REVIEW

Pediatric Dermatology Vol. 26 No. 6 669–675, 2009

The Benefits of Sunflower Oleodistillate (SOD) in Pediatric Dermatology

Lawrence F. Eichenfield, M.D.,* Alexandra McCollum, M.D.,† and Philippe Msika, Ph.D.‡

**Pediatrics and Medicine (Dermatology), Pediatric and Adolescent Dermatology, Rady Children's Hospital, University of California San Diego School of Medicine, San Diego, California, †Pediatric and Adolescent Dermatology, Rady Children's Hospital, San Diego, California, ‡Innovation, Research and Development, Laboratoires Expanscience, Epernon, France*

Abstract: **For millennia, sunflower seed oil has been used in folk medicine for both skin care and the treatment of skin disorders. In its natural state, the oil contains high levels of essential fatty acids, particularly linoleic acid, which has skin barrier-enhancing properties. A sunflower oleodistillate (SOD), which is produced through a molecular distillation process without the use of solvents, has been shown to increase the epidermal key lipid synthesis and to reduce inflammation in vitro and in animal models. It has also been shown to activate peroxisome proliferative-activated receptor-α (PPAR-α) in vitro. As PPAR-α agonists have been shown to stimulate keratinocyte differentiation, improve barrier function, and enhance lipid metabolism in the skin, it has been suggested that SOD might also be efficacious in atopic dermatitis (AD). An initial clinical evaluation of the care effect of a 2% SOD emulsion in 20 adult volunteers with atopic skin revealed the moisturizing properties of SOD. Finally, a strong steroid-sparing effect and a positive effect on quality-of-life parameters were clearly demonstrated for the 2% SOD cream in studies in infants and babies with AD.**

In recent years there has been increasing interest in skin care products for infants and children. Additionally health-conscious parents have gradually become more discerning of the baby products they buy and the consumer trends toward buying products containing fewer and more familiar, natural ingredients. Many natural ingredients, typically based on botanicals, may be considered by health-conscious consumers to be safe, gentle, ecologically sound, and esthetically appealing (1). Increasing attention is being devoted to the discovery and development of plant-based ingredients for inclusion in skin care products. The use of many of these substances in skin care dates back millennia. The desire for clinically relevant data on natural ingredients has led to increasing numbers of well-designed studies of the use of green tea extract (2), oatmeal (3), licorice (4), soy (5), and other botanicals (6).

Recently, there has been a resurgence of interest in the use of sunflower (*Helianthus annus*) oil for inflammatory skin disorders. Sunflowers are native to the

Address correspondence to Lawrence F. Eichenfield, M.D., Pediatrics and Medicine (Dermatology), Pediatric and Adolescent Dermatology, Rady Children's Hospital, University of California San Diego School of Medicine, San Diego, CA 92130, or e-mail: leichenfield@ucsd.edu.

DOI: 10.1111/j.1525-1470.2009.01042.x

© 2009 Wiley Periodicals, Inc.

southwestern United States and northern parts of Mexico. These flowers were used by indigenous peoples as food, medicinal ingredients, as well as a source of dyes (7). In the 1970s, it was shown that essential fatty acid (EFA) deficiencies in both animals and humans could be treated by topical application of sunflower seed oil (8).

COMPOSITION AND CUTANEOUS ACTIVITY OF NATURAL SUNFLOWER LIPIDS IN THE SKIN BARRIER

As it occurs in nature, sunflower oil is replete with EFA. Its major lipid constituent is linoleic acid in the form of a triglyceride (61.5%) and to a much lesser extent, oleic acid (24.3%), palmitic acid (9.3%), stearic acid (3.7%), and linolenic acid (1.0%) (9). These EFA help maintain the skin barrier and minimize transepidermal water loss (TEWL) (10,11). Linoleic acid, the primary lipid fraction of sunflower oil (9), converts to arachidonic acid and is a precursor to prostaglandin E2 (PGE2) (10). PGE2 is a known modulator of cutaneous inflammation (12). A study by Elias et al showed that linoleic acid may play a direct role in barrier function, independent of its role in prostaglandin metabolism (11).

The epidermal barrier functions to prevent the loss of water and to prevent the penetration of environmental contaminants into the skin (13). It has been described as having a bricks-and-mortar structure (14), composed of layers of corneocytes embedded in a matrix of lipid bilayers consisting primarily of fatty acids, ceramides, and the sterols and cholesterol sulfate, in specific proportions. The similarities of sunflower seed oil lipids and those constituting the epidermal barrier suggested their potential utility in a variety of cutaneous conditions.

STUDIES OF TOPICAL SUNFLOWER OIL IN DERMATOLOGY

Several studies have demonstrated the utility of topical application in patients who had EFA deficiency secondary to prolonged fat-free parenteral feeding or fat malabsorption secondary to surgery (8). An in vitro study by Van Dorp showed that topical application of sunflower oil on abdominal skin from EFA-deficient rats reduced the TEWL that is characteristic of EFA-deficient skin (15,16). In an unpublished study by Black and Hartop, it was noted that skin symptoms of EFA deficiency, which included extreme dryness, improved not only at the application site but also at remote sites on the skin (8, J.G. Black, P.F. Hartopp, and J.L. McCormack, unpublished data).

A later study demonstrated a similar result in three patients who became EFA-deficient following major bowel resection (8). Application of olive oil to the contralateral arm did not reduce TEWL, but sunflower oil reduced TEWL between 33% and 50% in the three patients in the study. The skin linoleic acid content began to increase within 4 days of topical application of sunflower seed oil but not olive oil. The authors noted that both oils penetrated the stratum corneum and were incorporated into the epidermal barrier (8,9).

More recently, Darmstadt et al demonstrated that the application of sunflower seed oil was beneficial in reducing the rate of nosocomial infections in preterm infants. Preterm infants less than 33 weeks gestation at birth were randomized to receive massages with either sunflower seed oil ($n = 159$) or a commercially available ointment containing petrolatum, mineral oil, mineral wax, and lanolin alcohol ($n = 157$). The incidence of nosocomial infections in the treatment group was compared with that of untreated controls ($n = 181$). Overall, infants massaged with sunflower oil were 41% less likely to develop a nosocomial infection than those massaged with the petrolatum ointment (17). Darmstadt et al later conducted a trial in which 497 preterm Bangladeshi infants (gestational age ≤ 33 weeks) were randomized to receive daily treatment with topical sunflower oil or the petrolatum ointment used in the aforementioned study. The sunflower oil treatment group had a significant reduction in infant mortality of 26% ($p = 0.042$) compared to that of controls who received neither form of emollient therapy. The petrolatum ointment treatment group also had reduced infant mortality by 32% ($p = 0.13$). The authors concluded that the use of skin barrier-enhancing emollients, particularly sunflower oil in the care of preterm infants (< 33 weeks gestation), improved overall survival rates and did so at a relatively low cost (18).

SOD

Recently, a sunflower oil distillate (SOD) has been patented and incorporated into pediatric skin care products. Two percent SOD contains 90% EFA, mainly oleic and linoleic acids, as well as 5% phytosterols and 1% vitamin E. The phytosterol content appears to be critical for anti-inflammatory, antioxidant activity. Vitamin E, derived from plants, is the most important lipid-soluble, nonenzymatic antioxidant available to protect the skin from oxidative stress. It has been shown to be an effective topical treatment for a variety of dermatologic disorders including atopic dermatitis (AD), dry eczema, and ichthyosis (19). In a murine model of 12-*O*-tetradecanoylphorbol-13-acetate (TPA)-induced ear inflamma-

tion, sterol and triterpene derivatives from plants were shown to be highly anti-inflammatory and also inhibited TPA-induced tumor-promoting activity (20,21).

Sunflower oleodistillate is obtained by the treatment of EFA-enhanced sunflower oil through physical processes using concentration of the unsaponifiable fraction with centrifugal molecular distillation and purification by steam distillation. This results in SOD that has a 10-fold higher unsaponifiable fraction than that which occurs naturally in sunflower oil (22).

In vitro studies of human skin sections showed that topical application of 2% SOD for 18 hours increased the synthesis of cerebrosides (+65% compared to vehicle), and significantly increased the synthesis of ceramides (+205%, $p < 0.05$), and cholesterol (+107%, $p < 0.05$) to a greater degree than either vehicle or positive control (10 ng/mL EGF) (23).

In an in vivo study Dubuquoy et al demonstrated that SOD has anti-inflammatory properties comparable to that of a mid-potency topical steroid. In their study, inflammation was induced by topical application of the 0.03% tumor promoter TPA on the inner and outer surfaces of the right ears of 27 mice. Vehicle alone was applied on the left ears. Forty-five minutes and 4 hours after TPA application, either 20 μl of 2% SOD or 25 mM fluocinolone acetonide (positive control) was applied to the inner and outer surfaces of both ears. Eighteen hours after the TPA-induced inflammatory insult, inflammation was assessed by means of the increase in ear thickness. Ears were then collected, one-half were processed for histology (OCT embedding), and the other half were used to measure cytokine mRNA levels as an inflammatory marker.

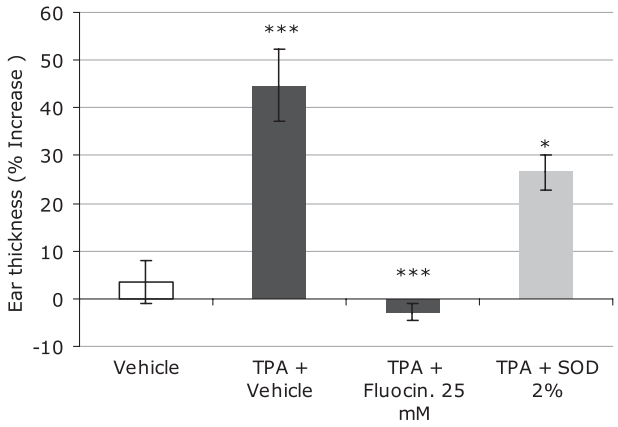

Figure 1. Ear thickness measurements. Ear thickness was measured 18 hours after TPA application with a digital caliper. The extent of inflammation was quantified according to the following equation: ear swelling (%) = $100 \times (a - b)/b$, where a is the thickness of the right (TPA-treated) ear and b is the thickness of the left (vehicle-treated) ear. *$p < 0.05$; ***$p < 0.001$ (24).

Figure 1 demonstrates that ear thickness was significantly increased (45%) after TPA application. Vehicle alone did not influence the intensity of the inflammatory response, whereas, fluocinolone acetonide 25 mM was associated with complete amelioration. Two percent SOD significantly decreased ear edema by 40.5% ($p < 0.05$), compared with vehicle. Total mRNA was extracted from ears and retro-transcripted in cDNA. Pro-inflammatory cytokines, tumor necrosis factor-α (TNF-α) and interleukin-1β (IL-1β) mRNA levels were measured by real-time polymerase chain reaction (PCR). The TPA-induced over-production of TNF-α and IL-1β mRNA was significantly reduced by 2% SOD, similar to the inhibition noted with the application of fluocinolone (24).

MECHANISM OF SOD ANTI-INFLAMMATORY ACTIVITY

Because of the ability of SOD to stimulate the synthesis of key epidermal lipids in vitro, it was suspected that it might have an effect on PPAR. PPAR are members of the nuclear-steroid hormone-receptor super-family acting as transcription factors involved in the regulation of a number of pathways. Three PPAR isoforms have been identified to date, PPAR-α, PPAR-β, and PPARγ (25).

In human keratinocytes, PPAR-α activators, including physiologic doses of linoleic acid, induced differentiation by increasing involucrin and transglutaminase protein and mRNA levels, while also inhibiting proliferation. This study suggested a regulatory role for PPAR-α in epidermal homeostasis (26). Linoleic acid and other PPAR-α activators were also shown to decrease TEWL and accelerate the formation of mature stratum corneum and functional epidermal permeability barrier in an in vitro model of fetal rat skin development (27,28). Sheu et al found that topical treatment with PPAR-α agonists, including linoleic acid and clofibrate, 45 minutes and 4 hours after TPA application, led to a decrease in ear swelling and weight. Clofibrate also reduced oxazolone-induced dermal inflammatory infiltrates (29).

In an in vitro model of inflammation induced by ultraviolet B irradiation on human keratinocytes, PPAR-α activators (WY-14,643; clofibrate) reversed expression of pro-inflammatory cytokines, IL-6 and -8. This effect was not obtained with a selective PPAR-β activator. This anti-inflammatory activity of WY-14,643 on skin cells was confirmed in vivo. In human volunteers, topical application of the 5% PPAR-α activator, WY-14,643, was able to markedly increase the minimal

erythema dose (MED) on UVB-irradiated forearm skin to 76.5 mJ/cm^2 whereas application of vehicle on the contralateral arm increased MED to approximately 36 mJ/cm^2 (30). This suggested the possibility that PPAR-α agonists may have application as anti-inflammatory molecules in the topical treatment of various cutaneous disorders such as AD.

In a reconstructed skin model, PPAR-α agonists have also been shown to stimulate synthesis of cutaneous lipids, including cholesterol, cholesterol sulfate, and ceramides (31). PPAR-α agonists increased the expression of several specific enzymes that are involved in ceramide synthesis or in cholesterol metabolism (31).

The activation of PPAR-α by SOD was assessed in an in vitro model based on the monkey kidney cell line CV 1 cells co-transfected with PPAR-expression vectors and a luciferase gene promoter-reporter vector (PPRE-luciferase). In this model the luciferase activity that was proportional to PPAR activation was followed by luminescence measurement 24 hours after agonist stimulation. PPAR synthetic ligands were used as positive controls: fenofibric acid for PPAR-α, GW501516 for PPAR-β/δ, and rosiglitazone for PPARγ (24). After treatment with fenofibric acid, CV-1 transfected cells showed a threefold increase in relative luciferase activity (Fig. 2). Despite a much lower dose, SOD also significantly increased luciferase activity (5.3–7.8-fold) compared with the vehicle-treated cells, suggesting that SOD is a PPAR-α activator. Although luciferase activity was significantly increased following treatment with both GW501516 and rosiglitazone, SOD did not activate PPAR-β/δ, or γ, suggesting a specificity of SOD for PPAR-α activation (24).

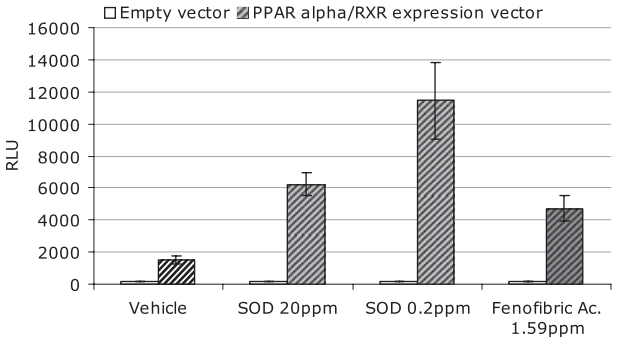

Figure 2. SOD activation of PPAR-α receptor. CV1 cells were co-transfected with expression vectors containing PPAR-α in combination with the reporter plasmid PPRE-luciferase or with empty vectors in combination with the reporter plasmid PPRE-luciferase. Transfected cells were treated for 24 hours with vehicle (negative control), SOD, or fenofibric acid (positive control) and relative luciferase activity (RLU) was determined using a luminometer (24).

THE USE OF 2% SOD IN THE MANAGEMENT OF AD

Atopic dermatitis is on the increase throughout the world (32,33). In addition to its uncomfortable cutaneous symptoms, AD leads to serious quality-of-life (QOL) issues for patients, particularly pediatric patients, and their families. In a study by Absolon et al, the psychosocial impacts of AD were similar to those in patients with epilepsy or leukemia. The rate of psychologic disturbances including excessive worries and fears and sleep difficulties discovered among eczema patients was nearly double that of controls (34).

Topical corticosteroids are the standard of care therapy for atopic flares in patients with AD (35). However, their extended use in children poses several potential risks including restriction of linear growth and bone density (35). Moreover, in addition to its well-known epidermal atrophogenic effect, topical corticosteroid therapy has been shown to lead to increased TEWL, decreased epidermal ceramides, cholesterols, and free fatty acids. Thus, although their anti-inflammatory effect is desirable, it must be balanced against the fact that the use of topical corticosteroids is limited by a significant side effect profile and may in fact contribute to skin barrier dysfunction (36). It was shown that even short-term (3 days) therapy with a potent topical corticosteroid inhibited normal epidermal lipid synthesis, leading to increased skin barrier permeability and affected stratum corneum integrity (37). The PPAR-α-agonist activity of SOD as well as the anti-inflammatory effect demonstrated in vitro and in vivo studies led to an exploration of its use in AD (38).

In a preliminary open-label clinical study, 20 women volunteers with AD and dry-to-very-dry skin and mild scaling were treated with an emulsion containing 2% SOD twice daily for 4 weeks. Table 1 shows the immediate and long-lasting improvement in skin hydration, as measured by corneometer at intervals between 1 and 24 hours following a single application of the SOD emollient (23). The twice-daily application of 2% SOD

TABLE 1. *Measurement of the Degree of Hydration of the Skin's Outer Layers Following a Single Application of 2% SOD via Corneometer™ (Electric Capacitance, Courage and Khazaka Electronic Gmbh, Köln, Germany)*

Hydration gain	Control area	2% SOD emulsion
1 hour	+0%	+48.6%*
2 hours	+1%	+58.7%*
3 hours	+0.5%	+64.4%*
24 hours	+2.9%	+34.2%*

*Statistically significant increase compared to nontreated (control) area.

emulsion for four consecutive weeks was associated with a significant restructuring of the micro-relief network (+10%) and skin surface aspect improvement (+52%). After 4 weeks of use, a 54% reduction from baseline in dryness and in flaking was noted. Study participants reported similar improvements (23).

These results were confirmed in a study with 227 children who had mild-to-moderate AD and were not receiving corticosteroid therapy for their condition. The 2% SOD cream was applied twice-daily for 30 days. Significant improvements were noted in several relevant clinical parameters, including reductions of 88% in dryness, 84% in flaking, and 80% in itching and redness (23).

The PPARα, β/δ, and γ, are ligand-activated transcription factors, and are known to exert anti-inflammatory properties. In skin, both PPAR-α and PPAR-β/δ, regulate keratinocyte proliferation/differentiation and contribute to wound healing. The three PPAR isoforms are expressed by several cell types recruited into the dermis during inflammation. Staumont-Sallé et al (39) investigated the role of PPAR-α in the regulation of AD. In order to mimic the human pathology, a mouse model of inflammatory dermatosis with immunologic features of AD was chosen. The results show that on antigen sensitization, PPAR-α-deficient mice displayed increased epidermal thickening, dermal recruitment of inflammatory cells, and lung inflammation. Topical application of a PPAR-α-agonist cream showed a significant decrease in antigen-induced skin inflammation in the AD model.

Recently Msika et al published a study demonstrating the efficacy and corticosteroid-sparing effect of an emollient containing SOD in the treatment of AD. Eighty-six patients aged 4–48 months, with moderate AD were randomized to receive corticosteroids with or without the study cream containing SOD in various treatment plans making up a total of five groups. All groups received topical corticosteroids (TRIDESONIT® desonide 0.05%; CS Dermatologie, Paris, France) to apply according to different regimens on affected skin with or without the 2% SOD cream formulation (STELATOPIA®; Mustela, DermoPediatrie, Laboratoires, Expanscience, France) over the entire body (Table 2). The subjects were evaluated by SCORAD, a clinical tool for assessing AD severity (i.e., surface area of atopic skin, erythema, edema/papulation, oozing/crusting, excoriation, lichenification, dryness of non-lesional skin, pruritus, and sleep loss). The five groups were homogeneous for SCORAD evaluation at entry in the study. After 7 and 21 days of treatment, mean SCORADs were listed for each group and at days 7 and 21, all five treatment groups showed statistically significant decreases in their SCORAD Index. However, the overall comparison of the five groups revealed no significant differences in SCORAD between the groups (Table 3). They also showed that when comparing the group applying topical corticosteroid (CT) twice-daily (group A) to the group applying the SOD-containing emollient twice-daily in conjunction with the CT once every other day (group E), group E did as well as the twice-daily CT group in reduction in the overall SCORAD index. The use of SOD-containing emollient was therefore concluded to be offering a 75% CT-sparing effect (22).

Each SCORAD item has been analyzed separately to evaluate the specific impact of the SOD emollient in group E compared with group A. Lichenification was significantly improved by −71% in group E versus −50% in group A after 7 days and an improvement of −89% and −13%, respectively, after 21 days (Fig. 3). Excoriation was significantly more improved ($p < 0.1$) in group

TABLE 3. *Outcome of the SCORAD Index After 7 and 21 Days of Treatment With or Without 2% SOD Emollient Compared to Initial SCORAD at Day 0 (22)*

Group	Score at day 0	Score at day 7	Day 0–day 7	Score day 21	Day 0–Day 21
A	33.28	13.27	−60%*	12.30	−63%*
B	34.60	13.82	−60%*	9.66	−72%*
C	34.50	10.60	−69%*	14.50	−58%*
D	35.18	12.82	−64%*	9.18	−74%*
E	35.1	16.70	−56%*	9.03	−75%*

*$p < 0.001$.

TABLE 2. *Study Groups Presenting with Mild to Moderate Atopic Dermatitis*

	A	B	C	D	E
Group size	18	17	15	17	19
Treatment					
A.M.	CT	CT + Em	CT	CT + Em	CT 1 day/2 + Em
P.M.	CT	CT + Em	–	Em	Em
Doses of corticosteroid/7 days	14	14	7	7	3.5
Corticosteroid-sparing/group A (%)	–	0	50	50	75

CT, corticosteroid; Em, 2% SOD. Each group received a treatment based on different doses of corticosteroids combined or not with application of a 2% SOD emollient (22).

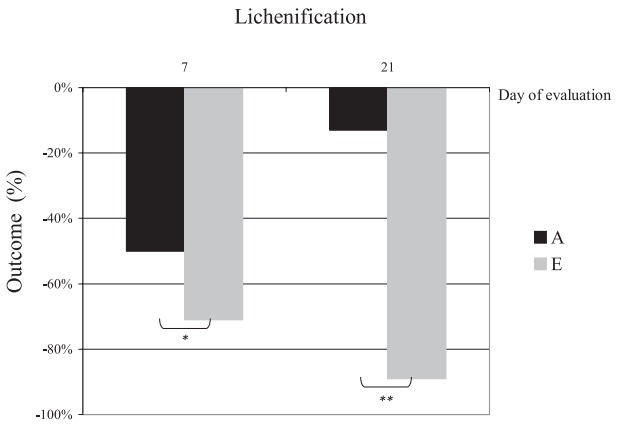

Figure 3. Outcome of lichenification after 7 and 21 days of treatment (22). Reprinted with permission from Msika P, De Belilovsky C, Piccardi N, Chebassier N, Baudouin C, Chadoutaud B. New emollient with topical corticosteroid-sparing effect in treatment of childhood atopic dermatitis: SCORAD and quality of life improvement. Pediatr Dermatol 2008;25:606–612.

E (−90%) than in group A (−73%) after 21 days of treatment, suggesting a significant steroid-sparing effect of SOD.

In addition at baseline and on day 21, QOL evaluations were performed based on Jones and Finlay criteria using two indices: the Infants' Dermatitis Quality of Life Index (IDQOL) and the Dermatitis Family Impact Questionnaire (40,41). Following study enrollment, the investigators were in charge of evaluating treatment. Enrolling pediatricians were asked to express their opinions regarding overall satisfaction with treatment. According to IDQOL results, parents reported a greater improvement in their child's quality of life with use of the 2% SOD formulation and CT for 21 days regardless of the doses of CT applied. In fact, quality of life in children treated with 2% SO cream was improved by 75% in group B, 67% in group D, and 65% in group E, whereas quality of life of children only treated with CT improved 55% in group A and 38% in group C. Furthermore, according to the Dermatitis Family Impact Questionnaire, parents also reported that the 2% SOD cream in combination with CT therapy produced better improvement in their own quality of life compared to parents of children receiving CT without 2% SOD cream. In fact, parents reported a quality of life improvement of 74% in group B, 73% in group Dm and 88% in group E, whereas group A and group C parents reported a quality of life improvement of 60% and 56%, respectively. (The most significant decreases in SCORAD for groups treated with 2% SOD cream can be correlated with the greatest improvements in QOL indexes reported for the same groups [B/D/E].) The positive effects of 2% SOD cream on AD clinically and on quality of life were confirmed by investigators' global evaluation of the treatment performed at day 0, 7, and 21 (22).

SUMMARY

Sunflower oil has been shown to be an effective emollient in a number of dermatologic settings. Recently a new SOD has been developed for use in dermatology.

Findings regarding the new SOD suggest that it may be useful for various inflammatory skin disorders characterized by an abnormal skin barrier and lipid deficiencies such as AD. Formulations of SOD have been shown to be significantly steroid-sparing, which is highly desirable when treating pediatric patients in whom the use of corticosteroids should be minimized. Sunflower oleodistillate has been shown to be a potent activator of PPAR-α. This activity suggests that there will be a number of future applications for SOD in conditions involving epidermal maturation and proliferation, such as psoriasis, as well as in barrier disorders including AD as already demonstrated.

Sunflower oleodistillate appears to be a worthwhile addition to the important player in the increasingly diverse pharmacopeia of active natural ingredients for skin care and medical therapeutics.

REFERENCES

1. Leyden JJ, Baumann LS, Downie JB, Draelos ZD. Highlights of a symposium: the role of natural ingredients in dermatology. Skin & Allergy News 2004;35(Suppl.):1–4.
2. Elmets CA, Singh D, Tubesing K et al. Cutaneous photoprotection from ultraviolet injury by green tea polyphenols. J Am Acad Dermatol 2001;44:425–432.
3. Bergfeld WF, Fowler JF, Baumann LS et al. The four seasons of skin care: the utility of natural ingredients. Cos Derm 2004;17(Suppl. 4):1–9.
4. Yokota T, Nishio H, Kubota Y et al. The inhibitory effect of glabridin from licorice extracts on melanogenesis and inflammation. Pigment Cell Res 1998;11:355–361.
5. Kang S, Chung JH, Lee JH et al. Topical *N*-acetyl cysteine and genistein prevent ultraviolet-light-induced signaling that leads to photoaging in human skin in vivo. J Invest Dermatol 2003;120:835–841.
6. Pinnell SR. Cutaneous photodamage, oxidative stress, and topical antioxidant protection. J Am Acad Dermatol 2003;48:1–19. quiz 20-12.
7. Lopez Perez G, Torres Altamirano M. Indications for sunflower oil concentrate in the treatment of atopic dermatitis. Rev Alerg Mex 2006;53:217–225.
8. Press M, Hartop PJ, Prottey C. Correction of essential fatty-acid deficiency in man by the cutaneous application of sunflower-seed oil. Lancet 1974;1:597–598.
9. Prottey C, Hartop PJ, Press M. Correction of the cutaneous manifestations of essential fatty acid deficiency in man by application of sunflower-seed oil to the skin. J Invest Dermatol 1975;64:228–234.

10. Prottey C. Essential fatty acids and the skin. Br J Dermatol 1976;94:579–587.
11. Elias PM, Brown BE, Ziboh VA. The permeability barrier in essential fatty acid deficiency: evidence for a direct role for linoleic acid in barrier function. J Invest Dermatol 1980;74:230–233.
12. Goldyne ME. Prostaglandins and cutaneous inflammation. J Invest Dermatol 1975;64:377–385.
13. Harding CR. The stratum corneum: structure and function in health and disease. Dermatol Ther 2004;17(Suppl. 1):6–15.
14. Elias PM. Epidermal lipids, barrier function and desquamation. J Invest Dermatol 1983;80(Suppl.):44–49.
15. Van Dorp DA. Essential fatty acids and prostaglandins. 24th International Congress of Pure and Applied Chemistry, Vol. 2:117. London: Butterworth, 1974.
16. Van Stratum PGC, Gottenbos JJ, Nugteren DH et al. Essential fatty acids and prostaglandins. 24th International Congress of Pure and Applied Chemistry, Vol. 2:117. London: Butterworth. 1974.
17. Darmstadt GL, Saha SK, Ahmed AS et al. Effect of topical treatment with skin barrier-enhancing emollients on nosocomial infections in preterm infants in Bangladesh: a randomised controlled trial. Lancet 2005;365:1039–1045.
18. Darmstadt GL, Saha SK, Ahmed AS et al. Effect of skin barrier therapy on neonatal mortality rates in preterm infants in Bangladesh: a randomized, controlled, clinical trial. Pediatrics 2008;121:522–529.
19. Nachbar F, Korting HC. The role of vitamin E in normal and damaged skin. J Mol Med 1995;73:7–17.
20. Yasukawa K, Takido M, Matsumoto T et al. Sterol and triterpene derivatives from plants inhibit the effects of a tumor promoter, and sitosterol and betulinic acid inhibit tumor formation in mouse skin two-stage carcinogenesis. Oncology 1991;48:72–76.
21. Rahman S, Bhatia K, Khan AQ et al. Topically applied vitamin E prevents massive cutaneous inflammatory and oxidative stress responses induced by double application of 12-*O*-tetradecanoylphorbol-13-acetate (TPA) in mice. Chem Biol Interact 2008;172:195–205.
22. Msika P, De Belilovsky C, Piccardi N et al. New emollient with topical corticosteroid-sparing effect in treatment of childhood atopic dermatitis: SCORAD and quality of life improvement. Pediatr Dermatol 2008;25: 606–612.
23. Piccardi N, Piccirilli A, Choulot JC, Msika P. Sunflower oil oleodistillate for atopy treatment: an in vitro and clinical evaluation. J Invest Dermatol. 2001;117 (2):390–423. [Abstract 169]
24. Dubuquoy L, Piccardi N, Msika P et al. Sunflower oleodistillate a new natural PPAR alpha activator with anti-inflammatory properties. J Invest Dermatol. 2005;124(4 Suppl.) [Abstract 349]
25. Kuenzli S, Saurat JH. Peroxisome proliferator-activated receptors in cutaneous biology. Br J Dermatol 2003; 149:229–236.
26. Hanley K, Jiang Y, He SS et al. Keratinocyte differentiation is stimulated by activators of the nuclear hormone receptor PPARalpha. J Invest Dermatol 1998;110:368–375.
27. Hanley K, Jiang Y, Crumrine D et al. Activators of the nuclear hormone receptors PPARalpha and FXR accelerate the development of the fetal epidermal permeability barrier. J Clin Invest 1997;100:705–712.
28. Komuves LG, Hanley K, Jiang Y et al. Ligands and activators of nuclear hormone receptors regulate epidermal differentiation during fetal rat skin development. J Invest Dermatol 1998;111:429–433.
29. Sheu MY, Fowler AJ, Kao J et al. Topical peroxisome proliferator activated receptor-alpha activators reduce inflammation in irritant and allergic contact dermatitis models. J Invest Dermatol 2002;118:94–101.
30. Kippenberger S, Loitsch SM, Grundmann-Kollmann M et al. Activators of peroxisome proliferator-activated receptors protect human skin from ultraviolet-B-light-induced inflammation. J Invest Dermatol 2001;117:1430–1436.
31. Rivier M, Castiel I, Safonova I et al. Peroxisome proliferator-activated receptor-alpha enhances lipid metabolism in a skin equivalent model. J Invest Dermatol 2000;114:681–687.
32. Guttman-Yassky E. Atopic dermatitis. Curr Probl Dermatol 2007;35:154–172.
33. Cambazard F, Guillet G, de Belilovsky C et al. Atopia: atopic dermatitis in more than 3000 young children. Epidemiology and management in Europe. Poster presented at 10th Meeting of Practical Pediatrics, Paris, France, January 27–28, 2006.
34. Absolon CM, Cottrell D, Eldridge SM et al. Psychological disturbance in atopic eczema: the extent of the problem in school-aged children. Br J Dermatol 1997;137: 241–245.
35. Hanifin JM, Cooper KD, Ho VC et al. Guidelines of care for atopic dermatitis, developed in accordance with the American Academy of Dermatology (AAD)/American Academy of Dermatology Association "Administrative Regulations for Evidence-Based Clinical Practice Guidelines." J Am Acad Dermatol 2004;50:391–404.
36. Kolbe L, Kligman AM, Schreiner V et al. Corticosteroid-induced atrophy and barrier impairment measured by non-invasive methods in human skin. Skin Res Technol 2001;7:73–77.
37. Kao JS, Fluhr JW, Man MQ et al. Short-term glucocorticoid treatment compromises both permeability barrier homeostasis and stratum corneum integrity: inhibition of epidermal lipid synthesis accounts for functional abnormalities. J Invest Dermatol 2003;120:456–464.
38. Imokawa G. Lipid abnormalities in atopic dermatitis. J Am Acad Dermatol 2001;45(1 Suppl.):S29–S32.
39. Staumont-Salle D, Abboud G, Brenuchon C et al. Peroxisome proliferator-activated receptor alpha regulates skin inflammation and humoral response in atopic dermatitis. J Allergy Clin Immunol 2008;121:962–968 e966.
40. Lewis-Jones MS, Finlay AY, Dykes PJ. The Infants' Dermatitis Quality of Life Index. Br J Dermatol 2001; 144:104–110.
41. Lawson V, Lewis-Jones MS, Finlay AY et al. The family impact of childhood atopic dermatitis: the Dermatitis Family Impact Questionnaire. Br J Dermatol 1998; 138:107–113.