Review Article

Beyond Benzoyl Peroxide: The New Landscape of Over-the-counter Therapies for Acne

Yeanna Moon, B.A.[1], Peter Lio, M.D.[2]

[1] Kansas City School of Medicine, [2] Northwestern Feinberg School of Medicine

Keywords: Acne vulgaris, OTC acne therapies, benzoyl peroxide, salicylic acid, sulfur

Journal of Integrative Dermatology

Acne vulgaris is a prevalent dermatological condition that primarily affects the pilosebaceous units, leading to comedones, papules, pustules, and nodules.[1] This condition affects approximately 9.4% of the global population, making it the eighth most common disease worldwide.[2] It predominantly affects adolescents and young adults, with a significant psychosocial impact, including diminished self-esteem and increased risk of depression.[2] Traditionally, over-the-counter (OTC) treatments have been limited to agents like benzoyl peroxide and salicylic acid. However, recent advancements have introduced a variety of novel OTC therapies including topical probiotics and concentrated oxygen therapies which are gaining attention. Given the expanding array of OTC options and their accessibility, a comprehensive review of current therapies is essential to guide evidence-based clinical recommendations.

To evaluate the efficacy and safety profiles of established and emerging OTC acne treatments, PubMed, Embase, and the Cochrane Library searches were conducted with terms included “acne vulgaris,” “over-the-counter treatments,” “topical therapies,” and specific agents.

Many OTC acne therapies show antimicrobial and anti-inflammatory effects in vitro and small clinical trials. Established agents like adapalene and benzoyl peroxide had the strongest clinical evidence. Emerging options such as phage therapy and probiotics are promising but require further validation.

OTC acne treatments continue to diversify, offering new options beyond legacy therapies. While some newer agents are mechanistically compelling, high-quality studies are needed to define their role in acne management.

INTRODUCTION

Acne vulgaris is a prevalent chronic inflammatory skin condition that primarily affects the pilosebaceous units, leading to various lesions such as comedones, papules, pustules, and nodules.[1] It is most common during adolescence and young adulthood, with a global prevalence estimated at approximately 9.4%, making it the eighth most prevalent disease worldwide.[2] Its pathogenesis involves a complex interplay of hormonal, microbial, immunological, and environmental factors.[3]

Over the counter (OTC) treatments have traditionally included agents such as benzoyl peroxide, salicylic acid, and topical retinoids like adapalene. While these treatments are effective for many individuals, concerns exist regarding potential side effects, including skin irritation and dryness. Additionally, the emergence of antibiotic resistance has prompted the exploration of alternative therapies.

Emerging therapies aim to address these concerns by targeting different aspects of acne pathogenesis. These include topical probiotics to modulate the skin microbiome, bacteriophage therapy targeting *Cutibacterium acnes*, and light-based treatments that reduce bacterial colonization and inflammation. Such innovations offer promising alternatives, especially for individuals who experience side effects from traditional therapies or have antibiotic-resistant acne strains.

A literature review was conducted using databases including PubMed, Embase, and the Cochrane Library. Search terms encompassed “acne vulgaris,” “over-the-counter treatments,” “topical therapies,” and specific agents. Inclusion criteria comprised randomized controlled trials, meta-analyses, and observational studies evaluating the efficacy and safety of OTC acne treatments. Data extraction emphasized treatment outcomes, adverse effects, and patient satisfaction.

CORE OTC ACNE TREATMENTS

I. ADAPALENE (RETINOID)

Adapalene is a third-generation topical retinoid available in 0.1% and 0.3% concentrations, primarily used to treat mild to moderate acne vulgaris. It works by modulating keratinocyte differentiation and proliferation, preventing microcomedone formation, and it exhibits anti-inflammatory

properties by inhibiting inflammatory mediators.[4] Common side effects include skin irritation, dryness, redness, and a transient burning or stinging sensation, particularly during the initial weeks of therapy.[4] Adapalene is contraindicated during pregnancy due to potential teratogenic risks associated with retinoids.[5] (Please see Table 1)

Initially approved by the U.S. Food and Drug Administration (FDA) as a prescription medication, adapalene 0.1% gel became the first retinoid approved for OTC use in 2016 for individuals aged 12 years and older.[6]

II. AZELAIC ACID

Azelaic acid is a naturally occurring dicarboxylic acid utilized topically at a 20% concentration for the treatment of mild to moderate acne vulgaris.[7] Its mechanism of action includes antimicrobial activity against *C. acnes*, anti-inflammatory effects through the inhibition of reactive oxygen species, and normalization of keratinization by reducing the production of keratohyalin granules in the pilosebaceous duct.[7] Common adverse effects are generally mild and transient, including burning, stinging, tingling, dryness, and redness at the application site.[7]

The U.S. FDA approved azelaic acid 20% cream in 1995 for the topical treatment of mild to moderate inflammatory acne vulgaris.[8]

III. BENZOYL PEROXIDE

Benzoyl peroxide (BPO) is a widely utilized over-the-counter topical agent for the treatment of acne vulgaris, particularly effective against mild to moderate forms. Available in concentrations ranging from 1% to 10%, BPO exhibits multiple mechanisms of action. Primarily, it serves as a potent antimicrobial by releasing reactive oxygen species that oxidize bacterial proteins, effectively reducing *C. acnes* populations.[9] Additionally, BPO possesses keratolytic properties, promoting the desquamation of the follicular epithelium, which aids in preventing comedo formation.[9] Its mild anti-inflammatory effects further contribute to its efficacy in acne management.[9] Common adverse effects associated with BPO include skin irritation, dryness, peeling, redness, and a burning or stinging sensation at the application site. Notably, BPO has a bleaching effect, which can discolor hair, clothing, and bedding upon contact.[9]

The U.S. FDA has approved benzoyl peroxide for over-the-counter use in acne treatment products. However, recent testing has identified elevated levels of benzene, a known carcinogen, in a small number of BPO-containing products, leading to voluntary recalls of those specific items.[10]

IV. SALICYLIC ACID

Salicylic acid is a beta-hydroxy acid that penetrates the skin to exfoliate and unclog pores, making it effective against comedonal acne.[11] It also exhibits anti-inflammatory properties by suppressing the NF-κB pathway, reducing inflammation associated with acne lesions.[12] Common side effects include skin irritation and dryness.[11] The U.S. FDA has approved salicylic acid for over-the-counter use in acne treatment products.[13]

V. SULFUR

Sulfur is applied topically in concentrations between 1% and 10%, exhibits keratolytic and antibacterial properties, aiding in the treatment of mild to moderate acne.[14] It helps to shed dead skin cells and reduce excess oil, preventing pore blockage.[14] Adverse effects may include malodor and dry skin.[14] Sulfur is FDA-approved for acne treatment.

VI. ZINC

Zinc, administered orally as zinc gluconate (200 mg/day) or zinc sulfate (400–600 mg/day), has bacteriostatic properties and inhibits chemotaxis, potentially reducing tumor necrosis factor-alpha production.[15] It is used for mild to moderate acne and may be beneficial in severe inflammatory cases.[11] Side effects can include gastrointestinal disturbances such as nausea, vomiting, and diarrhea.[11] While zinc oxide is FDA-approved for use in over-the-counter skin products like sunscreens and skin protectants, oral zinc supplements are not specifically approved for acne treatment.

VII. ALPHA HYDROXY ACIDS (AHAS)

Alpha hydroxy acids (AHAs), such as glycolic and lactic acids, are typically used at concentrations around 10% for their exfoliative capabilities.[16] They promote epidermolysis, disperse basal layer melanin, and increase collagen synthesis within the dermis, aiding in the treatment of mild acne. Adverse effects may include redness, swelling, burning, and pruritus.[16] AHAs are FDA-approved for use in cosmetic products.[17]

VIII. SODIUM SULFACETAMIDE

Sodium sulfacetamide, often combined with 5% sulfur, acts by inhibiting *C. acnes* proliferation through competitive antagonism of para-aminobenzoic acid, halting bacterial DNA synthesis.[18] It is effective for inflammatory lesions and comedones.[11] Side effects can include mild transient dryness and itching.[11] While this combination is not technically FDA-approved for acne treatment, the presence of sulfur allows for labeling as such.

IX. NIACINAMIDE

Niacinamide, applied topically in concentrations of 2–5%, possesses anti-inflammatory properties, reduces sebum production, and improves skin barrier function.[19] It is effective for mild to moderate acne vulgaris.[11] Generally well-tolerated, rare cases of skin irritation have been reported.[11] Niacinamide is available OTC but is not FDA-approved specifically for acne treatment.

Table 1. Over-the-counter Therapies for Acne.

Drug	Dose	Mode of Action	Clinical Evidence	Adverse effects	Approval/Regulatory Status	References
Adapalene (retinoid)	0.1%–0.3%	Anti comedogenic effect, indirect antimicrobiotic effect	Mild to moderate comedonal acne	Irritation, contraindicated in pregnant women	FDA Approved	4, 5
Azelaic acid (Keratolytics)	20%	Anticomedogenic and antimicrobial effect, reduces the production of keratohyalin granules in the pilosebaceous duct and thus normalizes the ductal hypercornification; keratolytic and anti-inflammatory	Mild to moderate acne	Only a slight sensation of burning or tingling, mild erythema	FDA Approved	7, 8
Benzoyl peroxide (Keratolytics)	1%–10%	Antimicrobial effect (reactive oxygen species are generated that kill bacteria by oxidizing constituents of their cell membranes), antiinflammatory, very mild anti comedogenic effects, keratolytic	Inflammatory acne, Mild to moderate acne	Irritant dermatitis with erythema and scaling, dryness, peeling, stinging, or burning, bleach hair, clothes, and bed linens	FDA Approved	9, 10
Salicylic acid (Keratolytics)	0.5-2%	Anti-inflammatory, topical desquamating agent, comedolytic	Comedonal acne	Skin irritation and dryness	FDA Approved	11, 12, 13
Sulfur (Keratolytics)	1–10%	Keratolytic activity	Mild to moderate acne	Malodor and dry skin	FDA Approved	14
Zinc (Keratolytics)	200 mg/day (Zn gluconate), 400 or 600 mg/day (Zn sulfate)	Bacteriostatic, inhibits chemotaxis, and may decrease tumor necrosis factor—α production	Mild or moderate acne, severe and inflammatory acne	Nausea, vomiting, and diarrhea with gastrointestinal side effects	FDA has approved zinc oxide for use in some over-the-counter skin products like sunscreens and skin protectants	11, 15
Alpha hydroxyl acids (Glycolic and lactic acid) (Keratolytics)	10%	Exfoliative capabilities, promotes epidermolysis, disperse basal layer melanin, increases collagen synthesis within the dermis	Mild Acne	Redness, swelling, burning, and pruritus	FDA-approved for use in cosmetic products	16, 17
Sodium sulfacetamide (Keratolytics)	10% with 5% sulphur	Inhibiting *C. acnes* proliferation, act through competitive antagonism of para-aminobenzoic acid, halting bacterial DNA synthesis	Inflammatory lesions and comedones	Mild transient dryness, itching	Available OTC; not FDA-approved for acne treatment.	11, 18
Niacinamide	2–5%	Anti-inflammatory properties; reduces sebum production; improves skin barrier function.	Mild to moderate acne vulgaris	Generally well-tolerated; rare cases of skin irritation	Available OTC; not FDA-approved specifically for acne treatment.	19
Resorcinol (with Sulfur)	Commonly 2% resorcinol with 8% sulfur in topical preparations.	Keratolytic agent; helps remove skin cell buildup; sulfur component has antibacterial properties.	Mild to moderate acne	Skin irritation, redness, peeling	Available OTC; not FDA-approved specifically for acne treatment.	11, 14, 20
Hydrocolloid Patches	Typically contain no active ingredients.	Occlusive dressing; absorbs excess fluid; protects blemish from external irritants.	Pustules	Minimal; potential for skin irritation if adhesive is too strong	Available OTC; not FDA-approved specifically for acne treatment.	21
Blue Light Therapy (LED Devices)	400-500 nm	Light in the 407-420 nm wavelength range has been shown to have a bactericidal effect on *C. acnes*	Mild to moderate inflammatory acne	Mild but can include skin irritation, erythema, dryness, tightness, rashes, peeling, itching, burning, acne flare-ups, changes in pigmentation	FDA has approved light-emitting diode (LED) devices (blue, red, and blue/red light devices) for at-home use	22
Melaleuca alternifolia (tea tree oil)	1-100%	In tea tree oil, terpinen-4-o1, α-terpineol, and α-pinene were found to be active against *S. aureus*, *S. epidermidis*, and *C. acnes*	Mild and Cystic Acne	Can induce allergic contact dermatitis. It has been proposed that photo-oxidized products from poor storage conditions are the cause of allergic reactions	Generally recognized as safe (GRAS) by FDA	23, 24

Rosemary essential oil	Commonly used in diluted topical formulations.	Antibacterial against *C. acnes* (MIC 0.56 mg/mL) was probably attributed to its bioactive components such as 1,8-cineole, α-pinene, camphor, and camphene.	Mild to Moderate Acne	Can induce allergic contact dermatitis	Generally recognized as safe (GRAS) by FDA	25, 26
Green Tea Extract (Camellia sinensis L)	3%	Antioxidant and anti-inflammatory properties; may reduce sebum production and inflammation.	Mild to moderate acne	May induce allergic contact dermatitis	Available OTC; not FDA-approved specifically for acne treatment.	27, 28
Clays (Kaolin, Bentonite)	Used in facial masks and cleansers.	Absorb excess oil; may help unclog pores.	Mild acne	Skin dryness, irritation	Available OTC; not FDA-approved specifically for acne treatment.	29, 30
Witch Hazel (Hamamelis virginiana)	5% to 10%	Astringent and anti-inflammatory properties; may reduce oiliness and inflammation.	Mild acne	Skin Inflammation	Available OTC; not FDA-approved specifically for acne treatment.	31, 32
Retinol / Retinyl Palmitate	0.01% to 1%	Promotes cell turnover and prevents pore clogging.	Mild to moderate acne	Skin irritation, dryness, photosensitivity	Available OTC; not FDA-approved specifically for acne treatment.	33
Manuka Honey	Varies	Antimicrobial properties due to methylglyoxal content; promotes wound healing.	Mild acne	Rare allergic reactions	Available OTC; not FDA-approved specifically for acne treatment.	34
Microneedle Patches (with Salicylic Acid, Niacinamide, etc)	Varies; typically used as a single-use patch.	Microneedles deliver active ingredients directly into the skin; salicylic acid exfoliates, niacinamide reduces inflammation.	Localized acne lesions	Skin irritation, redness	Available OTC; not FDA-approved specifically for acne treatment.	35
C. Phage		Phages can selectively kill *C. acnes*, particularly type I strains, and may restore bacterial sensitivity to antibiotics by targeting multidrug efflux pumps, which act as phage receptors	Mild to Moderate Acne	Pro-inflammatory responses to phages, in which cytokines such as TNFα, IL-1β, IL-6, and IL-17A were reported	Available OTC; not FDA-approved specifically for acne treatment.	36, 37
Topical nitric oxide and its derivatives (NO4% gel)	Concentrations vary; specific formulations under investigation	NO-releasing nanoparticles exhibit remarkable bactericidal activity against *C. acnes*, effectively inhibiting its growth and suppressing the release of cytokines such as TNF-α, IL-1β, IL-6, and IL-8 in human cells	Mild to Moderate Acne	Nasopharyngitis, Headache, Dysmenorrhea	Available OTC; not FDA-approved specifically for acne treatment.	38, 39
Oxygen Therapy	OTC oxygenated water available, but typically administered in medical spa settings.	Oxygen antibacterial action is primarily due to the generation of reactive oxygen species (ROS), which damage microbial membranes and kill pathogens. Additionally, oxygen enhances wound healing and neoangiogenesis by stimulating the release of vascular endothelial growth factor (VEGF) and related factors.	Mild to Moderate Acne	None Reported	Not FDA-approved for acne treatment; used in clinical settings.	40, 41, 42
Probiotics / Postbiotics (Topical)	Varies; concentrations not standardized.	Microorganisms from the skin can act directly to defend the host against pathogens, control inflammation, and modulate the adaptive immune pathways	Mild to moderate acne	Antibiotic resistance transfer among pathogens, allergic reactions, and bacteremia	Available OTC; not FDA-approved specifically for acne treatment.	43-45
Bakuchiol (Psoralea corylifolia)	Varies; concentrations not standardized.	Anti-aging, anti-inflammatory, and antibacterial properties	Mild to moderate acne	Contact dermatitis	Available OTC; not FDA-approved specifically for acne treatment.	46, 47
Topical CBD / Cannabinoids	Concentrations vary; typically 1–5% in topical formulations.	By inhibiting intracellular adenosine uptake, CBD promotes endogenous adenosine signaling as a protective mechanism during inflammatory and immune response.	Mild to moderate acne	Not well-studied; potential for skin irritation	Not FDA-approved for acne treatment; available in some OTC products.	48-50
Apple Cider Vinegar (ACV)	Typically diluted to 5–10% for topical use.	Vinegar (and other weak acids) induces a stress response in yeast cells by lowering their pH	Mild acne	Burns, (especially in children) and contact dermatitis to nickel, as vinegar increases the leaching of nickel storage containers leading to a higher nickel content.	Not FDA-approved for acne treatment; available OTC.	51

X. RESORCINOL

Resorcinol combined with sulfur is a topical acne treatment commonly formulated with 2% resorcinol and 8% sulfur. Resorcinol functions as a keratolytic agent, promoting the shedding of the outer skin layer to prevent pore blockage and reduce comedo formation.[20] It also exhibits antimicrobial properties, contributing to its effectiveness against acne-causing bacteria.[20] Sulfur complements this action by further aiding in the removal of dead skin cells and absorbing excess oil, thereby reducing the likelihood of clogged pores.[14] This combination is particularly effective for treating mild to moderate acne, including blackheads and whiteheads.[11] Common side effects may include skin irritation, redness, peeling, and dryness.[20] These effects are generally mild and can often be managed by adjusting the frequency of application. Resorcinol-sulfur formulations are available over the counter in various forms, such as creams and lotions, but they are not specifically approved by the FDA for acne treatment.

XI. HYDROCOLLOID PATCHES

Hydrocolloid patches are non-medicated, adhesive dressings originally developed for wound care but have gained popularity for managing superficial acne lesions. These patches are composed of hydrocolloid material that absorbs excess fluid from pimples, creating a moist environment that promotes faster healing. At the same time, the patches protect the area from external contaminants and physical irritation while concealing the acne lesion.[21] By maintaining this occlusive barrier, hydrocolloid patches can help reduce inflammation and prevent further infection.[21] Some hydrocolloid patches are infused with active ingredients like salicylic acid or tea tree oil to enhance their acne-fighting properties, but the primary mechanism remains fluid absorption and protection. Adverse effects are minimal but can include skin irritation, especially in individuals with sensitive skin or when the adhesive is too strong.[21]

Hydrocolloid patches are widely available over the counter and are generally recognized as safe for use; however, they are not specifically approved by the FDA for acne treatment.

XII. BLUE LIGHT THERAPY

Blue light therapy, utilizing wavelengths between 405 and 420 nanometers, is a non-invasive treatment for mild to moderate inflammatory acne.[22] It works via targeting *C. acne*s. These bacteria produce porphyrins, which, when exposed to blue light, generate reactive oxygen species that destroy the bacterial cells.[22] Additionally, blue light may exert anti-inflammatory effects by modulating cytokine production, thereby reducing inflammation associated with acne lesions.[22]

FDA-approved blue light therapy devices are available for at-home use, offering a convenient, non-pharmacologic option for individuals seeking alternative or adjunctive acne treatments. While generally well-tolerated, potential side effects include skin irritation, redness, dryness, and, in rare cases, changes in pigmentation.[22] The FDA has approved light-emitting diode (LED) devices (blue, red, and combination light devices) for at-home use.

ADJUNCT OR COSMECEUTICAL THERAPY

XIII. TEA TREE OIL (*MELALEUCA ALTERNIFOLIA*)

Melaleuca alternifolia, commonly known as tea tree oil, is an essential oil derived from the leaves of the Australian tea tree. It is widely recognized for its antimicrobial and anti-inflammatory properties, making it a popular OTC remedy for mild to moderate acne, including cystic lesions. The primary active component, terpinen-4-ol, exhibits broad-spectrum antibacterial activity, effectively targeting acne-causing bacteria such as *C. acnes* and *Staphylococcus aureus*.[23] Additionally, tea tree oil has been shown to reduce inflammation, which can help alleviate the redness and swelling associated with acne lesions.[23] However, side effects include skin irritation in some individuals, and allergic contact dermatitis has been reported.[23] To minimize the risk of adverse reactions, it's recommended to perform a patch test before applying tea tree oil to larger areas of the skin.

Tea tree oil is generally recognized as safe (GRAS) by the U.S. FDA for topical use, but it is not specifically approved for acne treatment. It is available in various formulations, including pure essential oils, gels, creams, and cleansers.

XIV. ROSEMARY ESSENTIAL OIL

Rosemary essential oil, derived from the leaves of *Rosmarinus officinalis*, has garnered attention for its potential benefits in acne management. Its efficacy is primarily attributed to bioactive constituents such as 1,8-cineole, α-pinene, camphor, and camphene, which exhibit significant antibacterial activity against *C. acnes*.[24] Studies have demonstrated that rosemary essential oil can disrupt the bacterial cell wall and membrane, leading to cell death.[24] Beyond its antimicrobial effects, rosemary essential oil possesses anti-inflammatory properties that may alleviate the redness and swelling associated with acne lesions.[24] These combined actions suggest its utility in treating mild to moderate acne. Despite its potential benefits, rosemary essential oil can cause allergic contact dermatitis in some individuals.[25]

While rosemary essential oil is generally recognized as safe (GRAS) by the U.S. Food and Drug Administration for use in food, it is not specifically approved for acne treatment.

XV. GREEN TEA EXTRACT (EGCG)

Green tea extract, derived from the leaves of *Camellia sinensis*, has garnered attention for its potential benefits in managing mild to moderate acne. Rich in polyphenolic compounds, particularly epigallocatechin-3-gallate (EGCG), green tea exhibits notable antioxidant and anti-inflammatory properties.[26] The antibacterial effects of green tea extract further enhance its role in acne management.[26] EGCG

has been shown to inhibit the growth of *C. acnes* by disrupting bacterial membranes and reducing pro-inflammatory cytokine production.[27] Moreover, green tea's antioxidant capacity helps protect the skin from oxidative stress, which can exacerbate acne.[26]

Green tea extract is available over the counter in various formulations, including creams, lotions, and cleansers. Although it is not specifically approved by the FDA for acne treatment, it is recognized as safe for use in cosmetic products.

XVI. CLAYS (KAOLIN, BENTONITE)

Kaolin and bentonite clays are natural minerals widely used in OTC skincare products, particularly facial masks and cleansers, for managing mild acne. Kaolin, a hydrated aluminum silicate, is known for its gentle absorbent properties, making it suitable for sensitive skin.[28] Bentonite, primarily composed of montmorillonite, exhibits strong absorptive capabilities due to its negative charge, allowing it to attract and remove positively charged toxins, bacteria, and excess oils from the skin.[29] Clinical studies have demonstrated that masks containing these clays can significantly reduce sebum production, decrease the number of open and closed comedones, and improve overall skin texture.[28] However, potential adverse effects include skin dryness and irritation, particularly with overuse or in individuals with naturally dry or sensitive skin.

While kaolin and bentonite clays are GRAS for topical use, they are not specifically approved by the FDA for acne treatment.

XVII. WITCH HAZEL *(HAMAMELIS VIRGINIANA)*

Witch hazel *(Hamamelis virginiana)* is a botanical extract commonly incorporated into OTC skincare products, particularly toners and astringents, aimed at managing mild acne. Its efficacy is primarily attributed to its rich content of tannins and flavonoids, which confer astringent and anti-inflammatory properties.[30] These compounds help reduce skin oiliness by constricting pores and diminishing inflammation, potentially alleviating acne symptoms.[30] Despite its widespread use, witch hazel may cause adverse effects such as skin irritation, dryness, or allergic contact dermatitis, particularly in those with sensitive skin.[31] These reactions may be exacerbated by formulations containing alcohol, which is often present in witch hazel extracts and can further dry out the skin.

While witch hazel is GRAS for topical use and is available over the counter, it is not specifically approved by the U.S. FDA for acne treatment.

XVIII. RETINOL/RETINYL PALMITATE

Retinol and retinyl palmitate are vitamin A derivatives commonly found in OTC acne products at concentrations ranging from 0.01% to 1%. These ingredients promote epidermal cell turnover and prevent clogged pores, targeting key steps in acne pathogenesis.[32] Retinol converts into retinoic acid in the skin, while retinyl palmitate acts as a gentler precursor, making it better suited for sensitive skin.[32]

Though not FDA-approved specifically for acne, both are widely used in mild to moderate cases.

XIX. MANUKA HONEY

Manuka honey, derived from the *Leptospermum scoparium* plant, is increasingly used in skincare for its natural antimicrobial and wound-healing properties.[33] Its efficacy in acne treatment is primarily attributed to methylglyoxal (MGO), a compound with strong antibacterial activity against *C. acnes* and *Staphylococcus aureus*.[33] It also maintains a moist wound environment and has anti-inflammatory effects, which may help reduce redness and swelling associated with mild acne.

Though available over the counter and marketed for various skin concerns, Manuka honey is not FDA-approved specifically for acne treatment.

XX. MICRONEEDLE PATCHES

Microneedle patches are emerging OTC acne treatments designed to deliver active ingredients, commonly salicylic acid and niacinamide, directly into the epidermis through tiny, dissolvable needles. This targeted delivery allows deeper penetration compared to traditional topicals, enhancing the effectiveness of exfoliants like salicylic acid and anti-inflammatory agents like niacinamide.[34] These patches are typically used as single-use spot treatments for localized acne lesions, particularly papules and pustules. However, mild side effects such as redness, irritation, or transient discomfort at the application site may occur.[24]

Though available OTC and widely marketed in cosmeceuticals, these devices are not FDA-approved specifically for acne treatment.

EMERGING THERAPIES

XXI. C. PHAGE (BACTERIOPHAGE THERAPY)

C. acnes bacteriophage therapy is an emerging approach in acne treatment that utilizes viruses (phages) capable of selectively infecting and lysing *C. acnes*, especially type I strains associated with acne pathogenesis.[35] Phages can also help reverse bacterial resistance by targeting multidrug efflux pumps that serve as phage receptors, potentially restoring antibiotic sensitivity.[35] Some bacteriophages show long-term stability, especially when formulated with appropriate stabilizers or in semisolid vehicles, but they generally require refrigeration and optimized buffer conditions to maintain efficacy. Some products are already available as over-the-counter preparations. This therapy has shown promise for mild to moderate acne, as it directly modulates the skin microbiome without harming commensal organisms.

Although bacteriophage therapy is promising and is being incorporated into skincare regimens, much remains to be elucidated and there is no FDA-approved product in this category for acne at this time.

XXII. TOPICAL NITRIC OXIDE / NO-RELEASING AGENTS

Topical nitric oxide (NO) therapies, particularly formulations like NO 4% gel, represent an innovative approach to acne treatment through controlled nitric oxide release. NO-releasing nanoparticles have demonstrated strong antimicrobial activity against *C. acnes*, significantly reducing bacterial viability.[36] In addition to their bactericidal effects, these agents also suppress pro-inflammatory cytokines, including TNF-α, IL-1β, IL-6, and IL-8, thereby addressing both microbial and inflammatory components of acne pathophysiology.[36]

Clinical studies have shown efficacy in patients with mild to moderate acne, with reductions in lesion counts and inflammatory markers. Reported adverse effects include nasopharyngitis, headache, and dysmenorrhea.[37]

Although topical nitric oxide is available in some OTC formulations and as cosmeceuticals, these agents are not yet FDA-approved for acne.

XXIII. OXYGEN THERAPY

Oxygen therapy for acne is a non-invasive treatment typically administered in medical spas or clinical settings rather than through OTC products. Its proposed mechanism involves the generation of reactive oxygen species (ROS), which exert potent antimicrobial effects by disrupting microbial membranes, including those of *C. acnes*.[38] Additionally, oxygen therapy promotes wound healing and skin rejuvenation by stimulating angiogenesis through the upregulation of vascular endothelial growth factor (VEGF) and other pro-healing cytokines.[39] This therapy is generally marketed for mild to moderate inflammatory acne and is often combined with other facial treatments.

Some newer topical formulations use oxygen and carbon dioxide in nanobubble suspensions to enhance transdermal gas absorption. These nanobubbles are taken up by the skin's outer layers, where carbon dioxide promotes local vasodilation, improving blood flow and tissue oxygenation via the Bohr effect, while oxygen supports cellular repair and antimicrobial activity.[40]

While adverse effects are rare and generally unreported, its clinical efficacy remains under investigation, and it has not received FDA approval specifically for acne treatment.

XXIV. PROBIOTICS/PARABIOTICS/POSTBIOTICS (TOPICAL)

Topical probiotics and postbiotics are emerging as promising adjunctive treatments for mild to moderate acne. Various formulations typically contain live or lysed commensal bacteria or their metabolites, designed to restore skin microbiome balance, suppress *C. acnes* overgrowth, and reduce inflammation. Key mechanisms include enhancing barrier function, producing antimicrobial peptides, and modulating both innate and adaptive immune responses.[41]

While this category of therapy is generally considered safe, concerns include the potential for allergic reactions, antibiotic resistance gene transfer, and, though rare, bacteremia particularly in immunocompromised individuals.[42,43]

There are a number of these products available OTC but none are FDA-approved specifically for acne.

XXV. BAKUCHIOL (RETINOL ALTERNATIVE)

Bakuchiol is a plant-derived compound extracted from *Psoralea corylifolia* and is gaining popularity as a botanical alternative to retinoids in acne management. It exhibits anti-inflammatory, antibacterial, and antioxidant properties that contribute to its efficacy in treating mild to moderate acne.[44] Mechanistically, bakuchiol downregulates *C. acnes* proliferation and inhibits inflammatory pathways involved in acne pathogenesis, including NF-κB signaling.[44]

Although structurally distinct from retinoids, bakuchiol mimics many of their effects, such as promoting cell turnover and reducing hyper keratinization, but with fewer reports of irritation or photosensitivity.[45] It also has demonstrated effectiveness in reducing hyperpigmentation and fine lines, making it a popular dual-purpose ingredient in acne and anti-aging regimens.[44] Bakuchiol is available OTC in various cosmetic formulations, but concentrations are not standardized across products. The most common adverse effect reported is allergic contact dermatitis, though this remains relatively rare. While promising, bakuchiol is not FDA-approved specifically for the treatment of acne.

XXVI. TOPICAL CBD / CANNABINOIDS

Topical cannabidiol (CBD), a non-psychoactive phytocannabinoid derived from *Cannabis sativa*, has emerged as a novel anti-inflammatory and sebostatic agent for acne. Its therapeutic potential is primarily attributed to its ability to inhibit intracellular adenosine uptake, which enhances endogenous adenosine signaling, a known pathway involved in reducing inflammation.[46] Additionally, CBD modulates the activity of sebaceous glands, decreasing sebum production and limiting the proliferation of *C. acnes*, thereby addressing key pathogenic mechanisms in acne development.[47] Formulations typically contain 1–5% CBD, though standardized concentrations are lacking across OTC products. While generally well-tolerated, reports of cannabinoid abuse accompanied by acne have been noted.[48]

Despite increasing commercial availability in OTC skincare, topical CBD is not FDA-approved for acne treatment.

XXVII. APPLE CIDER VINEGAR

Apple cider vinegar (ACV) is a popular home remedy used for managing mild acne, typically applied topically in diluted concentrations of 5 to 10%. Its therapeutic potential stems from its acetic acid content and associated low pH, which may exert antimicrobial effects by creating an inhospitable environment for acne-associated microbes and disrupting microbial membranes.[49] Despite its widespread use, ACV lacks clinical trials supporting its efficacy in acne. Furthermore, its acidic nature poses safety concerns. Case reports have documented chemical burns, particularly in

children, due to improper or undiluted use. ACV can also enhance the leaching of nickel from metal containers, potentially leading to contact dermatitis in nickel-sensitive individuals.[49] Though available OTC and widely accessible, ACV is not FDA-approved for acne treatment.

DISCUSSION

The growing availability of OTC acne treatments reflects a broader shift in dermatologic care, driven by rising antibiotic resistance, cost concerns, breakthroughs in technology, and accessibility barriers. Dermatologists increasingly recommend OTC options as first-line or adjunctive therapies, especially given the limitations of long-term antibiotic use in acne management and the rise of treatment-resistant *C. acnes* strains.[50] OTC products are significantly more affordable and accessible than prescription medications or dermatology appointments. For many patients, particularly those in underserved communities, OTC regimens offer an accessible alternative that avoids long wait times and out of pocket expenses. However, despite this convenience, lack of proper education on OTC product use may pose safety risks. Adverse event reports associated with OTC topical acne products include skin irritation, burning sensation, and dermatitis, highlighting the importance of proper usage and awareness of potential side effects.[51] Importantly, while a few ingredients used in OTC acne treatments have either received FDA approval or are recognized under the FDA's monograph system, the majority of agents have limited or no high-quality clinical evidence supporting their use. Furthermore, although certain ingredients (eg, salicylic acid) are included in the acne monograph, individual products and formulations are not subject to the same level of scrutiny or consistency, contributing to ongoing confusion among consumers and clinicians alike. The rise in novel OTC therapies such as blue light masks, probiotics, and nitric oxide donors further complicates consumer decision-making, as these agents are often marketed with minimal clinical evidence.

In conclusion, although the shift toward OTC acne management presents a valuable opportunity to broaden treatment access, it must be balanced with improved public education, regulatory oversight, and clinician guidance.

Abbreviations

BPO = Benzoyl Peroxide
FDA = Food and Drug Administration
AHA = Alpha hydroxy acids
GRAS = Generally Recognized As Safe
NO = Nitric Oxide
ROS = Reactive oxygen species
ACV = Apple Cider Vinegar
C. acnes = Cutibacterium acnes

ACKNOWLEDGMENTS

None

PATIENT CONSENT

Not applicable

CONFLICTS OF INTEREST

YM has no relevant disclosures. PL reports being on the speaker's bureau for AbbVie, Arcutis, Eli Lilly, Galderma, Hyphens Pharma, Incyte, La Roche-Posay/L'Oréal, Pfizer, Pierre-Fabre Dermatologie, Regeneron/Sanofi Genzyme, Verrica; reports consulting/advisory boards for Alphyn Biologics, AbbVie, Almirall, Amyris, Apogee, Arcutis, ASLAN, Astria Therapeutics, Boston Skin Science, Bristol-Myers Squibb, Burt's Bees, Castle Biosciences, Codex Labs, Concerto Biosci, Dermavant, Eli Lilly, Galderma, Kenvue, LEO Pharma, Lipidor, L'Oréal, Merck, Micreos, MyOR Diagnostics, Pelthos Therapeutics, Phyla, Regeneron/Sanofi Genzyme, Sibel Health, Skinfix, Soteri Skin, Stratum Biosciences, Sun Pharma, Theraplex, Thimble Health, UCB, Unilever, Verdant Scientific, Verrica, Yobee Care. Stock options with Alphyn Labs, Codex Labs, Concerto Biosci, Soteri Skin, Stratum Biosciences, Thimble, Yobee Care, Verdant Scientific. In addition, Dr. Lio has a patent pending for a Theraplex product with royalties paid and is a Board member and Scientific Advisory Committee Member emeritus of the National Eczema Association.

FUNDING

None

Submitted: September 11, 2025 PDT. Accepted: September 30, 2025 PDT.

REFERENCES

1. Aydemir EH. Acne vulgaris. *Turk Pediatri Ars*. 2014;49(1):13-16. doi:10.5152/tpa.2014.1943. PMID:26078626

2. Tan JK, Bhate K. A global perspective on the epidemiology of acne. *Br J Dermatol*. 2015;172(Suppl 1):3-12. doi:10.1111/bjd.13462. PMID:25597339

3. Sutaria AH, Masood S, Saleh HM, et al. Acne Vulgaris. In: *StatPearls [Internet]*. StatPearls Publishing; 2023. Accessed January 2025. https://www.ncbi.nlm.nih.gov/books/NBK459173/

4. Gollnick H, Schramm M. Topical therapy in acne. *J Eur Acad Dermatol Venereol*. 1998;11(Suppl 1):S8-12. doi:10.1111/j.1468-3083.1998.tb00901.x. PMID:9891903

5. Williams AL, Pace ND, DeSesso JM. Teratogen update: Topical use and third-generation retinoids. *Birth Defects Res*. 2020;112(15):1105-1114. doi:10.1002/bdr2.1745. PMID:32643315

6. U.S. Food and Drug Administration. FDA approves Differin Gel 0.1% for over-the-counter use to treat acne. FDA. July 8, 2016. Accessed May 2, 2025. https://www.fda.gov/news-events/press-announcements/fda-approves-differin-gel-01-over-counter-use-treat-acne

7. Sauer N, Oślizło M, Brzostek M, Wolska J, Lubaszka K, Karłowicz-Bodalska K. The multiple uses of azelaic acid in dermatology: mechanism of action, preparations, and potential therapeutic applications. *Postepy Dermatol Alergol*. 2023;40(6):716-724. doi:10.5114/ada.2023.133955. PMID:38282869

8. U.S. Food and Drug Administration. Application Number: NDA 20-428/S-001-S-007. Accessed May 2, 2025. https://www.accessdata.fda.gov/drugsatfda_docs/nda/96/20428S1S7_Azelex.pdf

9. Sagransky M, Yentzer BA, Feldman SR. Benzoyl peroxide: a review of its current use in the treatment of acne vulgaris. *Expert Opin Pharmacother*. 2009;10(15):2555-2562. doi:10.1517/14656560903277228. PMID:19761357

10. U.S. Food and Drug Administration. Limited number of voluntary recalls initiated after FDA testing of acne products for benzene; findings show a small number of products with elevated levels of benzene contamination. March 11, 2025. Accessed May 2, 2025. https://www.fda.gov/drugs/drug-safety-and-availability/limited-number-voluntary-recalls-initiated-after-fda-testing-acne-products-benzene-findings-show

11. Bowe WP, Shalita AR. Effective over-the-counter acne treatments. *Semin Cutan Med Surg*. 2008;27(3):170-176. doi:10.1016/j.sder.2008.07.004. PMID:18786494

12. Lu J, Cong T, Wen X, et al. Salicylic acid treats acne vulgaris by suppressing AMPK/SREBP1 pathway in sebocytes. *Exp Dermatol*. 2019;28(7):786-794. doi:10.1111/exd.13934. PMID:30972839

13. U.S. Food and Drug Administration. Beta hydroxy acids. March 10, 2022. Accessed May 2, 2025. https://www.fda.gov/cosmetics/cosmetic-ingredients/beta-hydroxy-acids

14. Gupta AK, Nicol K. The use of sulfur in dermatology. *J Drugs Dermatol*. 2004;3(4):427-431. PMID:15303787

15. Gammoh NZ, Rink L. Zinc in Infection and Inflammation. *Nutrients*. 2017;9(6):624. doi:10.3390/nu9060624. PMID:28629136

16. Kurtzweil P. Alpha hydroxy acids for skin care. *FDA Consum*. 1998;32(2):30-35. doi:10.1037/e543682006-006. PMID:9532954

17. U.S. Food and Drug Administration. Alpha hydroxy acids. November 22, 2022. Accessed May 2, 2025. https://www.fda.gov/cosmetics/cosmetic-ingredients/alpha-hydroxy-acids

18. Sinha P, Srivastava S, Mishra N, Yadav NP. New perspectives on antiacne plant drugs: contribution to modern therapeutics. *Biomed Res Int*. 2014;2014:301304. doi:10.1155/2014/301304. PMID:25147793

19. Berson DS et al. Niacinamide: A topical vitamin with wide-ranging skin appearance benefits. In: *Cosmeceuticals and Cosmetic Practice*. ; 2013:103-112. doi:10.1002/9781118384824.ch10

20. George CA, Chhabra N. Resorcinol in Dermatology. *Indian J Postgrad Dermatol*. 2024;2:20-23. doi:10.25259/IJPGD_108_2023

21. Chao CM, Lai WY, Wu BY, Chang HC, Huang WS, Chen YF. A pilot study on efficacy treatment of acne vulgaris using a new method: results of a randomized double-blind trial with Acne Dressing. *J Cosmet Sci*. 2006;57(2):95-105. PMID:16688374

22. Scott AM, Stehlik P, Clark J, et al. Blue-Light Therapy for Acne Vulgaris: A Systematic Review and Meta-Analysis. *Ann Fam Med*. 2019;17(6):545-553. doi:10.1370/afm.2445. PMID:31712293

23. Carson CF, Hammer KA, Riley TV. Melaleuca alternifolia (Tea Tree) oil: a review of antimicrobial and other medicinal properties. *Clin Microbiol Rev*. 2006;19(1):50-62. doi:10.1128/CMR.19.1.50-62.2006. PMID:16418522

24. Fu Y, Zu Y, Chen L, et al. Investigation of antibacterial activity of rosemary essential oil against Propionibacterium acnes with atomic force microscopy. *Planta Med*. 2007;73(12):1275-1280. doi:10.1055/s-2007-981614. PMID:17893831

25. Miroddi M, Calapai G, Isola S, Minciullo PL, Gangemi S. Rosmarinus officinalis L. as cause of contact dermatitis. *Allergol Immunopathol (Madr)*. 2014;42(6):616-619. doi:10.1016/j.aller.2013.04.006. PMID:23827646

26. OyetakinWhite P, Tribout H, Baron E. Protective mechanisms of green tea polyphenols in skin. *Oxid Med Cell Longev*. 2012;2012:560682. doi:10.1155/2012/560682. PMID:22792414

27. Yoon JY, Kwon HH, Min SU, Thiboutot DM, Suh DH. Epigallocatechin-3-gallate improves acne in humans by modulating intracellular molecular targets and inhibiting P. acnes. *J Invest Dermatol*. 2013;133(2):429-440. doi:10.1038/jid.2012.292. PMID:23096708

28. Zhang X, Zhang Z, Tao H, et al. Comprehensive assessment of the efficacy and safety of a clay mask in oily and acne skin. *Skin Res Technol*. 2023;29(11):e13513. doi:10.1111/srt.13513. PMID:38009030

29. Moosavi M. Bentonite Clay as a Natural Remedy: A Brief Review. *Iran J Public Health*. 2017;46(9):1176-1183. PMID:29026782

30. Piazza S, Martinelli G, Vrhovsek U, et al. Anti-Inflammatory and Anti-Acne Effects of Hamamelis virginiana Bark in Human Keratinocytes. *Antioxidants (Basel)*. 2022;11(6):1119. doi:10.3390/antiox11061119. PMID:35740016

31. Granlund H. Contact allergy to witch hazel. *Contact Dermatitis*. 1994;31(3):195. doi:10.1111/j.1600-0536.1994.tb01972.x. PMID:7821023

32. Khalil S, Bardawil T, Stephan C, et al. Retinoids: a journey from the molecular structures and mechanisms of action to clinical uses in dermatology and adverse effects. *J Dermatolog Treat*. 2017;28(8):684-696. doi:10.1080/09546634.2017.1309349. PMID:28318351

33. Burlando B, Cornara L. Honey in dermatology and skin care: a review. *J Cosmet Dermatol*. 2013;12(4):306-313. doi:10.1111/jocd.12058. PMID:24305429

34. Zhang T, Sun B, Guo J, et al. Active pharmaceutical ingredient poly(ionic liquid)-based microneedles for the treatment of skin acne infection. *Acta Biomater*. 2020;115:136-147. doi:10.1016/j.actbio.2020.08.023. PMID:32853804

35. Farfán J, Gonzalez JM, Vives M. The immunomodulatory potential of phage therapy to treat acne: a review on bacterial lysis and immunomodulation. *PeerJ*. 2022;10:e13553. doi:10.7717/peerj.13553. PMID:35910763

36. Qin M, Landriscina A, Rosen JM, et al. Nitric Oxide-Releasing Nanoparticles Prevent Propionibacterium acnes-Induced Inflammation by Both Clearing the Organism and Inhibiting Microbial Stimulation of the Innate Immune Response. *J Invest Dermatol*. 2015;135(11):2723-2731. doi:10.1038/jid.2015.277. PMID:26172313

37. Baldwin H, Blanco D, McKeever C, et al. Results of a Phase 2 Efficacy and Safety Study with SB204, an Investigational Topical Nitric Oxide-releasing Drug for the Treatment of Acne Vulgaris. *J Clin Aesthet Dermatol*. 2016;9(8):12-18. PMID:27672413

38. Sheridan RL, Shank ES. Hyperbaric oxygen treatment: a brief overview of a controversial topic. *J Trauma*. 1999;47(2):426-435. doi:10.1097/00005373-199908000-00045. PMID:10452491

39. Gill AL, Bell CN. Hyperbaric oxygen: its uses, mechanisms of action and outcomes. *QJM*. 2004;97(7):385-395. doi:10.1093/qjmed/hch074. PMID:15208426

40. LaMour J, Grimm D, Smith E, Yaniv Z, Hurwitz P. Treating Diabetic Peripheral Neuropathy Using a Novel, Nanotechnology-Based Topical Formulation to Improve Pain, Sensitivity, and Function. *Int J Diabetes Clin Res*. 2021;8:149. doi:10.23937/2377-3634/1410149

41. Cogen AL, Nizet V, Gallo RL. Skin microbiota: a source of disease or defence? *Br J Dermatol*. 2008;158(3):442-455. doi:10.1111/j.1365-2133.2008.08437.x. PMID:18275522

42. Naik S, Bouladoux N, Wilhelm C, et al. Compartmentalized control of skin immunity by resident commensals. *Science*. 2012;337(6098):1115-1119. doi:10.1126/science.1225152. PMID:22837383

43. Lee GR, Maarouf M, Hendricks AJ, Lee DE, Shi VY. Topical probiotics: the unknowns behind their rising popularity. *Dermatol Online J*. 2019;25(5). doi:10.5070/D3255044062. PMID:31220895

44. Dhaliwal S, Rybak I, Ellis SR, et al. Prospective, randomized, double-blind assessment of topical bakuchiol and retinol for facial photoageing. *Br J Dermatol*. 2019;180(2):289-296. doi:10.1111/bjd.16918. PMID:29947134

45. Puyana C, Chandan N, Tsoukas M. Applications of bakuchiol in dermatology: Systematic review of the literature. *J Cosmet Dermatol*. 2022;21(12):6636-6643. doi:10.1111/jocd.15420. PMID:36176207

46. Mecha M, Feliú A, Iñigo PM, Mestre L, Carrillo-Salinas FJ, Guaza C. Cannabidiol provides long-lasting protection against the deleterious effects of inflammation in a viral model of multiple sclerosis: a role for A2A receptors. *Neurobiol Dis*. 2013;59:141-150. doi:10.1016/j.nbd.2013.06.016. PMID:23851307

47. Peyravian N, Deo S, Daunert S, Jimenez JJ. Cannabidiol as a Novel Therapeutic for Immune Modulation. *Immunotargets Ther*. 2020;9:131-140. doi:10.2147/ITT.S263690. PMID:32903924

48. Makhakhe L. Topical cannabidiol (CBD) in skin pathology - A comprehensive review and prospects for new therapeutic opportunities. *S Afr Fam Pract (2004)*. 2022;64(1):e1-e4. doi:10.4102/safp.v64i1.5493. PMID:35695447

49. Elhage KG, St Claire K, Daveluy S. Acetic acid and the skin: a review of vinegar in dermatology. *Int J Dermatol*. 2022;61(7):804-811. doi:10.1111/ijd.15804. PMID:34350993

50. Dessinioti C, Katsambas A. Antibiotics and Antimicrobial Resistance in Acne: Epidemiological Trends and Clinical Practice Considerations. *Yale J Biol Med*. 2022;95(4):429-443. PMID:36568833

51. Szymanski L, Arekapudi KL. Adverse-Event Reports in Over-the-Counter Topical Acne Drug Products Containing Benzoyl Peroxide from a Specific Pharmaceutical Company in the USA. *Dermatol Ther (Heidelb)*. 2022;12(11):2397-2400. doi:10.1007/s13555-022-00808-9. PMID:36152215