Topical Cannabinoids in Dermatology

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PRACTICE **POINTS**

- Topical cannabinoids are advertised by companies as treatment options for numerous dermatologic conditions.
- Despite promising data in rodent models, there have been no rigorous studies to date confirming efficacy or safety in humans.
- Dermatologists should therefore inquire with patients about the use of any topical cannabinoid products, especially around the time of planned procedures, as they may affect treatment outcomes.

Topical cannabinoids are increasingly utilized by dermatology patients for a range of disorders; however, the acceptance of these over-the-counter products has far outpaced scientific investigation into their safety and efficacy. Here, we review the studies of topical cannabinoids in skin conditions and assess their current place in dermatology practice.

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The prevalence of topical cannabinoids has risen sharply in recent years. Commercial advertisers promote their usage as a safe means to treat a multitude of skin disorders, including atopic dermatitis (AD), psoriasis, and acne. Topical compounds have garnered interest in laboratory studies, but the purchase of commercial formulations is limited to over-the-counter products from unregulated suppliers. In this article, we review the scientific evidence behind topical cannabinoids and evaluate their role in clinical dermatology.

Background

Cannabis is designated as a Schedule I drug, according to the Controlled Substances Act of 1970. This listing is given to substances with no therapeutic value and a high potential for abuse. However, as of 2017, 29 states and the District of Columbia have laws legalizing cannabis in some capacity. These regulations typically apply to medicinal use, though several states have now legalized recreational use.

Cannabinoids represent a broad class of chemical compounds derived from the cannabis plant. Originally, this class only comprised phytocannabinoids, cannabinoids produced by the cannabis plant. Tetrahydrocannabinol (THC) is the most well-known phytocannabinoid and leads to the psychoactive effects typically associated with cannabis use. Later investigation led to the discovery of endocannabinoids, cannabinoids that are naturally produced by human and animal bodies, as well as synthetic cannabinoids.[1] Cannabidiol is a phytocannabinoid that has been investigated in neurologic and anti-inflammatory conditions.[2-4]

Cannabinoids act as agonists on 2 principal receptors—cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2)—which are both G protein–coupled receptors (Figure).[5] Both have distinct distributions throughout different organ systems, to which cannabinoids (eg, THC, cannabidiol, endocannabinoids) show differential binding.[6,7] Importantly, the expression of CB1 and CB2 has been identified on sensory nerve fibers, inflammatory cells, and adnexal structures of human skin.[8] Based on these associations, topical application of cannabinoids has become a modality of interest for dermatological disorders. These formulations aim to influence cutaneous morphology without producing psychoactive effects.

Topical Cannabinoids in Inflammatory Disorders

Atopic dermatitis has emerged as an active area of investigation for cannabinoid receptors and topical agonists (Table 1). In an animal model, Kim et al[9] examined the effects of CB1 agonism on skin inflammation. Mice treated with topical CB1 agonists showed greater recovery of epidermal barrier function in acutely abrogated

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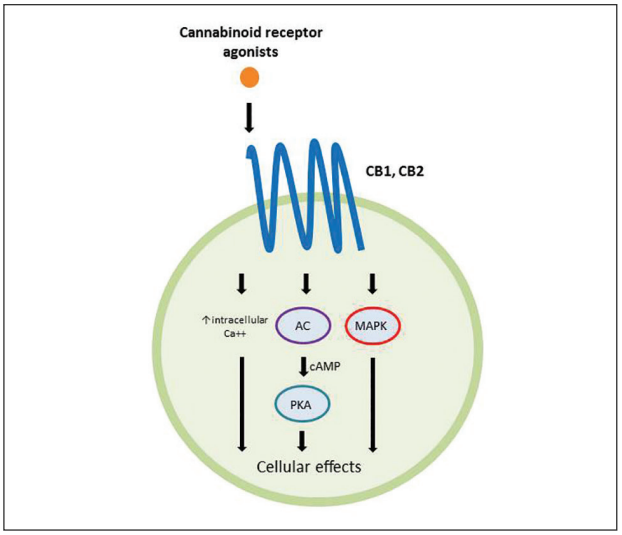

Signaling pathways associated with cannabinoid receptor activation. CB1 indicates cannabinoid receptor type 1; CB2, cannabinoid receptor type 2; AC, adenylyl cyclase; cAMP, cyclic adenosine monophosphate; PKA, protein kinase A; MAPK, mitogen-activated protein kinase.

skin relative to those treated with a vehicle preparation. In addition, agonism of CB1 led to significant ($P<.001$) decreases in skin fold thickness among models of acute and chronic skin inflammation.[9]

Nam et al[10] also examined the role of topical CB1 agonists in mice with induced AD-like symptoms. Relative to treatment with vehicle, CB1 agonists significantly reduced the recruitment of mast cells ($P<.01$) and lowered the blood concentration of histamine ($P<.05$). Given the noted decrease in the release of inflammatory mediators, the authors speculated that topical agonsim of CB1 may prove useful in several conditions related to mast cell activation, such as AD, contact dermatitis, and psoriasis.[10]

The anti-inflammatory properties of topical THC were evaluated by Gaffal et al.[11] In a mouse model of allergic contact dermatitis, mice treated with topical THC showed decreases in myeloid immune cell infiltration, with these beneficial effects existing even in mice with deficient CB1 and CB2 receptors. These results support a potentially wide anti-inflammatory activity of topical THC.[11]

Topical Cannabinoids in Pain Management

The effects of smoked cannabis in treating pain have undergone thorough investigation over recent years. Benefits have been noted in treating neuropathic pain, particularly in human immunodeficiency virus–associated sensory neuropathy.[12-15] Smoked cannabis also may provide value as a synergistic therapy with opioids, thereby allowing for lower opioid doses.[16]

In contrast, research into the relationship between topical application of cannabinoids and nociception remains in preliminary stages (Table 2). In a mouse model, Dogrul et al[17] assessed the topical antinociceptive potential of a mixed CB1-CB2 agonist. Results showed significant ($P<.01$) and dose-dependent antinociceptive effects relative to treatment with a vehicle.[17] In a related study, Yesilyurt et al[18] evaluated whether a mixed CB1-CB2 agonist could enhance the antinociceptive effects of topical opioids. Among mice treated with the combination of a cannabinoid agonist and topical morphine, a significantly ($P<.05$) greater analgesic effect was demonstrated relative to topical morphine alone.[18]

Studies in humans have been far more limited. Phan et al[19] conducted a small, nonrandomized, open-label trial of a topical cannabinoid cream in patients with facial postherpetic neuralgia. Of 8 patients treated, 5 noted a mean pain reduction of 87.8%. No comparison vehicle was used. Based on this narrow study design, it is difficult to extrapolate these positive results to a broader patient population.[19]

Commercial Products

Although preliminary models with topical cannabinoids have shown potential, large-scale clinical trials in humans have yet to be performed. Despite this lack of investigation, commercial formulations of topical cannabinoids are available to dermatology patients. These formulations are nonstandardized, and no safety data exists regarding their use. Topical cannabinoids on the market may contain various amounts of active ingredient and may be combined with a range of other compounds.

In dermatology offices, it is not uncommon for patients to express an intention to use topical cannabinoid products following their planned treatment or

TABLE 1. Review of Inflammatory Disorders in Murine Models Treated With Cannabinoids

Reference (Year)	Simulated Disorder	Treatment Agent	Results
Kim et al[9] (2015)	Atopic dermatitis	CB1 agonist	Increases in barrier recovery rate vs vehicle and noted anti-inflammatory effects
Nam et al[10] (2016)	Atopic dermatitis	CB1 agonist	Decreases in mast cell proliferation and recruitment, along with reduced blood histamine levels
Gaffal et al[11] (2013)	Allergic contact dermatitis	Topical THC	Decreases in keratinocyte-derived proinflammatory mediators

Abbreviations: CB1, cannabinoid receptor type 1; THC, tetrahydrocannabinol.

TABLE 2. Review of Cannabinoids for Pain Management

Reference (Year)	Reason for Pain Management	Research Model	Treatment Agent	Results
Dogrul et al[17] (2003)	N/A	Murine	Mixed CB1-CB2 agonist	Dose-dependent antinociceptive effects with topical application; topical and intrathecal administration produced a synergistic effect
Yesilyurt et al[18] (2003)	N/A	Murine	Mixed CB1-CB2 agonist	Synergistic antinociceptive effects with topical application combined with topical morphine
Phan et al[19] (2010)	Facial postherpetic neuralgia	Human	Open-label application of cream containing cannabinoid receptor agonist *N*-palmitoylethanolamine	5/8 patients reported a mean pain reduction of 87.8% (no adverse events reported)

Abbreviations: N/A, not available; CB1, cannabinoid receptor type 1; CB2, cannabinoid receptor type 2.

procedure. Patients also have been known to use topical cannabinoid products prior to dermatologic procedures, sometimes in place of an approved topical anesthetic, without consulting the physician performing the procedure. With interventions that lead to active areas of wound healing, the application of such products may increase the risk for contamination and infection. Therefore, patients should be counseled that the use of commercial topical cannabinoids could jeopardize the success of their planned procedure, put them at risk for infection, and possibly lead to systemic absorption and/or changes in wound-healing capacities.

Conclusion

Based on the results from recent animal models, cannabinoids may have a role in future treatment algorithms for several inflammatory conditions. However, current efficacy and safety data are almost entirely limited to preliminary animal studies in rodents. In addition, the formulation of topical cannabinoid products is nonstandardized and poorly regulated. As such, the present evidence does not support the use of topical cannabinoids in dermatology practices. Dermatologists should ask patients about the use of any cannabinoid products as part of a treatment program, especially given the unsubstantiated claims often made by unscrupulous advertisers. This issue highlights the need for further research and regulation.

REFERENCES

1. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. *Pharmacol Rev.* 2006;58:389-462.
2. Giacoppo S, Galuppo M, Pollastro F, et al. A new formulation of cannabidiol in cream shows therapeutic effects in a mouse model of experimental autoimmune encephalomyelitis. *Daru.* 2015;23:48.
3. Hammell DC, Zhang LP, Ma F, et al. Transdermal cannabidiol reduces inflammation and pain-related behaviours in a rat model of arthritis. *Eur J Pain.* 2016;20:936-948.
4. Schicho R, Storr M. Topical and systemic cannabidiol improves trinitrobenzene sulfonic acid colitis in mice. *Pharmacology.* 2012;89:149-155.
5. Howlett AC, Barth F, Bonner TI, et al. International Union of Pharmacology. XXVII. Classification of cannabinoid receptors. *Pharmacol Rev.* 2002;54:161-202.
6. Pertwee RG. The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol.* 2008;153:199-215.
7. Svizenska I, Dubovy P, Sulcova A. Cannabinoid receptors 1 and 2 (CB1 and CB2), their distribution, ligands and functional involvement in nervous system structures—a short review. *Pharmacol Biochem Behav.* 2008;90:501-511.
8. Stander S, Schmelz M, Metze D, et al. Distribution of cannabinoid receptor 1 (CB1) and 2 (CB2) on sensory nerve fibers and adnexal structures in human skin. *J Dermatol Sci.* 2005;38:177-188.
9. Kim HJ, Kim B, Park BM, et al. Topical cannabinoid receptor 1 agonist attenuates the cutaneous inflammatory responses in oxazolone-induced atopic dermatitis model. *Int J Dermatol.* 2015;54:E401-E408.
10. Nam G, Jeong SK, Park BM, et al. Selective cannabinoid receptor-1 agonists regulate mast cell activation in an oxazolone-induced atopic dermatitis model. *Ann Dermatol.* 2016;28:22-29.
11. Gaffal E, Cron M, Glodde N, et al. Anti-inflammatory activity of topical THC in DNFB-mediated mouse allergic contact dermatitis independent of CB1 and CB2 receptors. *Allergy.* 2013;68:994-1000.
12. Abrams DI, Jay CA, Shade SB, et al. Cannabis in painful HIV-associated sensory neuropathy: a randomized placebo-controlled trial. *Neurology.* 2007;68:515-521.
13. Ellis RJ, Toperoff W, Vaida F, et al. Smoked medicinal cannabis for neuropathic pain in HIV: a randomized, crossover clinical trial. *Neuropsychopharmacology.* 2009;34:672-680.
14. Wilsey B, Marcotte T, Deutsch R, et al. Low-dose vaporized cannabis significantly improves neuropathic pain. *J Pain.* 2013;14:136-148.
15. Wilsey B, Marcotte T, Tsodikov A, et al. A randomized, placebo-controlled, crossover trial of cannabis cigarettes in neuropathic pain. *J Pain.* 2008;9:506-521.
16. Abrams DI, Couey P, Shade SB, et al. Cannabinoid-opioid interaction in chronic pain. *Clin Pharmacol Ther.* 2011;90:844-851.
17. Dogrul A, Gul H, Akar A, et al. Topical cannabinoid antinociception: synergy with spinal sites. *Pain.* 2003;105:11-16.
18. Yesilyurt O, Dogrul A, Gul H, et al. Topical cannabinoid enhances topical morphine antinociception. *Pain.* 2003;105:303-308.
19. Phan NQ, Siepmann D, Gralow I, et al. Adjuvant topical therapy with a cannabinoid receptor agonist in facial postherpetic neuralgia. *J Dtsch Dermatol Ges.* 2010;8:88-91.