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Review Article

Comparative Study of Herbal and Synthetic Anti-Acne Gel

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ABSTRACT

Objective: To systematically compare herbal and synthetic anti acne gel formulations based on physicochemical properties, antimicrobial efficacy against Cutibacterium acnes, skin compatibility, and stability, thereby informing evidence based therapeutic choices. Methods: A standardized gel base (Carbopol 940, HPMC, propylene glycol, preservatives) is used to prepare both a synthetic gel (e.g., 1% clindamycin phosphate or 2.5% benzoyl peroxide) and an optimized herbal gel containing a defined extract mixture (e.g., 2% neem, 1% turmeric, 1% tulsi, 0.5% tea tree oil). Evaluations include pH, viscosity, spreadability, extrudability, drug/phytochemical content, in vitro release, accelerated stability, antimicrobial activity (zone of inhibition, MIC), and skin irritation (human patch test or animal model). Conclusion: Herbal anti acne gels offer a promising multi targeted alternative that addresses sebum, hyperkeratinization, C. acnes, and inflammation simultaneously, with a favourable safety profile. However, standardization, stability, and large-scale clinical validation are necessary before they can replace synthetic gels as first line therapy. The choice should be individualized based on acne severity, skin sensitivity, and patient preference.

INTRODUCTION

Acne vulgaris remains one of the most prevalent dermatological conditions worldwide, affecting approximately 85% of adolescents and young adults, with a significant proportion experiencing persistent disease into their thirties and forties. The psychosocial burden of acne—ranging from disfigurement and scarring to depression, anxiety, and social withdrawal—underscores the urgent need for safe, effective, and accessible treatments[1]. Despite a wide armamentarium of over-the-counter and prescription therapies, challenges such as antibiotic resistance, cutaneous irritation, allergic reactions, and high recurrence rates persist. In parallel, a global resurgence of interest in plant-based medicine has positioned herbal formulations as appealing alternatives, particularly among patients seeking natural, gentle, and long-term management options. However, rigorous comparative data between standard synthetic gels and optimized herbal2][3]

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gels remain limited. This study therefore undertakes a systematic comparison of herbal and synthetic anti-acne gel formulations—evaluating physicochemical properties, antimicrobial efficacy, skin compatibility, and stability—to inform evidence-based therapeutic choices[4].

ACNE VULGARIS

Acne vulgaris is a chronic inflammatory disease of the pilosebaceous unit, characterized by comedones (open and closed), papules, pustules, nodules, and, in severe cases, cysts and scarring. Its onset typically coincides with adrenarche and puberty, though adult-onset acne, particularly in women, is increasingly recognized[5].

Pathophysiology of Acne

The pathogenesis of acne is multifactorial and follows a well-established sequence: (1) increased sebum production under androgen control, (2) follicular hyperkeratinization leading to microcomedone formation, (3) colonization of the follicle by *Cutibacterium acnes* (*C. acnes*), and (4) release of pro-inflammatory mediators [6][7]that drive the visible inflammatory lesions. Sebaceous glands, concentrated on the face, chest, and back, secrete sebum—a complex lipid mixture. Under androgenic stimulation (testosterone and dihydrotestosterone), sebocyte proliferation and lipogenesis accelerate, creating a lipid-rich environment that favors *C. acnes* growth. Simultaneously, abnormal desquamation of follicular keratinocytes results in retention hyperkeratosis; instead of shedding freely, corneocytes aggregate, forming a plug that obstructs the follicular canal. This microcomedone evolves into an open comedone (blackhead) when the dilated follicle is oxidized, or a closed comedone (whitehead). As the follicle distends, hypoxia develops, triggering *C. acnes* proliferation. The bacterium, a Gram-positive anaerobe, hydrolyzes sebum triglycerides into free fatty acids via lipase enzymes, further irritating the follicular wall and promoting inflammation[8]

Acne vulgaris is the most common skin disorder worldwide, affecting up to 85% of adolescents and often persisting into adulthood. Its pathogenesis is not a simple linear chain but a complex, self-perpetuating cycle involving hormonal regulation, follicular biology, microbial ecology, and innate immunity. Understanding this multifactorial sequence is essential for developing targeted therapies. The classic four-step model—(1) increased sebum production, (2) follicular hyperkeratinization, (3) *Cutibacterium acnes* colonization, and (4) inflammation—remains the cornerstone, but recent discoveries have added nuance to each stage[9][10].

1. Androgen-Driven Sebum Hypersecretion: The Lipid Foundation

Sebaceous glands are holocrine glands concentrated in sebaceous follicles on the face, chest, and back. Their primary function is to produce sebum, a complex mixture of triglycerides (≈40%), wax esters (≈25%), squalene (≈15%), and free fatty acids (≈10%), along with cholesterol and cholesterol esters. Under normal conditions, sebum forms a hydrolipidic film that protects the skin[11].

Androgenic Control.

Sebocytes express all the enzymatic machinery to respond to androgens. Testosterone, produced by the gonads and adrenal glands, is converted intracellularly to the more potent dihydrotestosterone (DHT) by 5α-reductase type 1 (predominant in sebaceous glands). DHT binds to nuclear androgen receptors, activating transcription of genes involved in lipogenesis—

notably those encoding fatty acid synthase, acetyl-CoA carboxylase, and stearoyl-CoA desaturase. This accelerates both sebocyte proliferation and de novo lipid synthesis[12].

Why Acne-Prone Sites?

Sebaceous gland density is highest on the face (400–900 glands/cm²), upper chest, and back—the very areas where acne lesions cluster. Moreover, sebocytes from acne patients show increased baseline lipogenesis and heightened sensitivity to androgens, even with normal circulating testosterone levels. This suggests an intrinsic hyperresponsiveness, possibly due to increased androgen receptor density or polymorphisms in 5α-reductase[13][14].

Consequences of hyperseborrhea.

Excess sebum does more than just create an oily surface. It alters the follicular microenvironment in three critical ways:

- **Viscosity changes:** Sebum becomes less fluid, promoting follicular obstruction.
- **Lipid composition shift:** Acne patients often have reduced linoleic acid (an essential fatty acid) in sebum. Linoleic acid normally helps regulate keratinocyte desquamation; its deficiency directly promotes retention hyperkeratosis.
- **Growth substrate:** Sebum triglycerides provide an abundant energy source for lipophilic bacteria, especially *C. acnes[15][16]*.

Therapeutic translation: Isotretinoin (13-cis-retinoic acid) profoundly suppresses sebum production by inducing sebocyte apoptosis and downregulating androgen receptor expression, reducing sebum output by up to 90%[17].

2. Follicular Hyperkeratinization: The Microcomedone Origin

The second step is abnormal desquamation of keratinocytes lining the infrainfundibulum—the lower part of the follicular canal. In healthy follicles, corneocytes (anucleate keratinocytes) are shed into the lumen and extruded with sebum. In acne-prone follicles, this process fails[18].

Retention hyperkeratosis.

Instead of dispersing, corneocytes remain cohesive, forming a dense plug that obstructs the follicular ostium. Histologically, this is termed retention hyperkeratosis—distinct from the hyperproliferation seen in psoriasis. The plug consists of corneocytes embedded in a matrix of sebum and lipids.

- **Androgens** indirectly influence keratinocytes. While follicular keratinocytes have few androgen receptors, androgens act via dermal papilla cells to secrete paracrine factors like insulin-like growth factor-1 (IGF-1) and transforming growth factor-β (TGF-β), which promote keratinocyte proliferation and reduce desquamation[19].
- **Low linoleic acid** (mentioned above) is a potent physiological regulator: linoleate deficiency in cultured keratinocytes leads to hyperkeratosis. Topical linoleic acid reduces microcomedone formation.
- **Proinflammatory lipids** like squalene peroxides, generated when sebum oxidizes, can induce keratinocyte hyperproliferation[16].
- **Mechanical factors** – Follicular distension itself triggers stretch-activated channels that upregulate keratinocyte adhesion molecules [17].

Microcomedone to Visible Comedone.

The obstructed follicle dilates as sebum continues to be produced but cannot escape. If the follicular opening remains patent, the accumulated material oxidizes (especially squalene) and turns dark—an open comedone or blackhead. The dark color is not dirt but melanin and oxidized lipids. If the opening is narrow or closed, the contents remain white to flesh-colored, forming a closed comedone (whitehead). Closed comedones are more prone to rupture and inflammatory progression because their thinner follicular wall is stretched more tightly[21].

Current Treatment Landscape

Conventional acne treatment follows a severity-based ladder. Mild comedonal acne responds to topical retinoids (adapalene, tretinoin) or salicylic acid. Mild to moderate inflammatory acne is treated with topical antibiotics (clindamycin, erythromycin), benzoyl peroxide (BPO), or combinations thereof. Moderate to severe acne often requires oral antibiotics (doxycycline, minocycline), hormonal therapy (oral contraceptives, spironolactone), or isotretinoin for recalcitrant nodulocystic disease. While effective, each carries limitations: antibiotics drive resistance; BPO causes irritation and bleaching; retinoids induce initial flares, photosensitivity, and teratogenicity concerns; isotretinoin has significant systemic adverse effects. Moreover, none of these agents address all four pathogenic pillars simultaneously. This has motivated interest in multi-targeted, plant-derived alternatives delivered via optimized topical vehicles such as gels[22].

Anatomy and Physiology of Skin

To understand topical drug delivery, one must appreciate skin architecture. Human skin consists of three layers: epidermis, dermis, and hypodermis[23]. The epidermis, a stratified squamous epithelium, is dominated by keratinocytes that terminally differentiate to form the stratum corneum (SC)—the primary barrier. The SC comprises corneocytes embedded in a lipid matrix of ceramides, free fatty acids, and cholesterol, arranged in a "brick and mortar" pattern. Below the SC, the viable epidermis contains melanocytes, Langerhans cells, and Merkel cells. The dermis, a dense connective tissue, houses blood vessels, lymphatics, nerve endings, hair follicles, sebaceous and sweat glands. For acne therapy, the pilosebaceous unit is the target: the follicle extends from the skin surface to the sebaceous gland deep in the dermis. An ideal topical anti-acne gel must therefore deliver active agents across the SC into the follicular infundibulum, where *C. acnes* resides and comedogenesis begins[24].

Acne Vulgaris: Etiology and Pathogenesis

Building on the pathophysiology, etiology involves interactions among genetics, hormones, diet (high glycemic load, dairy), and environmental factors. Androgens—dehydroepiandrosterone sulfate (DHEA-S), testosterone, and 5α-dihydrotestosterone (DHT)—bind to sebocyte androgen receptors, upregulating lipogenesis and keratinocyte proliferation. Insulin-like growth factor-1 (IGF-1) amplifies these signals, while insulin resistance and hyperinsulinemia reduce sex hormone-binding globulin, raising free androgen levels[26].

Role of *Cutibacterium acnes*

C. acnes (formerly *Propionibacterium acnes*) is a commensal but opportunistic pathogen. Four phylotypes exist; phylotype IA and IB are most associated with acne. The bacterium produces porphyrins (coproporphyrin III) that fluoresce

under Wood's lamp and generate reactive oxygen species upon light exposure—a basis for photodynamic therapy. Virulence factors include lipases (releasing pro-inflammatory fatty acids), proteases (damaging follicular epithelium), and hyaluronate lyase. Moreover, *C. acnes* activates the host immune system via Toll-like receptor 2 (TLR-2) on keratinocytes and monocytes, triggering NF-κB-mediated production of IL-1α, IL-6, IL-8, and TNF-α[27].

Inflammation and Sebum Production

Inflammation is not merely a consequence but an early driver. Comedonal lesions already harbor CD4+ T lymphocytes and macrophages. As the follicle ruptures, keratin, bacteria, and sebum spill into the dermis, inducing a robust foreign-body reaction. Neutrophils release reactive oxygen species and matrix metalloproteinases (MMPs), causing tissue damage and scarring. Sebum itself acts as a pro-inflammatory signal: oxidized squalene and free fatty acids activate peroxisome proliferator-activated receptors (PPARs) and inflammasomes. Thus, therapies that simultaneously reduce sebum, suppress *C. acnes*, and modulate inflammation are theoretically superior[28].

Synthetic Anti-Acne Agents

Synthetic agents form the cornerstone of conventional acne therapy. For topical use, three are most common: benzoyl peroxide, clindamycin phosphate, and adapalene[29].

Benzoyl Peroxide (BPO)

BPO is a potent oxidizing agent with rapid bactericidal activity against *C. acnes*—no resistance has been reported. It releases free radicals that oxidize bacterial proteins, disrupt cell membranes, and generate oxygen, creating an anaerobic environment hostile to *C. acnes*. Additionally, BPO mildly comedolytic and anti-inflammatory via scavenging reactive oxygen species? Paradoxically, it can also induce oxidative irritation. BPO is available in 2.5–10% gels and washes. Side effects include erythema, scaling, dryness, and bleach staining of fabrics. Allergic contact dermatitis occurs in 1–2% of users[24][23].

Clindamycin Phosphate

Clindamycin is a lincosamide antibiotic that binds to the 50S ribosomal subunit, inhibiting bacterial protein synthesis. Its anti-acne activity derives almost exclusively from suppressing *C. acnes* and reducing inflammatory mediators. Clindamycin is typically used at 1% in gels, lotions, or solutions. The major drawback is bacterial resistance: >50% of *C. acnes* isolates in some regions are resistant, often cross-resistant to erythromycin. Moreover, topical clindamycin carries a rare risk of *Clostridioides difficile*-associated diarrhea (though minimal with proper use) and does not reduce sebum or keratinocyte adhesion[24][25].

Adapalene (Retinoid)

Adapalene is a third-generation synthetic retinoid that binds selectively to retinoic acid receptor β/γ (RAR-β/γ) and also activates PPAR-γ. Unlike tretinoin, adapalene has greater chemical stability, lower irritation, and enhanced anti-inflammatory properties. It normalizes follicular keratinization, prevents microcomedone formation, and reduces inflammatory lesions via NF-κB inhibition. Adapalene 0.1% or 0.3% gel is a first-line for comedonal and mild-to-moderate acne. Side effects include initial acne flare, photosensitivity, erythema, and desquamation. It is pregnancy category C[26][27].

Mechanism of Action and Side Effects Summary

Synthetic agents target discrete pathways but none is perfect. BPO is antimicrobial but irritating; clindamycin is anti-bacterial but resistance-prone; adapalene is comedolytic and anti-inflammatory but causes retinoid dermatitis. Combinations (e.g., BPO-clindamycin, adapalene-BPO) partially mitigate these limitations yet add cost and complexity. Furthermore, all synthetic gels require careful patient education and can discourage long-term adherence due to side effects[29].

Herbal Anti-Acne Agents

Herbal remedies have been used for centuries in traditional medicine systems (Ayurveda, Traditional Chinese Medicine, Unani). Their appeal lies in perceived safety, multi-component synergistic action, and lower cost. The following five plants have strong evidence for anti-acne activity.

***Azadirachta indica* (Neem)**

Every part of neem (leaves, bark, seeds) exhibits antibacterial, anti-inflammatory, and antioxidant properties. The active phytochemicals include nimbin, nimbidin, azadirachtin, and quercetin. Neem leaf extracts inhibit *C. acnes* with MIC values comparable to clindamycin (around 50–100 µg/mL). They also suppress COX-2 and LOX pathways, reducing prostaglandin-mediated inflammation. In gel formulations, neem enhances wound healing and reduces sebum secretion.

***Curcuma longa* (Turmeric)**

Curcumin, demethoxycurcumin, and bisdemethoxycurcumin are the major curcuminoids. Curcumin blocks NF-κB activation, downregulates IL-1β, IL-6, and TNF-α, and scavenges reactive oxygen species. It also inhibits *C. acnes*-induced TLR-2 expression. Poor bioavailability orally is less problematic topically; however, curcumin's intense yellow color can stain skin. Turmeric gels require low curcumin concentrations (0.5–2%) or use of colorless extracts.

Aloe vera

Aloe vera gel contains polysaccharides (acemannan), anthraquinones, and glycoproteins. It is primarily a soothing, moisturizing, and wound-healing agent. While its direct antibacterial effect against *C. acnes* is modest, aloe potentiates the activity of other antimicrobials, reduces benzoyl peroxide-induced irritation, and promotes epithelization. In comparative studies, aloe vera gel alone does not clear acne but significantly improves tolerability of concomitant therapies.

***Melaleuca alternifolia* (Tea Tree Oil, TTO)**

TTO is one of the best-studied herbal anti-acne agents. Its main active terpenes—terpinen-4-ol, α-terpineol, and 1,8-cineole—disrupt bacterial cell membranes and inhibit *C. acnes* at concentrations of 0.5–5% v/v. TTO also possesses anti-inflammatory activity by reducing histamine and TNF-α release. Clinical trials show that 5% TTO gel is as effective as 5% benzoyl peroxide but with significantly less scaling, dryness, and burning. Allergic contact dermatitis occurs in sensitized individuals, and TTO must be properly stored to avoid oxidation[30].

***Ocimum sanctum* (Tulsi, Holy Basil)**

Tulsi contains eugenol, ursolic acid, rosmarinic acid, and apigenin. It exhibits broad-spectrum antimicrobial activity, including against *C. acnes*, and suppresses COX-2 and iNOS. Tulsi extract also reduces sebocyte lipid synthesis via downregulation of SREBP-1. In gel formulations,

tulsi improves antioxidant capacity and prevents comedone formation.

Phytochemicals and Their Anti-Acne Mechanisms

The above herbs act via multiple mechanisms: (i) direct bactericidal (terpenes, alkaloids, phenolics), (ii) anti-inflammatory (curcuminoids, eugenol, nimbidin) blocking NF-κB and MAPK pathways, (iii) sebum reduction (flavonoids, ursolic acid), (iv) antioxidant (quercetin, rosmarinic acid) reducing oxidative tissue damage, and (v) modulation of keratinocyte differentiation. Importantly, herbs provide polypharmacy in a single extract, potentially targeting all four pathogenic pillars simultaneously. However, challenges include batch-to-batch variability, poor solubility of lipophilic actives, skin permeability limitations, and lack of standardized extracts.

Gel Formulation Technology

A gel is a semisolid system consisting of a dispersed phase (drug, herbal extract) in a three-dimensional network of gelling agent swollen by a solvent (usually water or hydroalcoholic). Gels are preferred for acne because they are non-greasy, easily spreadable, leave a thin film, and allow cooling evaporation.

Ideal Properties of Topical Gel

An ideal anti-acne gel should be: (i) non-irritating and hypoallergenic, (ii) pH compatible with skin (4.5–6.5), (iii) thixotropic (low viscosity on shear to spread, high viscosity at rest to remain on skin), (iv) stable to temperature and light, (v) easily washable without residue, (vi) allowing sustained or immediate release depending on need, and (vii) aesthetically acceptable (clear, odorless or pleasant fragrance, non-staining). For herbal gels, additional requirements include preservation against microbial growth (since aqueous herbal extracts are nutrient-rich) and color masking if the extract is pigmented.

Polymers and Gelling Agents (e.g., Carbopol, HPMC)

Synthetic polymers: Carbopol (cross-linked polyacrylic acid) is the gold standard. Carbopol 934, 940, and 980 grades differ in viscosity and clarity. At low concentrations (0.5–2% w/w), Carbopol forms clear, stable gels after neutralization with triethanolamine (TEA) or NaOH. Carbopol gels are elegant, have excellent spreadability, and are compatible with many drugs. Disadvantages: they are electrolytes-sensitive and require careful neutralization.

Semi-synthetic: Hydroxypropyl methylcellulose (HPMC) is a cellulose ether that gels by thermal swelling. HPMC produces clear, non-ionic gels, stable over pH 3–11, and less sensitive to salts. However, HPMC gels are more stringy and require higher concentrations (2–5%). Often, blends of Carbopol and HPMC are used to balance clarity, viscosity, and release profile. Natural polymers: Xanthan gum, guar gum, and sodium alginate are also used, particularly for “green” herbal gels, but they support microbial growth and often produce opaque, stringy gels. For comparative studies, a fixed gel base (e.g., 1% Carbopol 940, 0.5% HPMC, 10% propylene glycol as humectant, 0.2% methylparaben, 0.1% propylparaben as preservative, water to 100%) is typically prepared. The synthetic anti-acne gel contains, for example, 1% clindamycin phosphate or 2.5% benzoyl peroxide. The herbal gel contains a standardized extract mixture (e.g., 2% neem extract, 1% turmeric extract, 1% tulsi extract, 0.5% tea tree oil) incorporated into the same gel base. Both are then evaluated for pH, viscosity, spreadability, extrudability, drug/explant content, in vitro

release, and stability, followed by comparative antimicrobial and skin irritation studies.

CONCLUSION

The systematic comparison of herbal and synthetic anti-acne gels reveals that both formulation types have distinct advantages and limitations. Synthetic gels—exemplified by benzoyl peroxide, clindamycin, and adapalene—provide rapid, well-documented efficacy through specific, potent mechanisms: bactericidal oxidation, ribosomal inhibition, or retinoid-receptor modulation. However, their clinical utility is constrained by cutaneous irritation (erythema, scaling, dryness), emerging antibiotic resistance (particularly with clindamycin), and failure to address all four pathogenic pillars of acne simultaneously. In contrast, optimized herbal gels harness synergistic phytochemicals that collectively reduce sebum (flavonoids, ursolic acid), normalize follicular keratinization (linoleic acid-rich extracts), suppress *C. acnes* via multiple non-resistance-prone pathways (terpenes, alkaloids, phenolics), and dampen inflammation (curcuminoids, eugenol, nimbidin blocking NF-κB and COX-2). Additionally, herbal vehicles containing aloe vera or tulsi improve skin tolerability and wound healing, potentially enhancing long-term adherence. The main drawbacks of herbal gels are batch-to-batch variability, potential for colour and odour, lower stability of certain actives (e.g., tea tree oil oxidation), and the need for rigorous standardization.

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