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PSORIASIS (JAISHIN WU, SECTION EDITOR)

# Review Update on Topical Therapy for Psoriasis

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**Abstract**

**Purpose of Review** Studies show frequent usage but low adherence rates and poor satisfaction from topical therapy for psoriasis. These were attributed to low efficacy, inconvenience of application, and poor cosmetic quality for different body parts.

**Recent Findings** Multicenter surveys on patients suggest a two-way holistic approach, where patients convey what bothers them most and doctors explain how products address specific concerns. New rapid response targeted topical agents, in cosmetically acceptable preparations, applied less often, are undergoing efficacy and safety studies, ideally on large populations up to 1 year or more. Until available, this review addresses gaps in knowledge on how to maximize effects of emollients, used alone, with physiologic lipids, or as base for active topical therapy.

**Summary** Updates—on how psoriasis skin becomes itchy, red, dry, thick, and scaly from inflammation and barrier defects—explain clinical responses to the physical, chemical, and functional properties of psoriasis topical therapies.

**Keywords** Emollients · Psoriasis topical therapy · Stratum corneum barrier · Vegetable oils · Virgin coconut oil · Antimicrobial lipids

## Introduction

In mild to moderate [1, 2], as well as moderate to severe [3], psoriasis, 70–80% of patients start with topical agents, and continue to use them with other active therapies. However, there are numerous reports of low satisfaction for these agents [4, 5]. A web-based survey found that mild, moderate, and severe psoriasis patients were significantly least satisfied with them, and rated them highest on room for improvement for convenience and effectiveness [6•]. Poor satisfaction may have caused the reportedly "abysmal" long-term patient adherence, in an investigator-blind prospective 12-month study on 40 mild to moderate psoriasis patients. Randomized 1:1, a standard-of-care group (SOCG) applied a fluocinonide cream, which in the internet based reporting intervention group (IG) was equipped with a mechanism to objectively record each date and time of product opening. Adherence was higher in IG patients (50 vs. 35% $p = 0.08$). Low adherence in the short term worsened over time, even though the IG vs SOCG PASIs improved at months 1, 3, and 12, although at differences that were not statistically significant [7••].

Multicenter [8••] and multinational [9••] population-based surveys underscore poor satisfaction with disparities in patients' and physicians' perception of treatment goals, therapeutic options and responses, and disease severity ratings. The authors therefore recommend a more holistic treatment approach with ongoing communication between patients and physicians [10••]. We respond to this call by presenting old, new, and emerging topical therapies, with a focus on what, why, and how they can be used with less effort for better and quicker results. A key priority is the itchy and painful skin, not rated by the physician global assessment (PGA) or the PASI, yet patient rated as the most important contributing factor to disease severity. Another is the thick and scaly barrier-

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deficient skin and how topicals facilitate its repair. Effects of systemic and biologic agents in synergy with topical agents may help reduce the burden and achieve the quality of life our psoriasis patients deserve [11••].

### The Barrier in Psoriasis

Emollients have long been used to improve the look and feel of psoriasis skin and as base for active topical agents, from corticosteroids to botanicals [12, 13]. A novel function for emollients may be on the epidermal barrier. Similar to atopic dermatitis immunogenesis, psoriasis risk association studies have increasingly demonstrated genes encoding proteins and enzymes involved in SC barrier formation and repair [14–20, 21••]. These findings offer an alternate hypothesis that an underlying abnormality in epidermal function and repair may initiate, trigger, or exacerbate psoriasis [22••, 23••]. Results of a 2014 clinical study are consistent with this emerging concept of barrier-deficient skin in psoriasis. Compared with normal patients, progressive and stable psoriasis skin showed significantly increased trans-epidermal water loss (TEWL), and—like uninvolved skin—barrier recovery delay [24••]. Emollients affect the barrier, depending on the type of surface palisade they form, their penetration of, and action at the SC and at the lower viable cells.

## Emollients for Skin Barrier Recovery

### Lipids: Physicochemical Properties for Occlusive and Humectant Effects

The palisades formed by EMs vary with the physical properties of their component hydrocarbons [25••]. These include type, length, number of unsaturated or saturated bonds between carbons in the chains, and molar mass in daltons of the molecule. Petrolatum (PET), mineral (MO), vegetable (VGO), specifically coconut (VCO), and new physiologic lipids mimicking SC lipids are included in this review [26]. Essential oils reportedly have anti-inflammatory effects [27], but are also associated with cases of photo/contact dermatitis, that diminish the stratum corneum (SC) barrier [28], hence are not included in this review.

PET and MO are made of saturated, stable, straight, and long alkyl hydrocarbon chains. They pack well and form a tight palisade that helps keep water in, for both occlusive and humectant effects. PET is a thicker occlusive, but the thinner MO fully infiltrates extracellular domains of the SC for better humectant effect [29].

VGOs are processed from fruit parts—seeds and nuts—of almond, avocado, canola, cashew, cherry pit, coconuts, corn, cottonseed, grapeseed, hazelnut, olive, peanut, safflower, sesame, soy bean, sunflower, and walnut plants. Made up of triglycerides, three fatty acids (FAs) attach by ester linkages to each of the three-carbon atoms in a glycerin molecule. Double bonds give the carbon chain a kink or bend, so the oil stays liquid at any temperature, impart fluidity to cell membrane lipid bilayers, and form a palisade that is not highly occlusive. However, VGOs have some humectant properties from their glycerin component [30••].

Glycerin is absent from PET and MO, but is present in all VGOs. Each carbon in this three-carbon chain has a hydroxyl group that strongly bonds to water and changes water dynamics of products during application and usage. Extremely hygroscopic, glycerin absorbs water from the environment and lower skin layers, and increases water content in the upper layers, to make VGOs more humectant [31].

VCO and the other VGOs have similar properties and distinct differences**.** VCO uniquely has 65% medium-length and 92% saturated FAs which are straight and pack together well to form a palisade with excellent humectant and occlusive properties [32].

### Free Fatty Acids from Lipids: SC Penetration for Barrier Cell Repair

FFAs from VGO that arrive at the epidermis from topical preparations can be used for lipid synthesis [33•]. After skin insults—such as from psoriasis trigger factors—viable epidermal cells are shown to rapidly internalize and transport exogenous and endogenous FAs to distal Golgi apparatus. De novo synthesized lipids are then incorporated into lamellar bodies [34]. Almost all saturated and very long chain (20–32 carbons) cholesterol, ceramide FA, and FFAs in a roughly 1:1:1 M ratio within a single, coherent lamellar gel phase comprise the SC physiologic lipids [35].

The 500 Da rule states that particles with a molar mass below 500 Da readily diffuse into the skin's SC barrier [36]. Unless enhanced with novel carriers such as elastic liposomes [37], their ability to enhance barrier repair depends on the sum of the atomic weight in grams of each element that comprises the emollient molecule. Made up of 65% medium-chain and 35% long-chain FAs, VCO molar mass is $255.9 \pm 0.41$ Da [38]. All other VGO FAs are 100% long chain with 14 carbons or more. Molar mass in dalton of the long-chain FAs of olive oil is 857, sunflower is 876, and rapeseed 992 [39]. As such, VCO more readily penetrates intact SC to viable layers of the epidermis compared to other VGOs.

## Fatty Acids: Functional Properties to Help Ease the Red and Itchy Inflamed Skin

### Antimicrobial Effects

The exact mechanisms for psoriasis induction are not yet fully elucidated, but a pathogenetic model exists regarding events

that follow skin insults and lead to inflammation. Keratinocytes release antimicrobial peptide LL37 (cathelicidin), which mediates the breakdown of tolerance to self-nucleic acids. LL37 binds with pathogen-derived or self-DNA, released by stressed or dying cells and forms complexes that activate Toll-like receptor 9 on plasmacytoid dendritic cells (DCs). Cytokines are released, which activate local myeloid DCs, then promote the T cell-mediated inflammation that characterizes psoriasis. A top trigger for this cascade of events is infection [40••], for which the antimicrobial action of VGO lipids may help reduce the red and itchy inflamed skin.

Lipases hydrolyze sebum to FAs that contribute to the innate antimicrobial acid (pH ~5) mantle of the skin [41]. Antimicrobial effects of lipids have been demonstrated since the nineteenth century; however, these have been overshadowed by the advent of antibiotics [42–44]. With the continuing rise of antibiotic resistance [45], for many years, Kabara et al. led [46], followed by others [47••], in revisiting these antimicrobial lipids (AMLs).

Compared to antibiotics' typically *biochemical* mechanism of action (MOA) on bacterial cell targets [48], the tail of an AML FA and monoglyceride hydrocarbon chain inserts into and *physically* disrupts the microbial cell membrane. This results in increased membrane fluidity, aggregation, and fusion permeability to essential nutrients that affect cell metabolism and signaling [49]. This MOA applies to pathogenic bacteria, fungi, viruses, and protozoa, so AMLs are broad-spectrum, do not cause resistance, and help antibiotics overcome resistant microbes more effectively [50]. An AML report describes nanotechnology for improved therapeutic delivery, performance, and patentable inventions [51•].

## Anti-Inflammatory Effects from Omega 6:3 Ratio, Antioxidant/Pro-Oxidants, Trans Fats, Genetically Modified Properties

A psoriasis itch review concluded that while new drugs for neurogenic inflammation are under investigation, treatment should be directed toward lesion resolution, which often leads to itch remission [52•]. Emollients with VGO-derived FAs are able to diffuse through the SC and become incorporated in lipid bilayers, to facilitate cell repair and to address lesional inflammation and pruritus.

Balance is needed for continuing pro- and anti-inflammatory functions. Double bonds of monounsaturated/polyunsaturated FAs (M/PUFAs) are more readily oxidized than single bonds of saturated fatty acids. Liquidity of M/PUFAs should be balanced by these firm saturated fatty acids [53••, 54]. The higher omega (ω) 6:3 ratio of the dominant ω-6 PUFAs of seed oils compared to the low ratio from VCO FAs skews toward more pro-inflammatory eicosanoid hormones [55••, 56].

Olive oil, which permeates the dermal-epidermal junction and all levels of the SC, is considered anti-inflammatory due to its antioxidants but has been reported to be an irritant. Like propylene glycol and terpenes, often found in emollient formulations, olive oil can be applied on the skin as a penetration enhancer of emollients with added active ingredients [57].

Codex Alimentarius defines virgin olive (VOO) and VCO as extracted by mechanical means, without chemically altering the oil, purified by washing with water, settling, filtering, centrifuging, and the *application of heat only*. Cold pressed (CP), processed *without heat or chemicals*, is a separate class [58]. CP-VCO has greater anti-inflammatory effect, from retained flavonoids and phenolic antioxidants, balanced by a small amount of pro-oxidant hydrogen peroxide [59]. Other VGOs, not processed with heat or solvents and not partially hydrogenated, retain these heat labile antioxidants; however, most VGOs are highly processed to obtain the oil from tiny seeds and other plant parts [60].

Physiologic lipids are now marketed in skin barrier-type products. An important requisite for normal barrier function is an approximately equimolar 1:1:1 mix of the three families of physiologic lipids. Barrier repair with physiologic lipids at 3:1:1 optimal ratio is 10% greater after 45 min, 55% after 2 h, 75% after 4 h, and 90% after 8 h. With PET applied alone, barrier recovery after 45 min until 4 h is 50%, down to 40% by 8 h. Together with PET, the 3:1:1 lipid mix improves to 55% at 45 min, 70% by 2 h, 90% by 4 h, and 95% by 8 h [61••]. High-lipid content moisturizers with 3:1:1:1 ratio of cholesterol, ceramides, palmitate (a non-essential, saturated FA), and linoleate PUFA have been found to further accelerate normal barrier recovery [62••]. Table 1 presents a summary of how emollient topical therapies help reduce the thick, dry, scaly, itchy, and red skin in psoriasis.

## Current Active Psoriasis Topical Therapies: Hydrocarbons, Corticosteroids, Vitamin D Analogs, Retinoids, Calcineurin Inhibitors

Table 2 summarizes the mechanism of action, recent updates, and suggestions for future studies on long-term safety and efficacy, with emphasis on patient's perspectives.

### Hydrocarbons: Coal Tar and Anthralin

Although less popular in recent years due to side effects of hair discoloration, staining of clothes, odor, irritant contact dermatitis, folliculitis, and keratoacanthomas developing, there are recent reports on usage and effectivity.

**Coal Tar** Coal used in conjunction with UVB in the Goeckerman regimen is a well-recognized treatment for

**Table 1** Emollient topical therapies to help reduce the thick, dry and scaly, itchy, and red psoriasis skin

| Properties and Effects | | Petrolatum (PET) | Mineral oil (MO) | Vegetable Oils (VGO) | Coconut oil (VCO) |
|---|---|---|---|---|---|
| S. corneum Barrier | Chemistry | Alkanes: Hydrocarbons, Long – Chain (20-40 C) w/ Single Bonds | | Microbial Lipases hydrolyse Triglycerides to Monoglycerides, Fatty Acids and Glycerol | |
| | Film Palisade Formed | More Chains: Tight, Compact | Fewer Chains Less Tight, Compact | All Long-Ch: (14-22C+)<br>M/PUFAs: 75-85+ %<br>Saturated 15-25%<br>Kink @ Double Bonds | Long-35%;<br>Med- 65%<br>Un-Saturated - 8%<br>Saturated - 92%<br>Straight @ Single Bonds |
| | Occlusive Effect (+-+++) | (+++) | (+) | (+) | (+++) |
| | Humectant Effect | (+)<br>Occlude more | (++)<br>Occlude less Diffuse more | (++)<br>Occlude less<br>Has Glycerol | (+++)<br>Occlude more<br>Has Glycerol |
| | Molar Mass in Daltons (Da)<br><500 Diffuse thru SC & to viable cells | 350-650 & up<br>SC | 489-599 & up | Olive 857<br>Sunflower 876<br>Rapeseed 992<br>Kinked C Chain | 256 +/- 0.41<br>Straight C Chain |
| | | Diffuses less<br>(+) | Diffuses more<br>(++) | Diffuses less:<br>(+) | Diffuses more<br>(+++) |
| | On Dry, Thick, Scaly Skin Feel Barrier Repair Effect | Greasy, Flat tens scales, | Thin, diffuses more. Humectant, | Light & thin oil, Occlusion mild; Humectant, | Light & thin yet strong occlusive & Humectant, |
| | | Feels soft<br>No FAs to help cells repair | Feels soft less dry.<br>No FAs to help cells repair | Feels soft, less dry, FAs permeate less than VCO for cell repair. | Feels soft, less dry, scaly, itchy.<br>FAs penetrate quickly for cell repair. |
| Inflammation | FAs & MGs<br>Anti-Microbial<br>MOA | None from Alkanes | | Long Ch M-/PUFA<br>Oxidized@ Double bonds: more ROS to Oxidize Microbes,<br>Broad - spectrum | Med. Ch FAs insert into and destroy microbial cell walls.<br>Broad-spectrum |
| | Anti-Oxidants (AOxs) | If Oil is extracted/processed with high heat or chemicals, little or No AOxs left | | | |
| | | Highly Processed:<br>None or little AOxs | | Highly processed other Seed Oils (0 -+)<br>CP-VOO (+++) | CP-VCO (+++) |

**Table 1** (continued)

| Properties and Effects | Petrolatum (PET) | Mineral oil (MO) | Vegetable Oils (VGO) | Coconut oil (VCO) |
|---|---|---|---|---|
| Pro-I vs Anti- I from: | | | | |
| • ω 6:3 Ratio | | | • Ratio up to 70:1 Pro-I | • ω6:3 Ratio 2:1- Anti-I |
| • TransFats (TFAs) | | | • Double bonds trans formed to TFAs: Pro- I | • TFAs: 0-very few from 8%M-/PUFAs Anti-I |
| • Double bonds | No specific effect on inflammation | | • Double bonds oxidise to more ROS: Pro-I<br>More Pro-Inflammatory<br>VOO disrupts the barrier, helps actives penetrate SC;<br>VGOs High linoleic acid synthesizes SC ceramide, linoleate | • More Single bonds, Less ROS Anti-I<br>More Anti-Inflammatory |
| Feel & Effect on Itch, stinging pain & Red skin | | | Less Anti-Inflamatory from more Pro-I properties:less itch & sting reduction | More Anti-Inflammatory from Anti-microbial and Anti-Oxidant properties reduces itch & sting more |

Beyond the evidence, Dr. Verallo-Rowell shares her 17 years experience on using these EMs

Note that below 25 °C room temperature, VCO becomes a white butter. Scoop a teaspoon, apply, on the skin, and VCO becomes an oil again that diffuses in quickly, so there is no need to wait before applying any prescribed active topical products.

For convenience of once daily application: On 3–4+ itchy, dry, thick scaly skin, at bedtime, spread VCO thinly, massage gently, widely into psoriasis and normal skin. Next, apply on active lesions any prescribed active topical products. Grease up all over with PET. Occlude with thin flexible wrap or wear a pair of white, tight-weave polyester tights for several hours to overnight. On 1–2+ dry, thin, less itchy skin, apply the VCO all over followed by any active topicals. For very thick plaques or to enhance penetration of actives, mix VCO and VOO 10:1≤ and proceed as above.

Physiologic lipids—apply first, wait for several minutes, proceed as above. Verallo-Rowell VM. A 17-year experience with monolaurin and cold-pressed virgin coconut oil on steroid suppressed, barrier challenged and frequently colonized/infected cases of atopic dermatitis, acne, contact, photo contact dermatitis, and psoriasis at the VMV Skin Sciences Research Centre + Clinics. References [26, 32, 59, 63•, 64•, 65•, 66, 67–69]

*AOx* antioxidant, *C* carbon, *Ch* chain, *CP* cold-pressed, *FA* fatty acid, GM genetically modified, *MOA* mechanism of action, *Med* medium, *MG* monoglycerides, *M/PUFA* monounsaturated/polyunsaturated FA, ω-6:3 omega 6:3 ratio, *Pro-I/Anti-I* pro-/anti-inflammatory, *ROS* reactive oxygen species, *SC* stratum corneum, *TG* triglycerides, *VGO* vegetable oil, *VCO* virgin coconut oil, *VOO* virgin olive oil

**Table 2** Mechanisms of action of active topicals including keratolytics on lesional skin of psoriasis patients

| Names of topicals | Thick, dry, scaly skin from altered barrier and keratinocyte differentiation | Skin: red, itchy, stings | Gaps on efficacy and safety studies needs | |
|---|---|---|---|---|
| | | Anti-inflamm | On usage and side effects | +Other actives |
| Keratolytics<br>• Salicylic acid<br>• Urea<br>• AHA/PHAs | • Salicylic acid (SA): act on corneocyte desmosomes and reduce pH, thus desquamates, and increases SC hydration and softening.<br>• Urea: proteolytic, keratolytic, hygroscopic, enhance penetration, reduce basal DNA synthesis, induce cell differentiation<br>• AHAs/PHAs: increase SC turnover, cause desquamation of the SC without impairing barrier function | • SA at 0.5–5.0%<br>• Urea at 40%<br>Also anti-itch<br>• Hydroxy acids<br>AOx, moisturize | • Larger, longer, well randomized, blinded, controlled studies on the keratolytics used alone | Same types of studies on keratolytics (+) other active topicals |
| Corticosteroids | Antimitotic and apoptotic | Anti-inflammatory, vasoconstrictitive, immunomodulatory | • Same studies, all CS types for tachyphylaxis and atrophogenicity.<br>• Dose, duration in almost to clear psoriasis | Do one on one studies for best combinations, applications: #s time, duration:<br>TOP CS alone |
| Vitamin D/D3 analogs<br>• Calcipotriene<br>• Calcitriol<br>• Tacalcitol | Bind to vitamin D receptors, then to multiple responsive gene elements, normalize keratinocyte proliferation and differentiation.<br>Good studies on VitD analog + CS more effective than either alone | Inhibit dendritic cytokines that stimulate regulatory T helper cells. Modulates inflammation | • Same studies, calcitriol vs tacrolimus/pimecrolimus<br>Why mg/week dose differ:<br>Calcitriol 200<br>Calcipotriene 100 | vs. TOP CS (+) calcitriol or calcipotirene, tazarotene, tacrolimus, or pimecrolimus |
| Retinoid:<br>Tazarotene | Less effective than super potent CS, but longer remissions, no skin atrophy with long use. Warn patients on initial face, intertrigionous irritations. Lessen with EMs. | | | |
| Calcineurin inhibitors<br>• Tacrolimus<br>• Pimecrolimus | Regulates the normal, normalizes abnormal keratinocyte differentiation, potent antiproliferative effects. Dual action and 18-h half-life may allow one a day application<br>Mild to moderate irritation is common. Warn patients. Avoid, also treat with barrier repairing, anti-inflammatory EMs and/or use to enhance penetration of other actives. | | • Use on palm, sole, nail areas: more difficult to treat, resistant to irritant contact dermatitis<br>• Tacrolimus in small RCTs: effective on face, intertriginous, genitals.<br>• To enhance penetration on plaques, apply CP-VCO or CP-VOO first. | Reports of lymphoma and skin cancers need long-term safety studies |
| Hydrocarbons<br>• Coal tar<br>Anthralin | • Off label, blocks calcineurin phosphatase-dephosphorylation of the nuclear factor to activate T cells, and suppresses pro-inflammatory cytokines production.<br>• Unlike CS, not atrophogenic [6•]<br>• Coal tar; carbazole, a hydrocarbon in crude coal tar, reduces levels of IL-16 via inhibition of STAT3 activation, modulates inhibitory effects of IL-2 on Th17 cells.<br>• Anthralin: reduces keratinocyte proliferation, prevents T cell activation, and restores cell differentiation | | | |

*CS* corticosteroids, *EMs* emollients, *TOPs* topicals, *CP-VCO* cold-pressed virgin coconut oil, *CP-VOO* cold-pressed virgin olive oil

chronic plaque, palmoplantar, and scalp psoriasis. Carbazole, an aryl hydrocarbon in crude coal tar [70], reduces IL-17 levels via inhibition of STAT3 activation and modulates inhibitory effects of IL-2 on Th17 cells [71]. Khandpur et al. compared coal tar–salicylic acid ointment with calcipotriol/betamethasone dipropionate (BMD) ointment and concluded that both had comparable efficacy at the end of 12 weeks, although the calcipotriol/BMD ointment had faster onset of action [72]. In 2014, a novel solution of coal tar in 15% liquor carbonis distillate (Psorent; Neo Strata Co.) was released, which showed rapid absorption and less odor compared to traditional products [73].

**Anthralin (Dithranol)** A 2015 biomolecular study using HaCaT cells to replicate epidermal keratinocyte proliferation in psoriasis showed that anthralin has a clear effect on the cells' central metabolism, and appears to target the mitochondria [74].

**Keratolytics and Emollients** A systematic review from January 1983 to December 2013 noted the need for an integrated therapeutic approach by using keratolytics and emollients (K&E) with current first-line topical corticosteroids (TCS) and vitamin D analogs. Reviewed evidence supports the basic skin care role of K&Es to improve altered structure and function, but shows no solid evidence of distinct clinical disease

response. *Urea* reduces induration and/or scaling that may lead to increased patient satisfaction, but not the body surface area (BSA) affected. Articles on *alpha- and poly-hydroxy acid* articles are limited, short term, on small populations, with no control group, no clear randomization procedure, and use weak outcome variables. *Salicylic acid* (*SA*) monotherapy induces significant improvement of psoriasis BSA, and/or the overall degree of erythema, induration, and desquamation. Again, these lack comprehensive, high-quality trials and placebo control, which are important for SA use in young children, patients with renal/hepatic impairment, widespread psoriasis, on phototherapy, calcipotriene, or systemic salicylates. Exceptions are combined SA and TCS studies showing reduced severity parameters and area affected. Hence, there is the need for well-designed studies on keratolytic agents and suitable alternatives to SA [75].

**Corticosteroids** TCS are used universally to manage all grades of psoriasis. The MOA are anti-inflammatory, antimitotic, apoptotic, vasoconstrictive, and immunomodulatory, and these properties are closely associated with their efficacy [76]. Selecting the appropriate corticosteroid potency and its vehicle should consider the disease severity, body location, patient preference, and patient's age. Highly potent agents are best for short-term use. Some studies used superpotent corticosteroids to treat plaque-type psoriasis for 2–4 weeks. Gradual reduction of usage has been recommended following clinical response. The risks associated with long-term use are unknown. The next steps in the development of topical steroids include modifications of the molecule and to improvement of delivery systems to increase anti-inflammatory activity with favorable results [77].

**Vitamin D Analogs** Common vitamin $D_3$ analogs used for psoriasis include the naturally occurring active metabolite calcitriol (1α,25-dihydroxyvitamin $D_3$) and two synthetic analogs: calcipotriene and tacalcitol (1α,24-dihydroxyvitamin $D_3$). They bind to vitamin D receptors, which then bind to vitamin D responsive elements in multiple genes, normalizing keratinocyte proliferation and differentiation and modulating the immune response [78]. The most commonly reported adverse effect is skin irritation on or around the psoriasis plaques, and sensitive regions of the face and intertriginous areas. Although monotherapy with topical vitamin D analogs is effective for some patients, a Cochrane systematic review determined that combination therapy with TCS is more effective than either treatment alone [79].

**Retinoids** Tazarotene, a novel third-generation acetylenic, receptor-selective retinoid, normalizes the abnormal differentiation of keratinocytes and has direct potent antiproliferative effects on keratinocytes, and indirectly as a result of regulating normal differentiation. Like other topical retinoids, local irritation, mild to moderate pruritus, erythema, burning, and desquamation are common. Absorption of tazarotene and systemic side effects appears to be very low, yet caution should be exercised in women of childbearing age. Topical tazarotene, also recently studied in a non-ionic surfactant-based proniosomal gel form, is a promising agent in the treatment of psoriasis [80, 81].

**Calcineurin Inhibitors** Studies on topical calcineurin inhibitors, tacrolimus and pimecrolimus, show that they act by suppressing T cell activation and proliferation. By blocking calcineurin phosphatase, dephosphorylation of the nuclear factor of activated T cells is prevented. This leads to the inhibition of T cell activation and the production of pro-inflammatory cytokines. A review of double-blind and open studies showed their efficacy on facial, genital, and intertriginous areas, without the skin atrophy from TCS [82]. Newer formulations circumvent the limited cutaneous penetration of conventional vehicles and have promising results. Among these are tacrolimus-loaded polymeric micelles using biodegradable and biocompatible methoxy-poly(ethylene glycol)-dihexyl substituted polylactide (MPEG-dihexPLA) diblock copolymer [83], tacrolimus-composite hydrogels [84], and tocopheryl polyethylene glycol 1000 succinate (TPGS)-based microemulsions [85].

## Newly Released Topical Corticosteroids

*Enstilar* (LEO 90100; LEO Pharma) is an alcohol-free foam combination of calcipotriene and betamethasone dipropionate in a pressurized spray suitable for large areas of plaque psoriasis. It is applied once daily for up to 4 weeks. In phase 3 trials, over half of patients were "clear" or "almost clear" by week 4 assessed by Investigator Global Assessment score of disease severity, and more than half of treated patients achieved 75% improvement in PASI from baseline. The formulation was more effective than the ointment fixed combination and the individual components used alone. This enhanced efficacy is due to improved skin penetration of the active ingredients following the formation of a stable supersaturated solution on the skin. Studies have shown increased patient satisfaction, and this optimized formulation may improve adherence. Patients are cautioned against using over 60 g every 4 days and advised to discontinue its use once symptom control is achieved. [86]

*Sernivo* (DFD-01; Promius Pharma) is an oil-in-water lotion-like 0.05% betamethasone dipropionate spray shown to have a faster onset of action than superpotent betamethasone. It is convenient to apply on moderate to severe psoriasis erythema and scaling, with minimal residue and no stinging or burning [87].

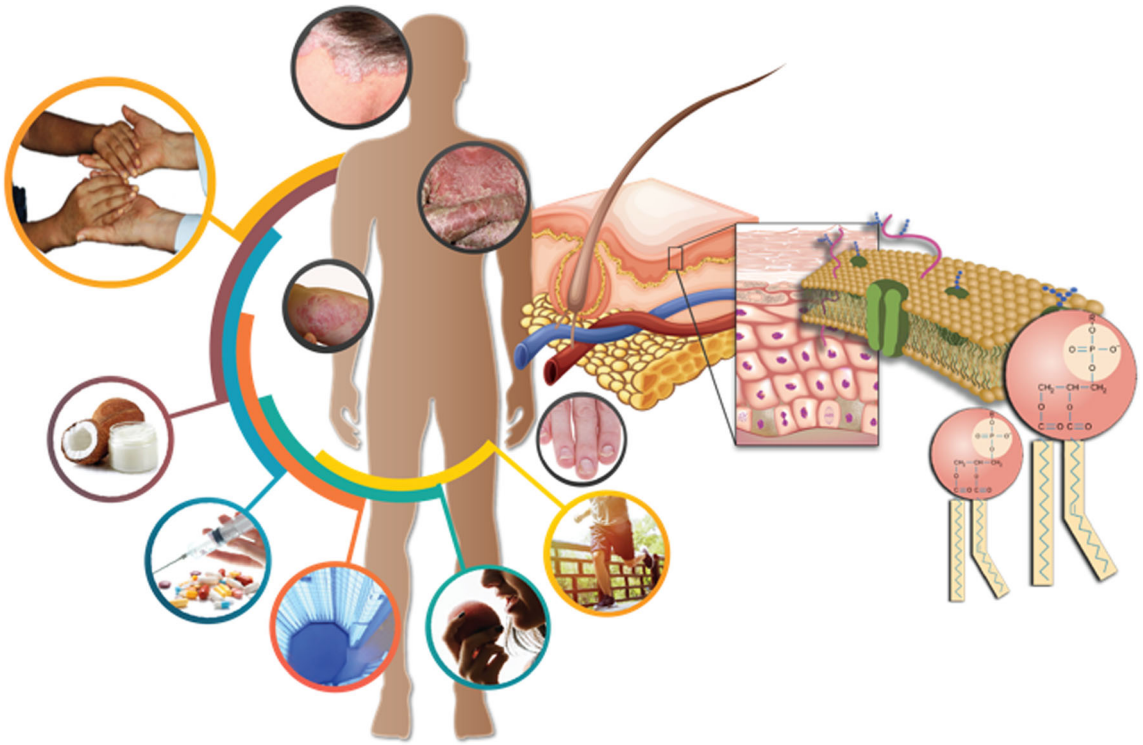

**Fig. 1** Evidence-based holistic dermatology practices for treatment of psoriasis. Artwork by Terese Monette O. Aquino, MD Skin and Cancer Foundation, Inc. chief resident

## New Topical Therapies in Development

There are several of these preparations now undergoing trials in phases 1, 2 and 3. They shall be mentioned here as topical agents to anticipate, but for most of these no trial results are available.

### Corticosteroid Combinations

*LEO 80190* (LEO Pharma) combines hydrocortisone with calcipotriol, for sensitive areas such as the face and intertriginous skin, applied once daily [88].

*LAS 41004* (Almirall, SA) is an ointment containing betamethasone dipropionate and bexarotene for mild to moderate psoriasis [89].

*IDP-118* (Valeant Pharmaceuticals International, Inc.) is a halobetasol propionate 0.01% and tazarotene 0.045% lotion, combined to enhance tolerability and therapeutic efficacy [90].

### Vitamin D Analogs

*P-3073* (Polichem, SA, Switzerland) is calcipotriol in an anhydrous medicated nail lacquer for mild to moderate nail psoriasis (https://clinicaltrials.gov/ct2/show/NCT02606760?term=p-3073&cond=Psoriasis&rank=1), while *M518101* (Maruho Co., Ltd.) is a novel topical vitamin $D_3$ analog (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5312630/) and *STF 115469* (GlaxoSmithKline) is a vitamin $D_3$ analog, calcipotriene 0.005% foam. (www.mdedge.com/…/clinical-trial-update-topical-therapy-plaque-psoriasis). *DPS-101* (Dermipsor Ltd.) is a combination of calcipotriol and niacinamide [91].

### Phosphodiesterase-4 Inhibitor

*Crisaborole* (AN2728; Anacor Pharmaceuticals, Inc.) blocks the inactivation of cyclic adenosine monophosphate, resulting in decreased production of inflammatory cytokines. In a randomized, double-blind phase 2 trial, 40% of patients treated with AN2728 5% ointment reported improvement of more than 2 points in overall target plaque severity score versus only 6% of the control group. In another randomized, double-blind, dose-response trial, those treated with AN2728 2% ointment twice daily reported a 60% improvement versus 40% improvement in those treated with AN2728 0.5% ointment once daily [92]. A phase 2 trial on mild to moderate plaque psoriasis showed that 17.4% of the AN2728 2% ointment group achieved a Physician's Global Assessment rating of clear or almost clear at 12 weeks, compared with 13.6% of those in the control group [93].

### pSTAT-3 Inhibitors

*MOL 4239* (Moleculin, LLC) is a novel topical agent for use in mild to moderate psoriasis that acts via phosphorylated

signal transducer and activator of transcription 3 (p-STAT3) inhibition [94].

*MOL4249* (Moleculin, LLC) is more potent than MOL4239 with better lipid solubility. In the MOL4249 subset of a placebo-controlled, double-blind, phase 2a trial of 16 patients with mild to moderate psoriasis, 10% of patients had complete clearance of plaques, 30% had 75% or greater improvement, and 50% of patients had 50% or greater improvement compared to 17% in the placebo group [95].

*TrkA inhibitor CT-327* (Creabilis SA) is a tyrosine kinase A (TrkA) inhibitor that offers a novel approach to treating pruritus by shifting the focus toward sensory neurons. TrkA is associated with pruritus and psoriatic plaque formation. In a phase 2b study of 160 patients, a 60% change in the visual analog scale rating of pruritus was noted at 8 weeks in the treatment group versus 21% in the placebo group, despite an absence of change in disease severity [96].

## JAK Inhibitors

*Tofacitinib* (CP-690,550; Pfizer Inc.) is a selective Janus kinase (Jak) 1 and Jak3 inhibitor that decreases expression of pro-inflammatory cytokines and inhibits helper T cells ($T_H17$) by downregulating expression of the IL-23 receptor. Epidermal keratinocyte proliferation in psoriasis is activated by $T_H17$ cells that release IL-17 as well as $T_H1$ cells that release IFN-$\gamma$ and TNF. A phase 2a trial showed statistically significant improvement from baseline in the target plaque severity score for tofacitinib ointment 2% versus vehicle [97]. A phase 2b study that compared two dose strengths of tofacitinib ointment—10 and 20 mg/g—versus placebo showed that 20 mg/g (2%) tofacitinib ointment applied once and twice daily had greater efficacy than vehicle at week 8, but not at week 12, and had an acceptable safety and tolerability profile [98].

*Ruxolitinib* (INCB18424; Incyte Corporation) is a selective Jak1 and Jak2 inhibitor. A phase 2 trial showed a 53% decrease in the score for mean total lesions in patients treated with ruxolitinib phosphate 1% cream versus 54% in those treated with ruxolitinib phosphate 1.5% cream and 32% in those treated with placebo, though these differences were not statistically significant [99]. A phase 2b trial demonstrated greater efficacy of ruxolitinib cream (0.5, 1, and 1.5% concentrations) versus vehicle for improving PASI scores in plaque-type psoriasis, over 3 months. Local irritation and respiratory infection were reported adverse effects. Epidermal hyperplasia and dermal inflammation were reduced in most patients, along with immunohistochemical changes (CD3, CD11c, Ki67, and K16), showing that ruxolitinib cream acts on multiple cell types involved in psoriasis pathogenesis [100].

## Topical Methotrexate

*MQX-5902* (MediQuest Therapeutics) is topical methotrexate for fingernail psoriasis. Methotrexate is a dihydrofolate reductase inhibitor and antimetabolite that inhibits folic acid metabolism, thereby disrupting DNA synthesis [101]. A phase 2b dose-ranging trial for efficacy and safety of this agent delivered via a proprietary drug delivery formulation for fingernail psoriasis has been listed with "unknown" recruitment status.

## Novel Topical Agent

*Tapinarof* or Benvitimod, WBI-1001 (Welichem Biotech Inc.) is a novel proprietary agent that inhibits pro-inflammatory cytokines. A randomized, placebo-controlled, double-blind, phase 2 efficacy and safety trial on physician's global assessment showed a therapeutic benefit of 62.8% in patients treated with WBI-1001 1% cream versus 13.0% on the placebo after a 12-week treatment period ($p < 0.0001$) [102].

# Conclusion

The scaly, dry, thick, and especially the red and itchy skin contributes to disease severity, unmet needs, and lack of satisfaction of psoriasis patients to current therapies, as reflected in multicenter studies.

Barrier defects make the skin scaly, dry, and thick. PET is greasy and occlusive, while the thinner and less greasy MO is less occlusive but diffuses into the SC; both have humectant effects. All VGOs have long-chain, unsaturated FAs and hence are poorly occlusive but have glycerin, a potent humectant. VCO is the exception with its 65% medium chain, 92% saturated FAs, and glycerin, which provide excellent occlusive and humectant effects.

Anti-inflammatory effects from an ω-6/ω-3 ratio of VCO FAs at 2:< 1 are anti-inflammatory. At a ratio of 10+ and often higher, other VGOs have more pro-inflammatory effects, although their *high linoleate* content contributes to barrier repair. Olive oil infiltrates the whole epidermis, has a less pro-inflammatory ω-6/ω-3 ratio at 7:1, but has been shown to disrupt the barrier, which has been used as penetration enhancer for active ingredients. Finally, antimicrobial properties of FAs and monoglycerides of saturated VCO, and less of the unsaturated VGOs, help address the growth and associated inflammation from pathogenic microbes.

Active topical therapies have for years shown high efficacy and safety on both inflammation and the barrier in psoriasis. These are led by TCS, now in more easily used sprays and foams. However, more detailed and specific studies especially on tachyphylaxis and atrophogenecity of TCS, used alone or in combination with vitamin D analogs and calcineurin inhibitors, need to be further clarified and quantified.

From many years of no new topical therapies, many have now emerged, using different combinations of the older actives, as well as novel analog, small molecule inhibitors, and sensory neuron inhibitors, in phase 2 and 3 studies. All these together with evidence-based holistic dermatology practices hold promise for higher satisfaction rates in future surveys of our patients with psoriasis (Fig. 1).

## Compliance with Ethical Standards

**Conflict of Interest** The authors declare that they have no conflict of interest.

**Human and Animal Rights and Informed Consent** This article does not contain any studies with human or animal subjects performed by any of the authors.

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