The role of cannabinoids in dermatology

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Twenty-eight states currently allow for comprehensive public medical cannabis programs, and this number continues to grow. Approximately 1 in 10 adult cannabis users in the United States use it for medical purposes. Numerous studies have investigated its uses for chronic pain, spasticity, anorexia, and nausea. In recent years, researchers have also investigated its use for the treatment of dermatologic conditions including pruritus, inflammatory skin disease, and skin cancer.

Perhaps the most promising role for cannabinoids is in the treatment of itch. In a study of patients with uremic pruritus on maintenance hemodialysis, topical application of a cream with structured physiologic lipids (derma membrane structure) and endogenous cannabinoids applied twice daily for 3 weeks completely eliminated pruritus in 8 of 21 patients (38%). The authors suggested that the well-tolerated product might work by reducing xerosis. Stander et al further studied 22 patients with prurigo, lichen simplex, and pruritus who applied an emollient cream with palmitoylethanolamide (PEA). PEA, which stimulates anandamide (endocannabinoid) activation of cannabinoid 1 (CB1) receptors, reduced itch by 86.4% and was well tolerated by patients. Most recently, WIN 55,212-2, a cannabinoid agonist, was found to reduce serotonin-induced itching in a dose-dependent manner through intraperitoneal administration in mice. When the investigators used neurotoxins to deplete serotonin in the spinal cord, they reported no change in these results. Thus, they suggested that the cannabinoids may work independently of descending inhibitory pathways.

Cannabinoids may also have anti-inflammatory properties useful for the treatment of both allergic contact dermatitis and atopic dermatitis. Petrosino et al reported that mice released PEA in response to 2,4-dinitrofluorobenzene—induced allergic contact dermatitis as an endogenous protective agent. PEA may work to reduce later stages of allergic contact dermatitis, including mast-cell infiltration, angiogenesis, and itching. Tetra-hydrocannabinol (THC) may also demonstrate anti-inflammatory effects independent of CB1 and cannabinoid 2 (CB2) receptors. In mice, topical THC decreased allergic-contact ear swelling and inflammation in both wild-type mice and mice lacking CB1 and CB2 receptors. Topical THC limited myeloid immune cell recruitment by a decreasing T-cell production of interferon-γ and keratinocyte production of CCL2, CCL8, and CXL10 chemokines. In terms of atopic dermatitis, the activation of CB1 receptors in mice has been found to improve epidermal barrier function, decrease Th2-mediated inflammatory response, and suppress mast cells.

Limited studies on its uses for other skin conditions also exist. Cannabinoids may be useful for...
psoriasis, as THC, cannabidiol, cannabinol, and cannabigerol have been found to inhibit keratinocyte proliferation in hyperproliferating human keratinocyte cell lines.\textsuperscript{13} In mice, CB1 knockout mice were protected from bleomycin-induced fibrosis, and the selective CB1 receptor agonist N-(2-chloroethyl)-5Z,8Z,11Z,14Z-eicosatetraenamide was shown to promote bleomycin-induced fibrotic effects. Tight skin/C\textsuperscript{0}1 mice, characterized by an accumulation of collagen fibers in the hypodermis and an absence of inflammatory infiltrates, were not protected against fibrosis in CB1 knockout models. Thus, the authors suggested that the profibrotic effects of CB1 are mediated by the effects of CB1 on leukocytes, and CB1 ablation may be used as a potential treatment for the early inflammatory stages of scleroderma and systemic sclerosis.\textsuperscript{14} It is important to note that other studies have demonstrated beneficial antitumorigenic effects of cannabinoid activation (see next paragraph),\textsuperscript{15} which were not mentioned in this study. Furthermore, in a recent single-blinded and comparative study in 11 humans, Ali et al\textsuperscript{16} investigated the use of 3% cannabis seed extract cream applied topically for the use of acne and seborrheic dermatitis. Treated patients had lower levels of skin sebum and erythema.


dermatologist are already implementing cannabinoid therapy into their practices. For pruritic patients without rash and with normal thyroid, liver, and kidney function, one of our authors recommends the use of a PEA-containing cream. A PEA-containing cream has also been investigated for use in pruritic patients with atopic dermatitis\textsuperscript{25} and has anecdotally relieved pruritus in several patients in our clinic at the University of Colorado. Although cannabinoids may have anti-inflammatory and antitumor effects, further clinical research is needed before they can be used for these purposes clinically. Table I includes a list of cannabinoids discussed and their potential dermatologic uses, sorted by psychoactive inactivity versus activity.

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<th>Weak/No psychotropic effects</th>
<th>Potential uses</th>
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<tr>
<td>Cannabinoid</td>
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<tr>
<td>Cannabidiol (CBD)</td>
<td>Psoriasis\textsuperscript{13}</td>
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<tr>
<td>Cannabigerol (CBG)</td>
<td>Psoriasis\textsuperscript{13}</td>
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<tr>
<td>Palmitoylethanolamide (PEA)*</td>
<td>Pruritus,\textsuperscript{6} allergic contact dermatitis,\textsuperscript{6-9} atopic dermatitis,\textsuperscript{25} other eczematous dermatoses,\textsuperscript{24} melanoma\textsuperscript{22}</td>
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<td>Cannabinoid</td>
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<tr>
<td>$\Delta$ 9-tetrahydrocannabinol ($\Delta$9-THC)</td>
<td>Allergic contact dermatitis,\textsuperscript{5} psoriasis,\textsuperscript{13} melanoma\textsuperscript{23}</td>
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<td>Cannabinol (CBN)</td>
<td>Psoriasis\textsuperscript{13}</td>
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*Not strictly considered an endocannabinoid; PEA does not bind to CB1 and CB2 receptors, but works by enhancing endocannabinoid binding to these receptors.
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REFERENCES


