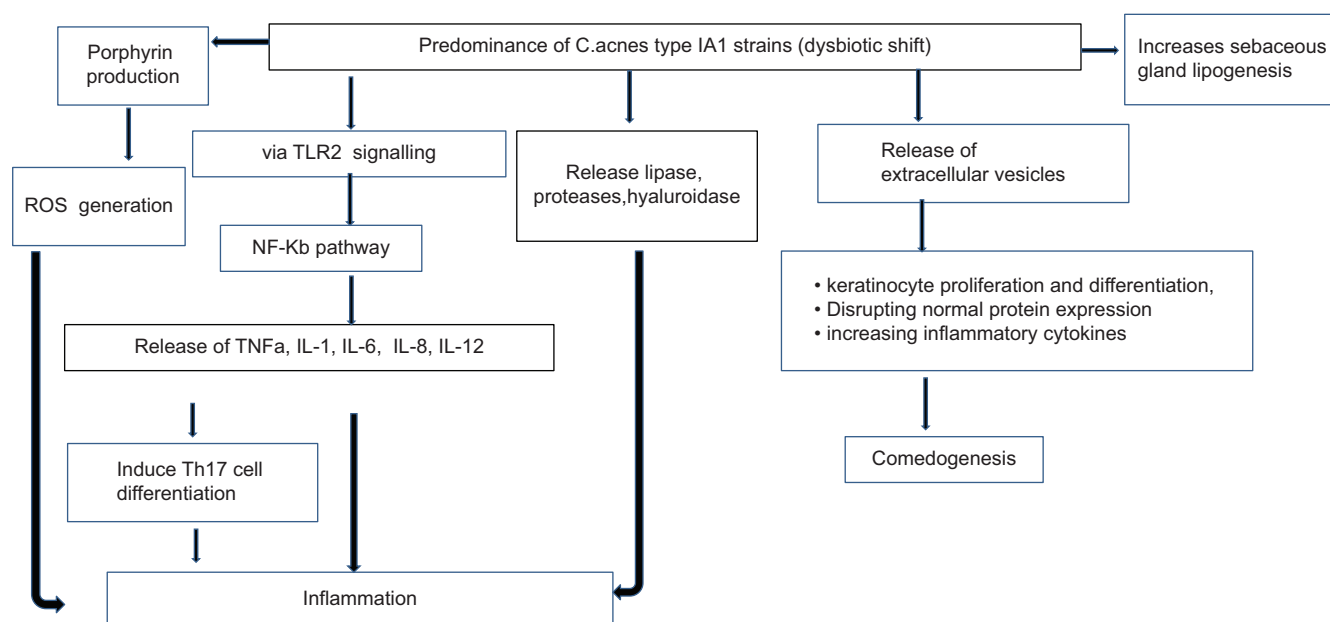
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## ADVANCEMENTS IN ACNE PATHOGENESIS-PAVING THE WAY FOR NOVEL THERAPEUTIC MOLECULES

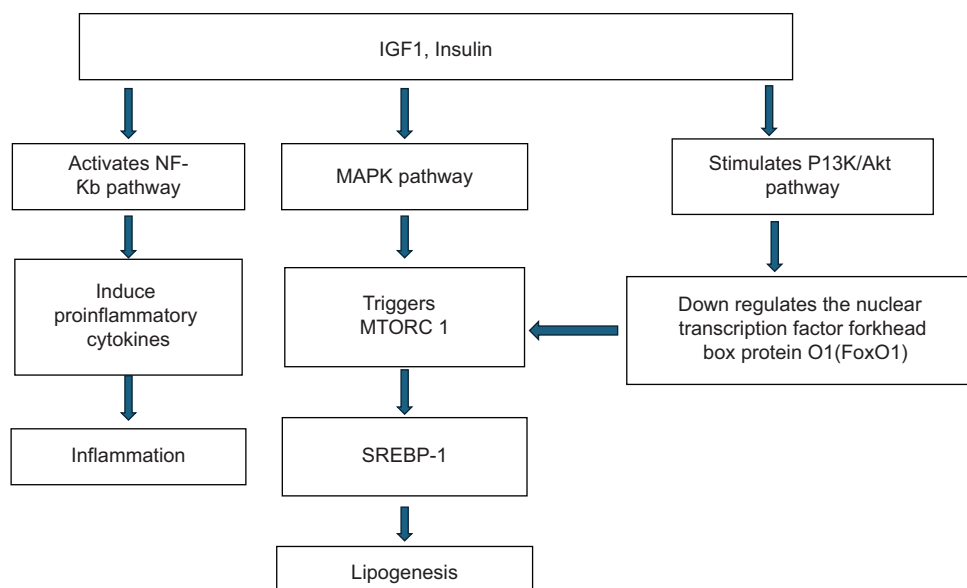
Recent research has redefined acne pathogenesis, emphasizing the interaction between microbial dysbiosis and host immune response rather than focusing on the singular role of *C. acnes*.<sup>[2]</sup> Dysbiosis, marked by an imbalance among *C. acnes* strains, particularly the predominance of certain *C. acnes* phylotypes, such as the acne-associated IA1, triggers the innate immune system, leading to skin inflammation, which is characteristic of acne.<sup>[2]</sup> Figure 1 illustrates the key pathological processes initiated by *C. acnes* associated with acne vulgaris.<sup>[2-4]</sup> Conversely, *Staphylococcus epidermidis* has been found to have anti-inflammatory properties through lipoteichoic acid, which suppresses toll-like receptor-2 expression, thereby reducing the production of pro-inflammatory cytokines such as interleukin (IL)-6 and tumor necrosis factor-alpha (TNF- $\alpha$ ) by keratinocytes.<sup>[3]</sup> In response to these discoveries, emerging therapeutic approaches are focusing on restoring the microbial balance of the skin. These include the use of probiotics, antimicrobial peptides (AMPs), and bacteriophages.<sup>[4]</sup> In addition, there is growing recognition of the roles of androgens, cannabinoid receptors, melanocortin-1 receptor, and peroxisome proliferator-activated receptors (PPARs) in sebaceous gland function, lipogenesis, and inflammation.<sup>[5]</sup> Therefore, the development of new agents aimed at inhibiting these receptors on sebocytes is currently being investigated. *C. acnes* lipases play a crucial role in breaking down sebum triglycerides into fatty acids, which can promote keratinization and inflammation. Elevated

levels of fatty acids such as oleic acid and squalene, enhance macrophage activity against *C. acnes*, while a depletion of linoleic acid leads to follicular hyperkeratosis, a precursor to comedone formation.<sup>[6]</sup> As a result, therapies aimed at restoring the balance of fatty acids, such as increasing linoleic acid levels or inhibiting the production of pro-inflammatory fatty acids, may offer novel therapeutic approaches for managing acne vulgaris. Recent evidence on the central role of mammalian target of rapamycin complex 1 (mTORC1) in acne pathogenesis makes it an attractive therapeutic target. Elevated androgen levels significantly enhance mTORC1 signaling. Increased levels of TNF- $\alpha$  and insulin-like growth factor-1 (IGF-1) further amplify mTORC1 activation.<sup>[7]</sup> The roles of IGF-1, Insulin, and mTORC-1 in the development of acne are summarized in Figure 2. Both metformin and epigallocatechin gallate (EGCG) serve as indirect inhibitors of mTORC1 through the activation of the AMP-activated protein kinase (AMPK) pathway, which negatively influences mTORC1 activity.<sup>[7]</sup> As a result, there is ongoing exploration into the application of these molecules in topical acne treatment. The importance of androgens in acne pathogenesis is well-established, and the introduction of topical antiandrogens represents a novel treatment option for dermatologists looking to address this key aspect of acne pathogenesis.

In parallel to these therapeutic advancements, newer drug delivery systems and formulations have been developed to optimize the effectiveness and absorption of topical acne treatments. These include microencapsulation, hydrogels, microsphere, polymeric nanoparticles, solid lipid nanoparticles, nanostructured lipid carriers, flexible



**Figure 1:** The key pathological processes initiated by *Cutibacterium acnes* associated with acne vulgaris. ROS: Reactive oxygen species, TLR: Toll like receptor, NF- $\kappa$ B: Nuclear factor kappa-light-chain-enhancer of activated B cells, IL: Interleukin, TNF: Tumour necrosis factor.



**Figure 2:** The role of IGF-1, Insulin, mTORC-1 in the development of acne. IGF1: Insulin-like growth factor 1, NF- $\kappa$ B: Nuclear factor kappa-light-chain-enhancer of activated B cells, MAPK: Mitogen-activated protein kinase, mTORC1: Mammalian target of rapamycin complex 1, SREBP-1: Sterol regulatory element binding protein-1, FoxO1: Forkhead box protein O1, PI3K/Akt: Phosphatidylinositol 3-kinase Akt.

liposomes, nanoemulsions, and microemulsions.<sup>[8]</sup> Sabouri *et al.* demonstrated that nanoemulsion formulations of 0.05% tretinoin offer enhanced therapeutic efficacy and better loading capacity compared to traditional emulsions.<sup>[9]</sup> In addition, newer supramolecular salicylic acid gels improve the bioavailability of poorly water-soluble salicylic acid while reducing skin irritation.<sup>[10]</sup> Another innovation is silica-based microcapsules, which minimize direct contact between active ingredients and the skin, enhancing ingredient penetration and molecular stability.<sup>[8]</sup> These advanced formulations not only improve the tolerability and efficacy of treatments but also allow for the use of lower concentrations of active compounds, ensuring more effective and comfortable acne management.

## NEWER ANTI ACNE TOPICAL RETINOIDS

### Trifarotene (0.005% cream)

Trifarotene is a recent addition to the fourth-generation topical retinoid and the first topical retinoid that selectively targets the retinoic acid receptor gamma (RAR- $\gamma$ ).<sup>[11]</sup> Approved by the Food and Drug Administration (FDA) in 2019, trifarotene became the first topical retinoid to specifically target RAR- $\gamma$ , marking a significant advancement in acne therapy. It is approved for the treatment of acne vulgaris in patients aged 9 years and older, based on two Phase III, vehicle-controlled studies that demonstrated

superior treatment success in patients with moderate facial and truncal acne.<sup>[11]</sup>

Trifarotene, in addition to promoting epidermal differentiation and desquamation, downregulates dystonin, which enhances comedolytic activity. It also upregulates aquaporin 3 channels, improving skin hydration and barrier function, and increases peptidyl arginine deiminase 1 activity, contributing to better skin health. Moreover, trifarotene downregulates membrane metalloendopeptidase, reducing the degradation of collagen and elastin fibers, thus improving skin texture.<sup>[11]</sup>

Trifarotene's antipigmenting properties help in managing post-inflammatory hyperpigmentation.<sup>[12]</sup> In addition, its selective targeting of RAR- $\gamma$  avoids the irritation often associated with RAR- $\beta$ , making it less likely to cause skin sensitivity or irritation. Since trifarotene is rapidly broken down by liver enzymes, it also offers a better systemic safety profile compared to other retinoids.<sup>[11]</sup> The low concentration trifarotene formulation makes it an ideal treatment for large areas of skin, such as the trunk.<sup>[12]</sup> However, its relatively high cost remains a limiting factor in widespread use. While trifarotene has shown promising results, it currently lacks an established pregnancy categorization, necessitating caution in its use during pregnancy.<sup>[13]</sup>

In 2023, trifarotene was launched in India, representing a significant step forward in the acne treatment options.

However, comprehensive clinical studies in Indian populations are needed to further assess its efficacy, safety, and tolerability in both facial and truncal acne.

### **Tretinoin 0.05% lotion**

In 2018, the FDA approved the tretinoin 0.05% lotion as a new formulation for acne treatment, offering significant advantages in terms of reduced irritation and improved tolerability.<sup>[14]</sup> This lotion formulation utilizes polymeric emulsion technology, which enhances the dispersion and penetration of tretinoin into skin follicles.<sup>[14]</sup> The lotion is yet to be launched in India, but its anticipated availability will likely provide more clinical insights into its efficacy and tolerability in the Indian population. Once it becomes accessible, it may offer a valuable addition to the therapeutic arsenal for managing acne.

### **Tazarotene 0.045% lotion**

Tazarotene, a well-established treatment for acne, has traditionally been available in 0.1% gel and cream formulations. However, these formulations are often associated with dryness, which can reduce patient compliance. To address the issue of skin irritation and dryness, the 0.045% lotion formulation of tazarotene was developed. Approved by the FDA in 2019 for the treatment of moderate to severe acne in individuals aged 9 years and older, this lotion formulation is not yet available in India.<sup>[15]</sup> This formulation makes it an ideal option for use even during colder months when skin tends to be more sensitive.<sup>[15]</sup> Clinical results support its effectiveness, and it is likely to enhance patient adherence to acne treatment. Tazarotene is contraindicated in pregnancy.<sup>[11]</sup>

### **Newer topical antimicrobial anti-acne agents**

The landscape of acne therapy has evolved with the introduction of newer topical antimicrobial agents, offering effective treatments with reduced risks of systemic side effects and antibiotic resistance. Among these, minocycline 4% foam/gel, dapsone 7.5% gel, and ozenoxacin have novel mechanisms and targeted action against *C. acnes* and reduce inflammation.

### **Minocycline 4% foam/gel**

Minocycline, a semi-synthetic second-generation tetracycline, has anti-inflammatory and bacteriostatic activity against target anaerobic microbes.<sup>[16]</sup> Minocycline in 4% foam formulation is the first topical minocycline preparation approved by the USFDA in 2019 for the treatment of non-nodular moderate-to-severe acne vulgaris in patients aged 9 years and above.<sup>[16]</sup> The formulation has micronized minocycline

hydrochloride crystals suspended in oleaginous foam base, which ensures stability, delivery of high minocycline levels to the pilosebaceous unit, thereby suppressing the emergence of resistance in *C. acnes*.<sup>[16]</sup> The high lipophilicity of minocycline allows trans-epidermal delivery, thereby decreasing systemic absorption and toxicity. In line with the recommendations for other topical antibiotics, minocycline is discouraged from being used as a single treatment or in combination with systemic antibiotics.<sup>[1]</sup> It is not recommended during pregnancy and lactation.<sup>[1]</sup> Sun protection and avoidance of Ultraviolet A / Ultraviolet B (UVA/UVB) light are advisable while using topical minocycline. Notably, minocycline has been available in India since 2022 as 4% gel rather than a foam due to concerns about thermostability. Studies on Indian patients with minocycline gel showed good tolerability and better efficacy than clindamycin gel.<sup>[17]</sup> Minocycline gel should be used in combination with other topical agents, including adapalene or benzoyl peroxide (BPO). Indian experts recommend applying topical adapalene in the evening, washing it off after an hour, then using topical minocycline 2–3 h later, while noting that minocycline can also be applied during the day with strict sun protection.<sup>[18]</sup> Minocycline gel can be combined with oral isotretinoin with improved outcomes without the risk of systemic absorption or pseudotumor cerebri.<sup>[19]</sup> The risk of hyperpigmentation associated with topical minocycline gel is minimal.<sup>[18]</sup> Its introduction fills the gap for patients with antibiotic resistance with the advantage of avoiding systemic side effects of oral minocycline.

### **Dapsone gel 7.5%**

Dapsone, an antimicrobial agent known for its anti-inflammatory and antibacterial properties, has been used in acne treatment for years. Although dapsone 5% gel has been on the market since 2008, a 7.5% formulation was approved in 2017 for the treatment of inflammatory acne for adults and children above 12 years of age.<sup>[20]</sup> Consequently 7.5% gel formulation of dapsone has received approval for the once-daily topical treatment of acne in patients  $\geq 9$  years of age.<sup>[20]</sup> There is no need for G6PD testing before topical dapsone use.<sup>[1]</sup> There are no data on the safety of dapsone in pregnancy.<sup>[1]</sup> One should avoid concurrent use of BPO and topical dapsone, as it can result in orange-brown discoloration of the skin.<sup>[1]</sup> The affordability and effectiveness of dapsone, especially in treating recalcitrant and inflammatory acne, make it a promising therapeutic option. Once 7.5% gel is available in India, it is expected to provide an alternative, cost-effective therapy for patients with persistent acne.

### **Ozenoxacin (1% and 2%)**

Ozenoxacin, a nonfluorinated quinolone, is another antimicrobial agent showing promise in acne treatment.

It has antimicrobial activity against *C. acnes* and is noted for inhibiting the production of pro-inflammatory cytokines such as IL-6, IL-8, and TNF- $\alpha$ , in human keratinocytes.<sup>[21]</sup> It has been shown to inhibit these cytokines more strongly than other topical antibiotics such as nadifloxacin and clindamycin, making it an attractive option for inflammatory acne lesions. The Japanese Dermatological Association Guidelines for acne vulgaris recommend topical antimicrobials, including ozenoxacin, as a first-line treatment for inflammatory acne lesions with an evidence level II.<sup>[21]</sup> Despite its efficacy, the lack of studies in India and concerns about the potential for antibiotic resistance limit its widespread use in acne management. While side effects are minimal, including mild dryness and desquamation, the risk of developing resistance may be a concern for long-term use. There is a lack of data on the use of ozenoxacin in pregnancy, but since there is negligible systemic absorption, adverse events are not expected.<sup>[22]</sup>

## NEWER TOPICAL ANTIANDROGEN

Clascoterone (cortexolone 17a-propionate) cream 1% is a topical antiandrogen that specifically binds to the androgen receptor and also exhibits an anti-inflammatory effect by inhibiting inflammatory synthesis from sebocytes.<sup>[23]</sup> The FDA approved this molecule in August 2022, providing one new topical armamentarium to manage acne with a novel mechanism of action.<sup>[23]</sup> The approval was mainly based on two identical phase-3, double blind vehicle-controlled 12-week randomized trial for individuals aged 9 years and older.<sup>[24]</sup>

Clascoterone has quicker onset of action as early as 2<sup>nd</sup> week and peaks in week 8. In all the studies, there was a tolerable side effects profile, local irritation almost similar to the vehicle. Since it gets hydrolyzed to cortexolone, there is a theoretical risk of adrenal suppression with its use, but it was noted in studies that it normalizes on stopping the drug within 4 weeks, with no clinical symptoms suggestive of adrenal suppression. There is no drug-to-drug interaction and no clear direction regarding its use in pregnancy and/or lactating women, hence better to avoid.<sup>[24]</sup> Its place in acne therapy is not yet clear; it may work as monotherapy or part of a combination regimen, for which more studies are needed. Recent American Academy of Dermatology guidelines appreciate its efficacy with high certainty of evidence but were guarded in their statement for conditional recommendation due to the high cost of treatment, but that can be revised further according to them.<sup>[1]</sup> Since it is yet to be available in India, no practical experience with us. We would be wiser after its use in Indian scenarios for its efficacy, adverse effect profile, and its place in acne treatment armamentarium; but it looks promising topical drug due to its unique mode of action and good efficacy records in trials.

## Combination topical treatments

Recent acne treatment has shifted toward combination therapies for enhanced efficacy and compliance by targeting multiple aspects of pathogenesis. These treatments combine multiple active ingredients to target different aspects of acne pathogenesis, offering a more comprehensive approach.

Clindamycin phosphate 1.2% / Adapalene 0.15 % / Benzoyl peroxide 3.1 % Triple combination of acne in individuals 12 years and above.<sup>[25]</sup> This combination integrates the antimicrobial effects of clindamycin, the anti-inflammatory properties of adapalene, and the keratolytic and bactericidal effects of BPO. It offers improved tolerability through micronized BPO and adapalene for better penetration, while clindamycin helps mitigate irritation from the other ingredients. As a result, patients experience fewer side effects, such as erythema, application site pain, dryness, and irritation.<sup>[25]</sup> Available data with this combination in pregnant women are insufficient.<sup>[26]</sup> The once-daily dosing improves compliance, and the formulation reduces antibiotic resistance risk. However, long-term studies are still needed to better understand its role in acne management. This combination was launched in India in January 2025, and we are presently in the initial phase of evaluating its efficacy and safety, as well as determining whether the outcomes are reproducible among Indian patients.

Fixed-dose combination 0.1% Tretinoin, 3% BPO cream: FDA-approved in 2021, this formulation combines tretinoin, which increases follicular epithelial cell turnover, with BPO, a bactericidal agent against *C. acnes*. Its innovative microencapsulation technology successfully protects tretinoin from BPO-induced oxidation and thermal degradation.<sup>[27]</sup> The cream simultaneously targets both follicular hyperkeratinization and bacterial colonization. Clinical trials demonstrate a favorable safety profile with side effects primarily consisting of erythema, pigmentation, dryness, scaling, and itching.<sup>[27]</sup> Additional comparative studies are needed to properly evaluate its effectiveness and cost-effectiveness compared to other established treatments for moderate-to-severe acne.

## TOPICAL ANTI-ACNE DRUGS IN CLINICAL TRIAL

As discussed earlier in the article, there is ongoing research and trials on topical anti-acne products which target various receptors, molecules, and enzymes in the acne pathogenesis. The aim is to create novel agents with the least adverse effects and avoid overuse of antibiotics to prevent antibiotic resistance. Table 1 provides an overview of the different topical anti-acne products currently available in the market, and Table 2 summarizes various topical anti-acne products under clinical trial.<sup>[28-33]</sup>

**Table 1:** List of newer FDA approved and available topical anti acne.

Sr. No.	Name of drug	FDA approval	Formulation	Availability in India	Indications: FDA approved/Off-label
1.	Trifarotene 0.005%	2019	Cream	Yes	Facial and Truncal Acne >12 years of age. *Can be combined with oral doxycycline
2.	Tretinoin 0.05%	2018	Lotion	No	Facial and Truncal Acne >9 years of age
3.	Tazarotene 0.045%	2019	lotion	No	Facial and Truncal Acne >9 years of age
4.	Minocycline 4%	2019	Foam	No	Moderate to severe acne vulgaris >9 years of age *Can be combined with Oral Isotretinoin. Not to be combined with oral antibiotics
			Gel	Yes	
5.	Dapsone 7.5%	2017	Gel	Yes	Moderate acne in patients aged >12 years, Adult females with acne.
6.	Ozenoxacin 2%	No	Cream, Lotion	Yes	Grade 2 acne. Not to be combined with oral antibiotics
7.	Clascoterone 1%	2022	Cream	No	Adult (both males and females), Paediatric acne >12 years of age, Hormonal acne. *Can be combined with oral antibiotics, Isotretinoin, oral Antiandrogens (in female acne patients)
8.	Clindamycin phosphate 1.2%/ adapalene 0.15%/BPO 3.1% Triple combination	2023	Gel	Yes	Adult and Paediatric acne >12 years of age
9.	FDC 0.1% Tretinoin, 3% BPO cream	2021	Cream	No	Adult and Paediatric acne >9 years of age
10.	FDC Clindamycin 1%, BPO 3.75%	2014	Gel	Yes	Comedonal and Inflammatory acne >12 years of age

BPO: Benzoyl Peroxide

**Table 2:** Summary of novel topical anti acne products under clinical trial.

Name of drug	Mechanism of action	Studies/trials
Metformin 30% gel <sup>[30]</sup>	It activates AMP-activated protein kinase, leading to inhibition of mTORC1 signalling pathway.	A split face placebo controlled study on 27 female acne vulgaris patients. Metformin and placebo gels were applied to either side of the face for 12 weeks. There was significant improvement in all type of lesions except pustules after 12 weeks. No adverse effects
Meclizine gel <sup>[31]</sup>	It is an H1 histamine receptor antagonist that is expressed on keratinocytes and involved in mediating inflammatory responses through cytokine production.	In a randomized, double-blind, placebo-controlled clinical trial on 60 volunteers, the acne severity score was reduced by 20% in the treated group after 12 weeks of treatment. No adverse event was reported.
Combination of Minocycline 3% and 0.3% adapalene foam <sup>[29]</sup> FCD105	Antimicrobial activity against <i>Cutibacterium acnes</i> , suppression of sebum production, reduced hyperkeratinization, and decreased production of pro-inflammatory cytokines	A randomized, multicenter, double-blind, vehicle-controlled, Phase 2 study in which comparison of FCD105 was done with adapalene, minocycline and vehicle individually. The FCD105 group had better IGA treatment success and statistically significant improvement in inflammatory and non-inflammatory lesion count than other three groups. Most adverse effects were mild in severity, no serious side effects were reported
VB-1953 topical gel <sup>[29]</sup> Fourth-generation fluoroquinolone	It is effective against clindamycin resistant strains of <i>C. acnes</i> . It has dual action as a bactericidal agent and acts as anti-inflammatory by TLR-MD2 inhibition.	Phase 2 trials in 471 patients demonstrated significant reduction of inflammatory lesions after 12 weeks of application of the formulation in patients with moderate to severe acne Another study was a non-randomised, prospective clinical study evaluating the safety, tolerability and efficacy of VB-1953 in adult subjects with moderate to severe facial acne vulgaris in non-responders to clindamycin who had clindamycin resistant <i>C. acnes</i> strains on laboratory studies. Topical application of 2% VB-1953

(Contd...)

**Table 2:** (Continued).

Name of drug	Mechanism of action	Studies/trials
		topical gel resulted in a significant reduction of mean absolute inflammatory and noninflammatory lesion counts by 53.1% and 52.2% respectively. No adverse effects
Acetyl Coenzyme A carboxylase inhibitor: OG 5%, 7.5% gel (OG) <sup>[32]</sup>	Inhibition of Acetyl coenzyme A carboxylase enzyme by OG reduces saturated and monounsaturated fatty acyl chains in sebaceous lipids and has sebum suppressive action	In Phase IIa, randomized, double-blind, vehicle-controlled, parallel-group study greater improvements in IGA score were observed with OG than with vehicle. Adverse effects: Nasopharyngitis, upper respiratory tract infection and application site pruritus.
Berdazimer sodium 2%, 4% gel <sup>[33]</sup> SB204 gel	It is a Nitric oxide releasing compound with antimicrobial, anti-inflammatory actions - Nitric oxide inhibits cytokine release from <i>C. acnes</i> - Antibacterial effects against <i>C. acnes</i>	RCT, Phase 2 study was carried out with topical SB204 2%, and 4% twice a day on individuals with acne vulgaris for 12 weeks. Both SB204 1% and SB204 4% demonstrated a notable reduction in the total number of lesions and the percentage change in noninflammatory lesion count compared to the control group at end of 12 weeks. No serious adverse effects.
NAC-GED 2%, 5% gel <sup>[34]</sup> PPAR $\gamma$ modulator	PPAR $\gamma$ modulator regulates gene expression to inhibit inflammation, alter differentiation markers, and restore normal sebum production in keratinocytes and sebocytes.	In a double blind Phase 2B RCT including patients with moderate-to-severe AV, the topical application of both 2% and 5% NAC-GED caused reduction in total lesion count compared with placebo though NAC-GED 5% was more effective than 2%. Adverse effects: Common cold, headache, sore throat
ASC- J9 cream dimethyl curcumin <sup>[33]</sup> AR degradation enhancer	Selectively promote the degradation of the AR itself by interrupting the interaction of AR and AR coregulators	A Phase 2, Multi-Center, Randomized, Double-Blind, Vehicle-Controlled Clinical Study in which safety and efficacy of 0.1% and 0.025% ASC-J9 Creams were assessed for the treatment of Acne Vulgaris. Percentage change in inflammatory lesion counts from baseline to week 12 was 44.8% with 0.025% ASC-J9 cream versus 37.4% with vehicle. Safe drug profile.
JNJ 10229570-AAA <sup>[33]</sup>	It is an antagonist of melanocortin receptor-5 expressed on human sebocytes	In a multicenter, double-blind, vehicle-controlled, phase II study, the trial drug performed only slightly better than placebo

AMP: 5' adenosine monophosphate, mTORC1: Mammalian target of rapamycin complex 1, TLR: Toll-like receptor, IGA: Investigator's global assessment, PPAR $\gamma$ : Peroxisome proliferator-activated receptor gamma, RCT: Randomized controlled trial, OG: Olumacostat glasaretil, AR: Androgen receptor, NAC-GED: N-acetyl-GED, ASC: Andro Science Corp, FDC: Fixed drug combination

## FUTURE DIRECTION OF TOPICAL ANTI-ACNE THERAPY

As research progresses, several promising therapies for acne are emerging. Topical Cannabinoids (BTX 1503 gel) show promise through lipostatic, antiproliferative, and anti-inflammatory effects.<sup>[33]</sup> Green tea compound EGCG, an mTORC1 inhibitor, inhibits lipid synthesis in sebocytes and demonstrates potential as an anti-acne treatment.<sup>[33]</sup> Studies on topical sprays and lotions from cell-free culture supernatant of *Enterococcus faecalis* SL-5 and *Lactobacillus plantarum* extract (5%) have shown positive results in reducing acne lesions.<sup>[34]</sup> A three-phage cocktail gel containing naturally occurring phages targeting *C. acnes* bacteria to improve acne-prone skin is under study.<sup>[35]</sup>

## CONCLUSION

The treatment landscape for acne vulgaris is evolving rapidly, with new topical agents emerging alongside established first-

line treatments. Key innovations include fourth-generation retinoids, topical antimicrobials, and antiandrogens. Combination therapies enhance efficacy while improving tolerability. Advanced drug delivery systems optimize ingredient stability and penetration, enabling lower active concentrations and reduced irritation. Clinical trials explore novel agents targeting AMPK, PPAR $\gamma$ , nitric oxide, and androgen degradation to circumvent antibiotic resistance and broaden therapeutic options. Despite progress, challenges remain, including high costs, regional availability issues. Furthermore, there is a need for more comparative studies to optimize treatment algorithms, considering safety, efficacy, and cost-effectiveness of the new molecules.

## Multiple Choice Questions

- Which of the following is a novel topical retinoid approved for the treatment of acne?
  - Tazarotene
  - Adapalene

- c. Trifarotene
- d. Isotretinoin

Answer: c) Trifarotene

2. What is the primary advantage of clascoterone as a novel topical therapy for acne?
- a. It is a topical antibiotic
  - b. It acts as an androgen receptor antagonist
  - c. It provides keratolytic effects
  - d. It is a retinoid derivative

Answer: b) It acts as an androgen receptor antagonist

3. Which of these statements about clascoterone is FALSE?
- a. It can be used in both males and females
  - b. It has systemic anti-androgenic effects
  - c. It can be used in patients 12 years and older
  - d. It targets androgen receptors in sebaceous glands

Answer: b) It has systemic anti-androgenic effects

4. Trifarotene is unique among topical retinoids because
- a. It has a more potent keratolytic effect
  - b. It selectively targets retinoic acid receptor gamma (RAR- $\gamma$ )
  - c. It is the only retinoid approved for body acne
  - d. It has anti-androgenic properties

Answer: b) It selectively targets retinoic acid receptor gamma (RAR- $\gamma$ )

5. Which investigational drug is a topical nitric oxide-releasing agent under trial for acne treatment?
- a. FMX101
  - b. B) SB204
  - c. BPX-01
  - d. D) DRM01

Answer: b) SB204

6. What is the primary mechanism by which cannabinoids may help in acne management?
- a. Stimulation of sebum production
  - b. Anti-inflammatory and sebostatic effects
  - c. Promoting bacterial colonization of the skin
  - d. Increasing androgen receptor activity

Answer: b) Anti-inflammatory and sebostatic effects

7. What is the primary effect of PPAR activation on sebum production?
- a. Decreases lipogenesis only
  - b. Increases lipogenesis only
  - c. Both increase lipogenesis and promote differentiation
  - d. Has no effect on lipogenesis

Answer: c) Both increase lipogenesis and promote differentiation

8. Which melanocortin receptor is predominantly expressed in human sebocytes?
- a. MC1R
  - b. MC2R

- c. MC3R
- d. MC5R

Answer: d) MC5R

9. What is the chemical classification of ozenoxacin?
- a. Macrolide antibiotic
  - b. Non-fluorinated quinolone
  - c. Fluoroquinolone
  - d. Tetracycline derivative

Answer: b) Non-fluorinated quinolone

10. What is the effect of IGF-1 on inflammatory mediators in acne?
- a. Increases IL-1 $\alpha$  production
  - b. Enhances TNF- $\alpha$  expression
  - c. Stimulates Matrix Metalloproteinases
  - d. All of the above

Answer: d) All of the above

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