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Emerging Horizons in Acne Therapy: A Comprehensive Review of Conventional and Novel Anti-Acne Drugs

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ABSTRACT

Acne vulgaris is a multicausal skin disorder influenced by excess sebum production, follicular hyper keratinization, Cutibacterium acnes proliferation, and inflammation. Until recently, standard treatments have remained the mainstay of therapy, which includes topical retinoid, benzoyl peroxide, antibiotics, hormonal agents, and many of which have their use severely limited due to side effects, antibiotic resistance, and lack of patient compliance. Recent advances include the utilization of novel drug delivery systems such as liposomes, ethosomes, and nanoparticles that enhance drug penetration while minimizing systemic exposure. Biologics, antimicrobial peptides, probiotics, and phytochemical-based formulations are newer, promising, targeted, and safer alternatives. This review comprehensively discusses traditional and next-generation anti-acne agents, focusing on their mode of action, therapeutic potential, and clinical efficacy, with emphasis on current challenges and future directions toward personalized, sustainable, and patient-friendly acne management.

KEYWORDS: Acne vulgaris, novel drug delivery, antimicrobial peptides, nanotechnology, personalized therapy.

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INTRODUCTION

Conventional acne therapies often face significant limitations, including the development of bacterial resistance, undesirable side effects, and low patient compliance [1]. These challenges highlight the urgent need for next-generation treatment approaches that offer enhanced efficacy, improved safety profiles, and personalized outcomes tailored to individual patient characteristics [2].

CLASSIFICATION OF ANTI-ACNE THERAPIES

Acne management strategies are typically categorized based on two key criteria: route of administration and mechanism of action [3].

By route of administration, treatments are divided into:-

- Topical agents, which include medications like benzoyl peroxide, retinoid, and topical antibiotics, are commonly used for mild to moderate acne [4].
- Systemic agents, such as oral antibiotics, hormonal therapies, and isotretinoin, which are more appropriate for moderate to severe or treatment-resistant cases [5].

By mechanism of action, anti-acne drugs can be further classified into:-

- Antibacterial agents, such as clindamycin and benzoyl peroxide, which reduce C. acnes bacterial load on the skin [6].
- Anti-inflammatory agents, including retinoid and dapsone, that help modulate the inflammatory response associated with acne [7].
- Keratolytic and comedolytic agents, like salicylic acid and tretinoin, that aid in normalizing follicular desquamation and preventing comedone formation[8] .
- Hormonal therapies, including oral contraceptives and anti-androgens, which target androgen-induced sebum production [9],[10].

Sebum-reducing agents, such as isotretinoin, that shrink sebaceous glands and lower sebum output

CONVENTIONAL ANTI-ACNE DRUGS

Conventional acne therapy remains the clinical foundation for managing mild to severe acne vulgaris, relying primarily on topical and systemic pharmacologic agents that target the major pathogenic mechanisms of the disease . These therapies act by suppressing Cutibacterium acnes proliferation, normalizing follicular keratinization, reducing inflammation, and inhibiting excessive sebum production [11]. While newer molecules and delivery systems continue to emerge. classical agents such as

benzoyl peroxide, retinoids, and antibiotics retain significant therapeutic importance due to their well-established efficacy and safety profiles.

Topical therapies are preferred for mild-to-moderate acne because they deliver high local concentrations of active ingredients while minimizing systemic exposure. Benzoyl peroxide (BPO) is one of the oldest and most effective agents. acting through oxidative bacterial killing and keratolytic effects. Its broad antimicrobial spectrum effectively reduces C. acnes resistance when used in combination with topical antibiotics [12]. Topical retinoids, including tretinoin. adapalene, and tazarotene, normalize desquamation and prevent microcomedone formation by modulating gene expression through retinoic acid receptors [13]. Among these, adapalene exhibits superior photostability and tolerability, making it suitable for long-term use. Topical antibiotics such as clindamycin and erythromycin exert bacteriostatic effects against C. acnes but are now commonly formulated with benzoyl peroxide to minimize bacterial resistance [14]. Azelaic acid, a naturally occurring dicarboxylic acid, provides both antibacterial and anti-keratinizing effects while improving post-inflammatory hyperpigmentation, which enhances cosmetic outcomes [15]. Salicylic acid, a beta-hydroxy acid, promotes exfoliation and comedone clearance through corneocyte desmosome disruption and is often used as an adjunct in combination formulations [16].

treatment For moderate-to-severe acne or cases unresponsive to topical monotherapy, systemic agents form the mainstay of Oral antibiotics, particularly tetracyclines (doxycycline, minocycline, carecycline) and macrolides (azithromycin, erythromycin), act by inhibiting bacterial protein synthesis and providing anti-inflammatory effects independent of antimicrobial action [17]. Among these, carecycline has emerged as narrow spectrum tetracycline with reduced gastrointestinal and photosensitivity effects and minimal disturbance to the gut microbiome [18]. Hormonal therapies are valuable for female patients with androgen-driven sebum overproduction. Combined oral contraceptives containing estrogen and progestin decrease androgen levels, while anti-androgenic agents such as spironolactone or cyproterone acetate block androgen receptors within sebaceous glands [19]. Isotretinoin, a systemic retinoid, remains the only drug capable of inducing long-term remission by simultaneously targeting all four major pathogenic pathways of acne-sebum production, follicular keratinization, bacterial colonization, and inflammation [20]. However, it is associated with teratogenicity, mucocutaneous dryness, and psychiatric adverse effects, requiring strict risk-management programs and patient monitoring [21].

Despite their widespread use and proven clinical efficacy, conventional therapies have several limitations that have prompted the development of newer treatment approaches. Long-term use of systemic and topical antibiotics contributes to the emergence of antimicrobial resistance, reducing overall treatment success and compromising future therapeutic options [22]. Retinoids and benzoyl peroxide frequently cause skin irritation, erythema, and dryness. leading to poor adherence, particularly among younger patients [23]. Additionally, systemic retinoids like isotretinoin require rigorous laboratory monitoring due to potential hepatotoxicity and dyslipidemia [24]. Hormonal therapies. while effective, are restricted to female patients and carry risks of thrombosis and endocrine imbalance [25]. These challenges highlight the need for innovative, patient-friendly, and resistance-free therapeutic modalities that can provide sustained remission with improved safety and compliance profiles**.**

NOVEL AND EMERGING ANTI-ACNE DRUGS

Emerging Pharmacological and Biologically-Inspired Strategies in Acne Management

Modern acne therapy has evolved beyond conventional retinoids and antibiotics, moving toward precision treatment that targets underlying inflammatory and microbial triggers while improving cutaneous delivery. Current development focuses on drugs with selective mechanisms, localized actions, and improved safety, supported by advanced delivery technologies and phytochemical-based interventions [26].

4.1 Targeted Antimicrobial Approaches

Novel topical antimicrobials are designed to achieve follicular drug deposition with minimal systemic exposure. Topical minocycline formulations allow localized delivery to the pilosebaceous unit, limiting systemic absorption and reducing adverse neurological and gastrointestinal effects typically associated with oral forms [27]. Similarly, sarecycline, a narrow-spectrum tetracycline, exhibits focused activity against Cutibacterium acnes with lower disruption of commensal gut flora [28], reducing the risk of antibiotic-associated dysbiosis and resistance. Beyond bacterial suppression, both agents down-regulate inflammatory mediators, offering dual therapeutic benefits [29].

4.2 Localized Androgen Antagonism

Excessive sebum synthesis is a central driver of acne pathophysiology. Clascoterone, a topical androgen receptor blocker, interferes with dihydrotestosterone signaling directly within sebaceous glands [30]. Unlike systemic anti-androgens, clascoterone acts locally, avoiding endocrine-related adverse effects and presenting a viable option for both male and female patients where hormonal modulation is necessary [31].

4.3 Selective Retinoid Receptor Activation

Retinoid tolerance remains a challenge in acne therapy. Trifarotene, designed with high affinity for cutaneous RAR-γ receptors, demonstrates significant comedolytic activity with reduced irritation potential [32]. Its utility in both facial and truncal acne has broadened clinical retinoid applications, particularly in cases resistant to older molecules [33].

4.4 Nitric Oxide-Mediated Immunomodulation

Nitric-oxide releasing platforms offer a hybrid antimicrobial and immunomodulatory mechanism. Controlled NO delivery disrupts C. acnes biofilm integrity while tempering inflammatory pathways [34]. This positions the approach as a promising candidate for treatment-resistant inflammatory acne [35].

4.5 Nano-enabled Dermal Drug Transport

Nanocarrier innovation has enhanced bioavailability and sustained delivery of lipophilic and unstable drugs. Systems such as liposomes, niosomes, ethosomes, solid-lipid nanoparticles, and nanostructured lipid carriers improve follicular distribution while shielding compounds like retinoids from oxidative degradation [36]. Polymeric nanoparticles including PLGA provide prolonged therapeutic release [37], and microneedle arrays further augment dermal penetration by temporarily bypassing the stratum corneum barrier [38].

4.6 Phytochemical-based Acne Modulation

Natural actives with anti-inflammatory and antimicrobial properties are gaining traction as complementary options. Tea tree oil demonstrates bactericidal and anti-inflammatory effects via terpenoid constituents [39]; aloe-derived bioactives promote epithelial repair and reduce erythema [40]; and green-tea catechins, particularly EGCG, modulate sebaceous gland activity and inhibit bacterial enzymes [41]. Key phytochemicals including flavonoids and terpenoids also interfere with pro-inflammatory cytokine signaling and sebum-regulation pathways [42]. However, variability in extraction processes, inconsistent phytochemical concentration, and limited controlled clinical data highlight the need for standardization and evidence-driven validation before routine integration [43].

4.7 Outlook

The therapeutic landscape is shifting toward biologically selective agents, localized hormonal manipulation, and advanced dermal delivery platforms, complemented by rigorously evaluated phytotherapeutics [44]. This integrated approach represents the future of patient-centered acne therapy with improved tolerability and mechanistic precision.

INNOVATIVE THERAPEUTIC APPROACHES

Acne research has expanded beyond conventional antimicrobial approaches, shifting toward biologically sophisticated interventions that correct underlying dysregulation in immunity, microbial composition, sebaceous gland activity, and cellular signaling. These next-generation strategies emphasize precision rather than broad suppression, aiming for long term disease control and reduced risk of antimicrobial resistance.

5.1 Light-Activated and Energy-Based Therapies

Photodynamic therapy (PDT) has emerged as a non-systemic alternative for persistent inflammatory acne, with recent studies highlighting improvements in moderate to severe cases [45]. Laser and light-based systems including blue light, pulsed dye lasers, and fractional devices further enhance selective photothermolysis of sebaceous glands and bacterial targets [46]. Combination protocols using PDT and topical retinoids have shown improved outcomes in antibiotic-refractory acne, providing both anti-inflammatory and comedolytic effects [47]. Advancements in nano-encapsulated photosensitizers aim to enhance precision, reduce discomfort, and improve post-procedure tolerability.

5.2 Microbiome-Restorative Approaches

Understanding acne as a microbiome-associated disorder has increased interest in probiotic and postbiotic dermatologic therapies. Topical formulations containing Lactobacillus and Bifidobacterium strains have shown the ability to modulate microbial ecology, strengthen the skin barrier, and suppress inflammatory cytokine release [48]. Prebiotic and postbiotic compounds including bioactive peptides and short-chain fatty acids provide similar immunomodulatory benefits while improving formulation stability [49]. These strategies offer a promising foundation for microbiome targeted dermocosmetics.

5.3 Gene-Directed Interventions

Gene-level modulation represents an emerging frontier. CRISPR-Cas constructs designed to selectively target Cutibacterium acnes genes demonstrate proof of concept potential for precision microbial eradication [50]. Complementary approaches using bacteriophage engineering have also been explored, providing pathogen-specific targeting without disturbing commensal organisms [51]. Delivery challenges including RNA degradation and limited skin penetration are currently addressed through lipid-based and nanoparticle carriers.

5.4 Peptide-Based Pharmacology

Antimicrobial and immunomodulatory peptides are gaining recognition as alternatives to conventional antibiotics. Engineered variants of host-defense peptides demonstrate robust activity against C. acnes while promoting wound healing and down-regulating inflammatory pathways [52]. Nanocarrier-assisted delivery further enhances peptide stability and skin penetration, broadening their therapeutic applicability in acne management.

5.5 Digital and Bioengineered Tools for Personalised Therapy

Digital tools such as AI-supported skin-analysis platforms enable automated lesion quantification, severity grading, and customised treatment planning. On the research side, 3D-bioprinted skin constructs offer biologically relevant models for testing topical interventions, improving accuracy in predicting irritation, penetration, and pharmacodynamic responses. These technologies collectively accelerate personalised therapy development.

5.6 Overall Perspective

Together, these advancements illustrate a shift toward individualized, mechanism based acne therapy. Precision biotechnology, microbiome modulation, gene-directed tools, peptide therapeutics, and computational analytics are collectively reshaping future treatment pathways. Efforts toward acne vaccines targeting C. acnes virulence factors and immunomodulatory pathways further support the movement toward disease-modifying therapy rather than symptomatic control [53,54].

COMBINATION THERAPIES AND PERSONALIZED MEDICINE

Combination therapy has emerged as a cornerstone in modern dermatological practice, offering enhanced therapeutic efficacy through synergistic mechanisms. The rationale for combining agents lies in their ability to produce complementary effects, minimize drug resistance, and improve patient outcomes [55]. For instance, combining retinoids which normalize keratinization with antibiotics that reduce Cutibacterium acnes load provides a dual benefit in acne management. Similarly, benzoyl peroxide combined with clindamycin significantly reduces bacterial resistance while maintaining antibacterial effectiveness. In chronic and multifactorial skin disorders such as psoriasis, atopic dermatitis, and acne, combination therapies target multiple pathogenic pathways such as inflammation, hyperproliferation, and infection, leading to comprehensive disease control [56].

Fixed-dose combinations (FDCs) are widely used to improve compliance and convenience. Common dermatological FDCs include adapalene with benzoyl peroxide for acne, calcipotriol with betamethasone dipropionate for psoriasis, and clotrimazole with beclomethasone for fungal infections with inflammatory components. These formulations provide synergistic action and reduce dosing frequency [57].

Pharmacogenomics plays a pivotal role in the evolution of personalized dermatology by linking genetic variation to individual drug responses. Genetic polymorphisms, such as those in the CYP450 family, affect retinoid metabolism and can influence both efficacy and adverse effects. Similarly, testing for HLA-B variants before dapsone administration helps prevent severe hypersensitivity reactions. Personalized dermatology integrates genetic, environmental, and lifestyle data to optimize therapy selection, especially for biologic treatments targeting pathways like TNF-α, IL-17, or IL-23 in psoriasis. This precision-based approach enhances therapeutic outcomes while minimizing systemic toxicity and adverse effects [58].

FORMULATION ADVANCES AND DELIVERY INNOVATIONS

Recent advances in formulation science have transformed dermatological therapy, focusing on controlled and targeted drug delivery systems that improve efficacy, stability, and patient compliance. Microsponges and hydrogels represent significant innovations in topical formulation technology. Microsponges are porous polymeric microspheres that encapsulate active ingredients, enabling controlled release, reduced irritation, and enhanced stability commonly employed in benzoyl peroxide formulations for acne [58,60,62]. Hydrogels, on the other hand, are three-dimensional polymeric networks with high water content, providing a cooling and soothing effect along with sustained drug release, making them beneficial for wound healing, burns, and inflammatory skin conditions [63].

Transdermal patches and microneedle systems further advance non-invasive delivery strategies. Transdermal patches offer controlled and prolonged systemic drug delivery, bypassing first-pass metabolism and maintaining consistent plasma levels [59]. Microneedle systems use microscopic needles to transiently disrupt the stratum corneum, allowing enhanced drug permeation without pain; they are increasingly explored for vaccines, insulin, and cosmetic peptide delivery [64].

Emerging smart and responsive drug-delivery systems represent the frontier of dermatological therapeutics. pH-sensitive systems respond to altered skin pH in acne or infections to selectively release drugs. Enzyme-responsive formulations exploit disease-related enzyme activity for localized activation in wounds or inflamed tissue. Temperature-sensitive hydrogels undergo sol gel transitions near skin temperature, enabling on-demand release of corticosteroids or anti-inflammatory agents [58,61,65]. Additionally, smart wearable patches integrating biosensors can monitor real-time skin parameters and modulate drug release accordingly.

FUTURE PERSPECTIVES AND RESEARCH CHALLENGES

Advances in acne therapy are steadily moving toward technologies that can bridge the persistent divide between laboratory performance and clinical effectiveness. Despite promising in-vitro and in-vivo outcomes, many nanocarrier-based formulations continue to show inconsistent results in real-world use due to interpatient variability in skin architecture, instability of carrier systems, and insufficient long-term clinical validation [66,68,70]. Future research must prioritize standardized experimental models, robust pharmacodynamic evaluations, and large-scale trials capable of capturing therapeutic performance across diverse populations.

Regulatory complexity represents another critical barrier to translation. Emerging platforms such as nanoparticles, microneedle systems, and nitric oxide releasing technologies fall within regulatory categories that are still evolving, requiring extensive data on pharmacokinetics, degradation behavior, immune interactions, and safety under repeated exposure [67,69,70]. The absence of internationally aligned standards for advanced drug delivery systems further restricts commercial progression. Collaborative efforts among academic groups, industry, and regulatory authorities are essential to streamline approval pathways without compromising patient safety.

Therapeutic success is also heavily influenced by patient adherence, highlighting the need for formulations optimized for everyday use. Increasingly, research aims to incorporate genetic predisposition, hormonal milieu, microbiome characteristics, and lifestyle-related triggers into individualized treatment frameworks [71]. To support this shift, future products must emphasizenon-irritant profiles, improved aesthetic acceptability, and simplified application particularly for adolescents and individuals with reactive or sensitive skin [67,68].

In parallel, the field is witnessing a growing focus on sustainable and environmentally conscious dermatology. Strategies involving biodegradable materials, solvent-free fabrication processes, and reduced-waste manufacturing are expected to gain

traction as both regulatory expectations and consumer preferences shift toward eco-responsible therapeutic solutions.
Overall, these research directions point toward a future defined by mechanistically sophisticated, patient centered, and ethically sustainable acne treatments. Overcoming the scientific, regulatory, and manufacturing barriers described above will be critical for translating current technological innovations into effective, accessible, and clinically reliable solutions [66,71].

CONCLUSION

Advances in novel agents and nanocarrier-based delivery systems have transformed acne therapy by enhancing efficacy, minimizing side effects, and improving patient adherence. Personalized, mechanism-driven approaches and innovative formulations like ethosome-loaded minocycline gel exemplify the future of targeted, safe, and sustainable acne management.

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