



From Monotherapy to Adjunctive Therapies: Application of Dermocosmetics in Acne Management Across Australia and New Zealand

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ABSTRACT

Acne vulgaris is a globally prevalent dermatological disease, with its severity ranging from mild to severe. While moderate to severe acne often requires topical or systemic pharmaceutical therapy, mild to moderate acne may be managed with dermocosmetics, which are over-the-counter skincare agents with active ingredients that target acne pathophysiology. Dermocosmetics can also be effective as adjunct therapy for the management of more severe acne. For example, they can be used to complement the mode of action of pharmaceuticals or to mitigate side effects and improve treatment compliance. This review discusses the roles of commonly available dermocosmetics in the context of both mild and severe acne management protocols.

1 | Introduction

Acne vulgaris is recognised as one of the most common inflammatory skin conditions globally [1] and is the eighth most prevalent disease worldwide, affecting 9.4% of people [2]. Acne is most common in teenagers, universally affecting 85% of adolescents [3]; however, adult acne is on the rise with a 10% increase in women over the past 10 years [3]. Acne can have a profound impact on the psychosocial wellbeing and quality of life of individuals, potentially contributing to depression. Furthermore, acne can potentially lead to permanent scarring [1, 4–10].

Acne has a complex pathophysiology, with four main factors: (i) hyperkeratinisation of the pilosebaceous infundibulum; (ii)

inflammation; (iii) Cutibacterium acnes dysbiosis [11, 12]; and (iv) aberrant sebaceous gland function [13]. Recent evidence suggests that acne is caused by defective differentiation of the LRIG1-expressing stem cells (residing in the hair follicle junction zone) into microcomedones instead of normally functioning sebaceous glands [14]. This aberrant stem cell differentiation may be caused by abnormal Wnt signalling [15]. The Cutibacterium acnes (C. acnes) phylotype present on the skin can also impact acne development; different C. acnes phylotypes have been shown to secrete extracellular vesicles containing proteins that differentially alter the communication between the skin microbiota and the host [16, 17].

While the selection of acne treatment is often based on the severity and duration of acne, skin type, psychosocial factors and

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lifestyle [18], most clinical guidelines focus solely on the use of prescription medicines [19]. Adherence to acne prescription medicines is poor, with an estimated global adherence rate of 50% [20]. Poor compliance is independently correlated with various factors, including the occurrence of side effects [20]. Factors that may positively impact treatment adherence include the use of dermocosmetics (also known as cosmeceuticals) such as cleansers and moisturisers [20]. Increasingly, dermocosmetics are being adopted for the management of acne to improve both treatment adherence and outcomes and to minimise possible side effects from pharmacotherapy [21, 22].

Dermocosmetics can be applied either as a monotherapy for milder forms of acne, or as an adjunct to prescription medications in more severe forms [22, 23]. Once acne is under control, dermocosmetics may continue to play a role in maintenance therapy and the prevention of new breakouts. Dermocosmetics are becoming increasingly popular as an alternate management strategy for patients with chronic acne, during periods of relapse, and in ameliorating side effects of other acne medications [24]. There is an increase in the number of published clinical studies on the use of dermocosmetics in the management of acne; however, these studies often have a small sample size and/ or less rigorous study design and hence do not have the same strength of evidence as pharmaceutical studies.

Dermocosmetics contain active ingredients that have a measurable biological action on the skin [23, 25]. The active ingredients target different aspects of acne pathophysiology, including aberrant keratinisation, inflammation, sebum production and microbiome imbalance. Such ingredients may also help manage acne by protecting and improving epidermal barrier function.

The aim of this review is to discuss the use of dermocosmetics in acne management, both as monotherapy for mild acne or as adjunctive treatment to prescription therapy in the Australian and New Zealand landscape.

2 | Dermocosmetics as Monotherapy

Acne severity is commonly categorised into four levels of severity: mild, moderate, severe and very severe. There are several acne severity assessment scales available. The Global Acne Grading System (GAGS) is a simple and internationally recognised grading system that divides the face, chest and back into six areas, and the severity in each zone is then assessed on a scale of 0 to 4 (0, no lesions; 1, comedones; 2, papules; 3, pustules; and 4, nodules). A total score for all six zones is then calculated, and the acne severity is classified as either mild [1–18], moderate [19–30], severe [31–38], or very severe (> 39) [26].

The use of dermocosmetics as monotherapy is appropriate for mild acne (especially prior to Dermatologist input); as maintenance therapy following treatment with pharmaceutical drugs; or during pregnancy and lactation when prescription acne treatments are contraindicated [27, 28]. Moderate and severe acne usually require treatment with pharmaceutical drugs; however, dermocosmetics can be useful adjunctive treatments to these prescription medicines to either complement a drug's mode of action and efficacy or to improve treatment tolerance and therefore treatment adherence and optimise results.

Mild acne can be managed by dermocosmetics (Table 1) as they have been shown to reduce acne lesions and improve global assessment scores [11, 24, 29]. Dermocosmetics can also aid in maintaining acne clearance after discontinuation of pharmaceutical treatment [11, 30]. Active ingredients aiming at improving milder forms of acne target the key pathogenic pathways shown in Figure 1.

TABLE 1 | Recommendations for the use of dermocosmetics as monotherapy and adjunctive therapy for the management of acne.

Type of dermocosmetics use Recommendation Dermocosmetics including multitargeting ingredients (keratolytics + anti-inflammatory, and/or anti Monotherapy sebum production, and/or microbiome targeting ingredients) can be recommended as monotherapy for: · Earlier forms of acne to aid the decrease of acne lesions, improve global acne, reduce skin oiliness, improve PIHP while having a good tolerance • Maintenance following prior acne treatments Adjunctive therapy Dermocosmetics including multitargeting ingredients (keratolytics + anti-inflammatory, and/or anti sebum production, and/or microbiome targeting ingredients) may be recommended as adjunctive therapy: · to augment prescription medical acne treatment mode of action · to improve tolerability of acne treatments Dermocosmetics with ingredients targeting skin barrier, skin microbiome and inflammation and sebum production might be recommended in acne as adjunct to acne topical and/or systemic treatments with a view to: · improve tolerability of prescription acne treatments, especially retinoid-based products (topical or systemic) • reduce irritation and/or adverse events from washes, cleansers, etc. reduce skin oiliness • improve barrier function (corneometer and TEWL scores) · further improve patient adherence, satisfaction and quality of life

Abbreviations: PIH, post-inflammatory hyperpigmentation; TEWL, transepidermal water loss.

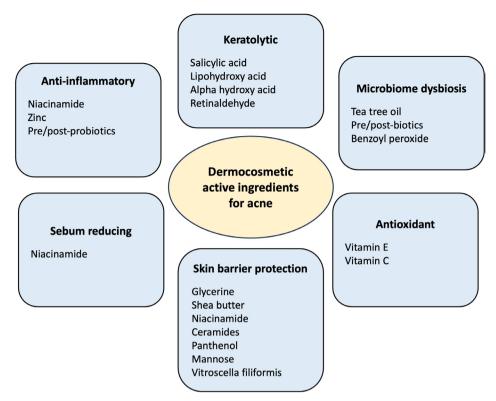


FIGURE 1 | Common acne active ingredients used in dermocosmetics.

3 | Anti-Inflammatory Agents

3.1 | Niacinamide

Niacinamide (also known as nicotinamide, 3-pyridinecarboxamide) is the physiologically active form of vitamin B3 [31]. It has a range of dermatological therapeutic effects, including anti-inflammatory and anti-bacterial properties. Its mechanisms of action remain unclear; however, it is postulated to have a broad range of activities, given that it is a key precursor of the coenzymes NADH and NADPH [31].

Topical niacinamide 4% has been shown to reduce inflammatory papules (-60%) and acne lesions (-52%) [32]. Three double-blind RCTs comparing topical niacinamide and the topical antibiotic clindamycin showed that 4%-5% niacinamide has comparable efficacy on acne lesions and acne severity as 1%-2% clindamycin [32-34]. As such, niacinamide is used not only for its efficacy, but it also does not contribute to anti-microbial resistance.

Topical niacinamide can also reduce sebum production [35]. In an in vitro study where viable human facial biopsies (from facelift surgery) were treated with niacinamide, there was a significant dose-dependent reduction in total sebaceous lipid components (namely triglycerides and fatty acids) [31, 36]. However, there might be differences in the effect of niacinamide based on skin type. Two separate double-blind placebo-controlled studies examining the use of 2% niacinamide for 6 weeks were conducted on Japanese participants and on Caucasian participants. Niacinamide was shown to significantly lower the sebum excretion rate in the study with Japanese participants, but not in the study with Caucasian participants. Conversely, niacinamide reduced sebum levels in Caucasian participants, but not in their Japanese counterparts [35].

Topical niacinamide has also been shown to improve overall skin appearance in Caucasian women by reducing erythema, wrinkles, yellowing and hyperpigmentation [37].

3.2 | Zinc Salts

Zinc has been shown to act as an anti-inflammatory on acne lesions through its inhibition of leucocyte chemotaxis [38]. Clinical studies have demonstrated a benefit of both topical and systemic zinc in acne treatment. A systematic review and meta-analysis examining the efficacy of both topical and oral zinc in acne treatment found that patients treated with either oral or topical zinc (either as monotherapy or as an adjunctive treatment) had a significant improvement in mean inflammatory papule count compared to those not treated with zinc [39]. Oral zinc at doses of 50 mg elemental zinc up to TDS was found to be effective in early studies [40].

Topical Zinc has also been shown to benefit mild to moderate acne. A single-blind trial of 47 patients showed a benefit in reducing the number of inflammatory lesions [41]. Moreover, a single-blind, randomised study of 73 patients showed the topical combination treatment erythromycin (4%) plus zinc acetate (1.2%) showed a benefit in reducing the number of inflammatory lesions [42].

3.3 | "Probiotic" Preparations

Probiotic lysates or fractions (which have pre-biotic action or some similar probiotic activity to live bacteria) have been shown to have beneficial effects on the skin [43]. Although evidence is weak and mostly derived from in vitro studies, *Staphylococcus*,

Streptococcus, Lactococcus, Lactobacillus and Enterococcus have shown potential to control acne [44]. A randomised double-blind split-face RCT of 34 patients compared the topical application of Lactobacillus-fermented Chamaecyparis obtusa (LFCO) to tea tree oil; LFCO led to a greater reduction in inflammatory lesions (-65.3%) than tea tree oil (38%), and reduced sebum excretion and sebaceous gland size [45]. Lactobacillus fermentation of the Chamaecyparis obtusa plant is thought to induce biochemical conversions of metabolites with enhanced antimicrobial or antioxidant activities [46]. Furthermore, a 5% extract of Lactobacillus plantarum has been reported to exhibit anti-acne effects, reducing skin erythema and acne lesions [47].

4 | Keratolytic Agents

Hyperkeratinisation occurs when follicles become occluded, preventing normal skin cell shedding and inducing microcomedones with the potential for progression to acneiform lesions. Comedonal acne usually responds to topical keratolytic agents, and there are a number of keratolytic agents used in dermocosmetics [48].

4.1 | Salicylic Acid

Salicylic acid, a lipid-soluble beta-hydroxy acid, is used as a topical treatment for acne both as monotherapy and as adjunctive therapy [24]. It is thought to dissolve intercellular lipids and reduce comedones, thus ameliorating abnormal keratinisation and reducing inflammation [24]. There are only a small number of studies examining the effect of salicylic acid on acne [49-51]. A study of 30 acne patients showed that treatment with a 2% salicylic acid cleanser for 2 weeks significantly reduces comedones [51]. A study of 60 people with moderate to severe acne showed that the addition of 20% topical salicylic acid to oral isotretinoin treatment significantly improves the clearance of acne than monotherapy with isotretinoin [50]. Furthermore, a study of 20 comedonal acne patients showed that fortnightly peels with salicylic acid significantly reduced noninflammatory lesions [49]. Current Australian Therapeutic Guidelines for acne recommend the use of over-the-counter topical salicylic acid for mild acne [52].

4.2 | Lipohydroxy Acid

Lipohydroxy acid (LHA) is a lipophilic derivative of salicylic acid that exhibits slower penetration and better tolerability [53]. Like salicylic acid, LHA has comedolytic properties due to its exfoliating effects [53]. In a small study of 28 acne-prone women, LHA decreased the number and total size of microcomedones. This effect was not seen in untreated controls [54]. A study of 80 patients with mild or moderate acne demonstrated that LHA was equally as effective as 5% benzoyl peroxide at decreasing inflammatory and non-inflammatory lesions and is a suitable alternative for patients who are intolerant to benzoyl peroxide or for patients who wish to avoid the unwanted bleaching effect of benzoyl peroxide [55]. Furthermore, a split-face study of 20

people with comedonal acne showed that LHA is as effective at decreasing non-inflammatory lesions as salicylic acid [49]. Current Australian Therapeutic Guidelines for acne recommend the use of over-the-counter topical LHA for mild acne [52].

4.3 | Alpha Hydroxy Acids (AHAs)

AHAs such as lactic acid and glycolic acid are used in acne management as they limit follicular blockage, promote skin peeling and reduce abnormal keratinisation [24, 56]. Low concentration AHAs have a moisturising effect, while high concentrations have keratolytic and exfoliating actions [56]. AHA-containing formulations have been shown to improve acne, and AHAs can be used as a topical treatment for acne both as monotherapy and as adjunctive therapy [24]. Glycolic acid peels, either alone [57] or in combination with retinoic acid [58–60], have been shown to reduce acne lesions [61, 62].

4.4 | Retinaldehyde

Topical retinoids (such as adapalene, isotretinoin and tretinoin) are widely used prescription medicines for acne therapy as they target multiple pathogenic mechanisms. They are anti-inflammatory and increase epithelial turnover, thus providing a comedolytic action [6]. There is strong evidence for their use in acne treatment, with several randomised, double-blind, placebo-controlled studies demonstrating their efficacy [63–65]. Adapalene, isotretinoin and tretinoin are schedule 4 therapies (requiring prescription) and are associated with side effects including erythema, irritation, dryness and peeling [6]. However, retinaldehyde, a direct retinoic acid precursor, has been shown to be effective in reducing comedones and microcysts when combined with erythromycin [66], and has been shown to be less irritating than other retinoids [60].

5 | Antimicrobial Agents

Historically, C. acnes was thought to be the aetiological agent of acne, leading to high prescription rates of antibiotics. Although data remain limited, growing evidence is associating acne with a disequilibrium in the composition of the skin's microbiome [67]. For example, some C. acnes and Staphylococcus epidermidis strains are thought to contribute to acne, while other strains are thought to promote healthy skin by inhibiting the invasion of pathogens [67]. As such, there is a need to manage C. acnes phylotypes, rather than eradicate them completely. This is of high importance as there has been a clear overuse of topical and/or systemic antibiotics leading to increased antibiotic resistance [68]. Indeed, antibiotic resistance has been associated with antibiotics used to treat acne, and an increase in C. acnes resistance to antibiotics is seen worldwide [69, 70]. Other antimicrobial agents, including bakuchiol, probiotics, tea tree oil and decanediol, are commonly found in dermocosmetics and aid in the reduction of acne-causing microbes [24]. These agents may play a role in the reduction of antibiotic resistance since they may, in some cases, substitute for antibiotics in acne treatment.

5.1 | Benzoyl Peroxide

Benzoyl peroxide shows a strong efficacy profile for mild acne treatment [6, 71]. It acts by reducing C. acnes colonisation. A study of 30 healthy subjects showed that daily use of a 6% benzoyl peroxide cleanser decreases C. acnes colonies, including erythromycin/tetracycline-resistant strains [72]. Current Australian Therapeutic Guidelines for acne recommend the use of over-the-counter topical benzoyl peroxide for mild acne [52]. Similarly, European and United States guidelines also recommend benzoyl peroxide for the treatment of mild to moderate acne [6, 71]. For moderate to severe acne, benzovl peroxide is primarily recommended in combination with topical or systemic antibiotics since it has been shown to be more effective in combination with adapalene or clindamycin; the strength of evidence to support its use with antibiotics is low to medium [6, 71]. However, benzoyl peroxide can have poor tolerance as it can cause significant irritation, contact dermatitis and bleaching of clothes and hair [56, 73].

5.2 | Tea Tree Oil

Tea tree (*Melaleuca alternifolia*) oil is an extract from tea tree leaves. It exhibits broad-spectrum anti-microbial properties and has been shown to effectively treat mild acne [74]. In a placebo-controlled randomised double-blind trial performed in 60 patients with mild to moderate acne, topical 5% tea tree oil significantly reduced total acne lesions and acne severity [75]. Other comparative trials have shown that tea tree oil is better than placebo in reducing acne lesions and is equivalent to comparators including 5% benzoyl peroxide and 2% topical erythromycin [74]. Tea tree oil has been reported to cause allergic contact dermatitis in several studies [76]. As such, patch testing is recommended prior to use.

6 | Sebum-Reducing Agents

Sebum is comprised of wax, triglycerides, esters, squalene and cholesterol. Excess sebum is one pathogenic pathway in acne development [11]. A range of dermocosmetic agents is used to reduce excess sebum production.

6.1 | Antioxidants

Oxidative stress has been shown to play a key role in acne progression [77]. Lipid peroxidation in sebum and the activation of immune cells in response to bacterial invasion potentially increase reactive oxygen species (ROS) production [78]. As such, antioxidants have been trialled in the management of acne. Antioxidant agents that have shown some therapeutic effect on acne include fullerene, epigallocatechin-3-Gallate, vitamin C and vitamin E [11].

6.2 | Skin Barrier Protection

Skin barrier function is often compromised in acne-affected skin [79]. Acne patients are more likely to exhibit increased

facial skin pH, mirroring a chronic state of stratum corneum instability, which may contribute to acne lesions [79]. Moreover, some acne treatments such as benzoyl peroxide and retinoids can impact an intact skin barrier, leading to irritation and dryness [80]. These side effects can lead to a decrease in treatment adherence or even treatment cessation. Dermocosmetics are an important tool in reducing these side effects. Products such as moisturisers and non-comedogenic cleansers can reduce skin irritation [81]. Agents thought to aid in skin barrier protection include procerad, glycerine, shea butter, niacinamide, ceramides, panthenol, mannose, *Vitroscella* filiformis/ APF [23].

7 | Dermocosmetics as Adjunctive Therapy

Dermocosmetic products are useful as adjunctive therapy to pharmacological treatments (Table 1). The combined use of different dermocosmetic compounds augments the effect of pharmaceuticals, presumably by targeting additional pathogenic factors and increasing compliance. For example, the use of glycolic acid in conjunction with tretinoin has been shown to improve treatment outcomes [24]. Moreover, a single-centre, clinician-blind, randomised study of 67 acne patients found that the clinical outcomes of 5% benzoyl peroxide treatment (reduction in comedones, lesions and papules) were enhanced by the additional use of a topical combination cream containing octyl salicylic acid, linoleic acid, nicotinamide and piroctone olamine [82]. Furthermore, the use of dermocosmetics containing compounds such as salicylic acid and niacinamide has been shown to reduce the need for benzoyl peroxide with no impact on the efficacy of mild to moderate acne [30].

Dermocosmetics can help mitigate side effects of pharmacological treatments and improve treatment tolerability and treatment adherence [30, 83-85]. Adherence to acne treatment is poor, with a mean global adherence rate of 50% [20]. This is thought to be in part due to skin irritation and side effects caused by some topical and systemic acne pharmaceuticals. Although there is limited supporting evidence, dermocosmetics are thought to help patients better tolerate topical prescription treatments, thus improving compliance and patient quality of life [81]. For example, a global survey of 3339 acne patients revealed that the use of moisturisers and cleansers in addition to anti-acne dermocosmetics had a positive effect on treatment adherence [20]. Moreover, a single-arm study of 40 patients receiving pharmacological acne treatment found that the daily use of a sun protection cream improved adherence to pharmacological therapy and improved acne symptoms [86].

Dermocosmetics can also play a role in maintenance therapy as they can help prevent acne relapse (Table 1). The use of dermocosmetics may reduce the need for pharmaceutical therapies in the treatment of mild to moderate acne. For example, a single-centre, randomised, double-blind RCT in 100 mild-to-moderate acne patients demonstrated that the concomitant use of a dermocosmetic containing salicylic acid, niacinamide and thermal spring water reduced the quantity of benzoyl peroxide needed to reach the same efficacy as benzoyl peroxide alone [30]. As such, appropriate dermocosmetics containing antimicrobial, anti-inflammatory, antibiotic, or sebum-controlling

properties might be recommended to acne patients to complement their pharmacological regimen. Selection of the most suitable adjunctive dermocosmetics should be guided by prescribers to avoid the use of inappropriate products. Acne has been shown to worsen from inadequate product choice or products that cause irritation, photodermatitis, or xerosis [87].

8 | Patient Education

Educating patients about which products to use can be challenging for healthcare professionals [23]. While many people with acne source information from their dermatologist (64.8%) or family doctor (7.5%), the internet and social media are the second most commonly used sources of acne information, with 39.3% of people stating they source information this way [88]. This leads to the propagation of myths and misconceptions around acne and its treatment and may, in turn, result in ineffective or inappropriate practices. Educational resources accessible to the public, particularly teenagers, are needed to address these commonly held misperceptions and improve care and personal practices [88–91]. Common areas where there is misconception surrounding acne include the effect of sun exposure, diet, hygiene, the need for prescription medicines and the impact of acne on wellbeing.

8.1 | Sun Exposure and Acne

Although the cause and management of acne are similar globally, the Australian/New Zealand region presents a unique treatment landscape due to higher levels of ultraviolet (UV) radiation and elevated cumulative sun damage caused by the outdoor lifestyle. Sun exposure and acne have been postulated to have a dichotomous relationship, whereby acne may be improved with some sun exposure but can also worsen [92]. UVA radiation, visible light and infrared light have been suggested to decrease C. acnes colonisation on the skin and therefore reduce inflammation [93]. However, there is no evidence to show that sunlight has a beneficial effect on acne [94, 95] and UV exposure is not considered an acne treatment [96]. UVB radiation may exacerbate acne development as it increases the expression of proinflammatory cytokines such as IL-8 and IL-1β, leading to keratinocyte proliferation and sebum production [97]. Sunlight may also aggravate post-inflammatory hyperpigmentation (PIH) or post-inflammatory erythema following active acne [92]. Dermocosmetics may protect the skin against UV exposure, reducing the development of PIH [23]. Sun exposure without a broad-spectrum UVB and high UVA protection SPF 30+ sunscreen should be avoided. Moreover, several medications used to treat acne result in photosensitivity and therefore require minimisation of sun exposure combined with consistent use of sunscreen [6].

8.2 | Hygiene and Acne

There is no evidence to support the misconception that acne is caused by poor facial hygiene [95, 98]. On the contrary,

excessive face washing or scrubbing will affect the epidermal barrier and exacerbate acne [5, 95], and further complicate the use of prescription therapies such as retinoids. Optimal facial skin cleansing usually depends on the individual's skin conditions and the presence of comedonal lesions. Patients should be educated on the importance of maintaining appropriate skin hygiene habits, especially following cessation of active acne treatment plans to prevent recurrence. Appropriate facial skin cleaning can prevent excess sebum accumulation, one of the primary causes of acne.

Evidence suggests that facial cleansing should be performed twice a day to help reduce erythema, papules and total inflammatory lesions [99]. Cleansers have also shown benefit in removing mild to moderate truncal acne [100] and facial acne [101]. Acne cleansers remove sebum and remove hair follicle plugs that obstruct the hair follicle [56]. To avoid skin irritation, acne cleansers should be soap-free and pH-balanced or acidic cleansers containing foaming and emulsifying surfactants are suitable for acne-prone skin [56].

8.3 | Acne and Prescription Medicines

Management of moderate and severe acne requires the use of prescription medications, including topical and/or systemic therapies, based on severity [102]. However, milder forms of acne may be effectively managed with dermocosmetics. Dermocosmetics are an important component of dermatologists' therapeutic armamentarium, including in the setting of adjunct to prescription medicines, either to complement the mode of action of the medicines or to mitigate their side effects.

9 | Limitations

A limitation of this review is that the level of evidence for the use of all dermocosmetic products in the treatment of acne is limited, and evidence mainly consists of lower quality studies. However, the randomised controlled studies reviewed in this article demonstrate that dermocosmetics have a beneficial role in the management of acne, either as a monotherapy, as adjuncts to medication, or as maintenance therapy post-acne medication. This highlights the need for further randomised controlled trials in this area to facilitate a greater level of evidence.

10 | Conclusions

Dermocosmetics can add significant value in the effective management of acne and have the potential to be effective monotherapy in mild disease. Although the evidence base is limited, we believe that dermocosmetics can complement pharmaceutical-grade therapies in moderate or severe acne, either by enhancing their efficacy or reducing their side effects and thereby increasing compliance. All clinicians, both in primary care and prescribing dermatologists, should be abreast of dermocosmetics as effective monotherapy in mild acne and as adjuncts to pharmacotherapy across all acne severities.

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Conflicts of Interest

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Data Availability Statement

The authors have nothing to report.

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