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Review

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Nanotechnology to deliver cannabinoids in dermatology

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Abstract

Cannabis-derived compounds and therapies targeting the endocannabinoid system (ECS) benefit clinical conditions beyond current indications. As our understanding of the ECS in the skin continues to develop, cannabinoids rapidly show promise for treating cutaneous pathology. However, unstable pharmacokinetics, bioavailability, and skin permeability have been significant constraints on their utility in dermatology. As cannabinoids shift from commercial herbal preparations to prescription drugs, nano-sized drug delivery strategies can tackle these physiochemical limitations and allow well-designed clinical trials to establish safety and efficacy. This review summarizes the latest evidence for cannabinoids for skin disease, details the challenges of formulating cannabinoids, and highlights how the success of nanomedicine across therapeutic fields can translate to novel nano-cannabinoid therapeutics in dermatology.

Keywords: nanomedicine, cannabinoids, endocannabinoid system, dermatology, inflammation, pharmacokinetics

Purpose and Rationale

Cannabinoids are increasingly showing promise for treating a wide range of diseases. With the discovery of a rich endocannabinoid system (ECS) in the skin,[1] exploration of various compounds for dermatological conditions has been surging. The molecular mechanisms of cannabinoid activity in inflammatory and neoplastic skin conditions are complex,[2] and although mixed evidence has complicated understanding of their roles, cannabinoids exhibit anti-inflammatory and antitumor effects against cutaneous pathologies, including asteatotic eczema, pruritus, melanoma, and psoriasis.[3-6] The utility of cannabinoids has been limited by significant variations in bioavailability, pharmacokinetics, skin permeability, and accompanying ingredients in formulations.[7-9] Leveraging nanotechnology can overcome the physiochemical limitations of promising active ingredients by stabilizing solubility and degradation kinetics and controlling the release of loaded molecules.[10] In this review, we briefly summarize the evidence for dermatological applications of cannabinoids and highlight the potential for nanoformulation in effective, targeted delivery.

Summary of Literature

Pathophysiology

The pharmacological class of cannabinoids includes endogenous (endocannabinoids), plant-derived (phytocannabinoids), and synthetic analogs. CB1 and CB2 are G protein-coupled receptors (GPCR) that mediate the effects of cannabinoid ligands. CB1, present in high levels in the central nervous system, is associated with the psychoactive effects of cannabinoids, whereas CB2 modulates inflammation and immune infiltration. The ECS receptors and other regulatory proteins are expressed in cutaneous nerves, mast cells, fibroblasts, melanocytes, and keratinocytes.[1,11] Cannabimimetic agents that bind selectively to CB2 may exhibit anti-inflammatory activity without the potent psychoactive effects through CB1. Cannabinoids have also been shown to interact with other receptor families, such as peroxisome-proliferative-activated receptor-γ (PPAR-γ) and the arachidonic acid pathway.[12,13] In fact, endocannabinoids' structural similarity to arachidonic acid and

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other membrane fatty acids may explain their role in innate immunity. Endocannabinoids, such as arachidonoylethanolamide (AEA), are produced by various immune cell populations to respond to microbial antigenic stimuli, such as lipopolysaccharide (LPS),[14] and function as chemotactic agents for leukocytes.[15] The activated immune cells also upregulate expression of CB1 and CB2, suggesting that the ECS may be pro-inflammatory in the setting of infection.[16]

In models of chronic inflammation, however, non-psychoactive synthetic cannabinoids, such as WIN55,212-2, have been shown to decrease pro-inflammatory cytokines and chemokines, such as tumor necrosis factor (TNF), interleukin (IL)- 1β, and CXC-chemokine ligand 8 (CXCL8).[17,18] Additionally, CB2 agonists seem to exhibit T_H2 immune bias, with increased expression of T_H2-cell-promoting transcription factor GATA-binding protein 3 (GATA3) and decreased T_H1-cell-promoting cytokines.[19,20], GPCRs, such as those activated by cannabinoid ligands, actively promote the resolution of inflammation rather than a passive dissipation of chemoattractants. The specialized pro-resolving mediators (SPM) from GPCR activation, including resolvins and protectins, halt polymorphonuclear leukocyte (PMN) infiltration, clear apoptotic debris, and drive inflammatory tissue back to homeostasis.[21] These dynamic counterregulatory pathways stimulate wound healing and restore normal structure and function. Although the immunomodulatory mechanisms vary among different compounds and disease models and even largely remain unelucidated, cannabinoids demonstrate therapeutic potential through their antimicrobial, anti-inflammatory, and pro-resolution properties.

Applications in Dermatology

The abundance of CB1, CB2, and regulatory proteins of the ECS in various cell populations of the skin drive the utility of cannabinoids in treating an array of cutaneous diseases (Figure 1). Pre-clinical findings are rapidly leading to large, randomized controlled trials (RCTs), and commercially available cannabinoid preparations are increasingly indicating results for individual patients.

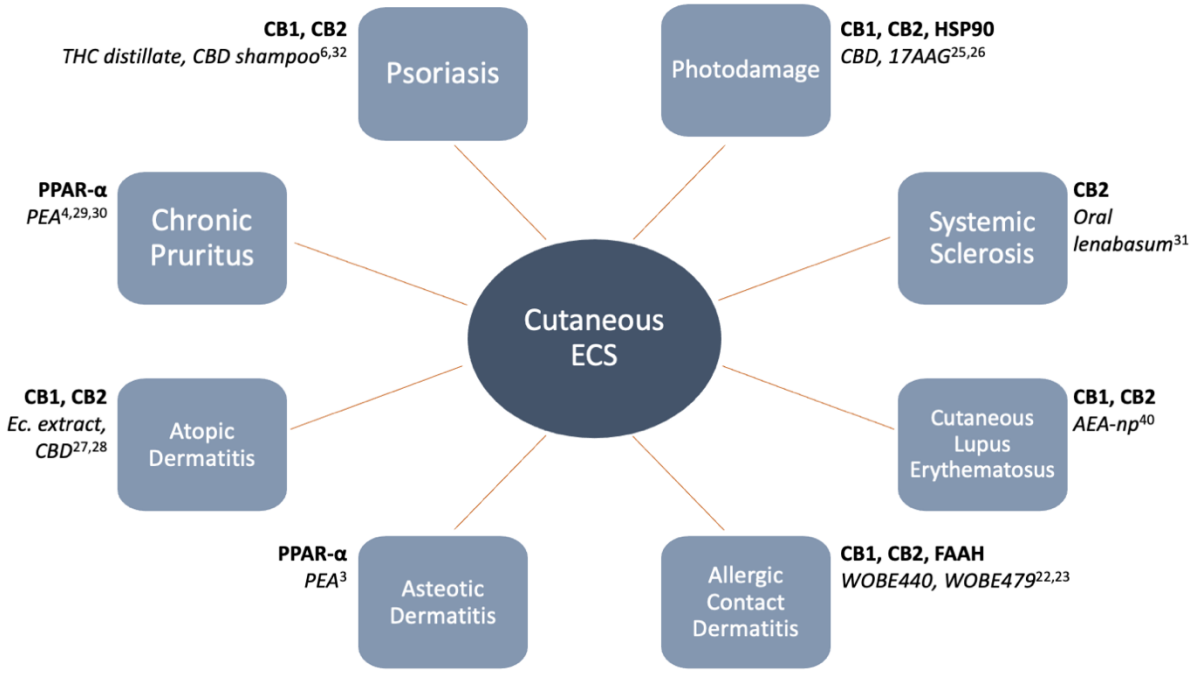

*Figure 1: Pharmacologic targets of the cutaneous endocannabinoid system (ECS) for treating various skin disorders. Targeted receptors are indicated in **bold**, and the investigative treatments discussed are italicized. References for supporting evidence are indicated. CB1: cannabinoid receptor 1; CB2: cannabinoid receptor 2; CBD: cannabidiol; HSP90: heat shock protein 90; 17AAG: HSP90 inhibitor AEA-np: arachidonoylethanolamide nanoparticles; FAAH: fatty acid amide hydrolase; WOBE440, WOBE479; FAAH inhibitors; PPAR-a: peroxisome-proliferative-activated receptor- a; PEA: N-palmitoylethanolamine; Ec.: Echinacea purpurea; THC: tetrahydrocannabinol*

Translational research models propose that homeostatic endocannabinoid signalling may be integral to regulating cutaneous immune processes, with implications for many inflammatory dermatologic diseases. Downregulating CB1 and CB2 through genetic deletion or pharmacologic inhibition exacerbated allergic skin inflammation in a murine model, whereas genetic deletion of the endocannabinoid-degrading enzyme fatty acid amide hydrolase (FAAH) or pharmacologic activation of CB1 and CB2 reduced cutaneous contact hypersensitivity.[22]

Furthermore, topical FAAH inhibitors attenuate the inflammatory response induced by Toll-like receptor (TLR)-2 by increasing endocannabinoid levels with subsequent activation of CB1 and CB2 in keratinocytes.[23] A non-psychotropic phytocannabinoid cannabidiol suppresses seborrhoea-mimicking lipogenesis, sebocyte proliferation, and pro-inflammatory cytokines induced by TLR-4, reflecting its potential for acne vulgaris.[24] Proteomic data of 3D-cultured keratinocytes pre-treated with cannabidiol and subsequently irradiated with UVA/B exhibits decreased nuclear factor kappa B (NFκB)-dependent inflammation and carcinogenic heat shock protein 90 (HSP90), proposing photoprotective effects of the phytocannabinoid.[25,26]

Asteatotic dermatitis, atopic dermatitis, and pruritus have the most evidence to date through clinical studies. Compared to control emollient, emollient with 0.3% N-palmitoylethanolamine (PEA) and 0.21% N-acetylethanol-amine decreased scale, dryness, and itching, accompanied by improved skin capacitance and hydration by corneometer, in patients with asteatotic dermatitis.[3] In patients with atopic dermatitis, *Echinacea purpurea* extract 2 mg/cm^2 significantly reduced local SCORAD and increased levels of epidermal lipids, [27] and topical cannabidiol 1% improved Eczema Area and Severity Index (EASI), Visual Analogue itch severity Scale (VAS), and 5-D Pruritus scores with minimal stinging or discomfort.[28] Topical PEA 0.3% formulations decreased VAS and verbal itching rating scale (VRS) scores, reduced transepidermal water loss, and improved sleep quality in patients with chronic pruritus.[29,30] A phase II RCT of an oral CB2 agonist (lenabasum 5 mg, 20 mg, 40 mg daily) safely improved skin burden, patient-reported function, and inflammation and fibrosis under skin histology with diffuse cutaneous systemic sclerosis.[31] Cases of individual patients with recalcitrant inflammatory skin disease or preference for "natural" treatments, resolving with topical medical cannabinoids, are increasingly reported, [4,6,32,33] emphasizing the need for further, well-designed clinical trials assessing safety and efficacy in larger samples.

Overall, novel, safe, and effective topicals with more favorable risk-benefit profiles, compared to topical corticosteroids or calcineurin inhibitors, are sorely needed for chronic cutaneous inflammation, and anti-inflammatory properties cannabinoids show promise for effective topical application with minimal local or systemic side effects.

Challenges for Cannabinoid Applications

Although commercially available topicals and United States Food and Drug Administration (FDA)-approved oral and oromucosal cannabinoid preparations are flooding the market, incomplete mechanistic understanding and the physiochemical properties of cannabinoid compounds have hindered wider medical adoption to date. Limitations in solubility, stability, permeation, and metabolism result in high individual variability in pharmacokinetics. Many cannabinoids are lipophilic, rendering their oral and transmucosal bioavailability irregular.[34] These compounds are also readily degraded due to changes in light and temperature, requiring appropriate oil matrices to reduce oxidation and impurities.[7] Rapid permeation and metabolism after systemic and even topical delivery may curb the intended effects.[7]

For topical cannabinoid formulations, few *in vitro* and *in vivo* studies have explored how the vehicle affects the permeation profile. The therapeutic ingredient must penetrate the hydrophobic stratum corneum, permeating and retaining the more hydrophilic lower layers of the epidermis. The poor aqueous solubility and rapid degradation *in vivo* have been key obstacles for topical administration. In addition, multiple inherent crystalline structures for many cannabinoid compounds further complicate formulation as these polymorphisms can lead to changes in molecular conformations that can also influence solubility and degradation.[8,35] Drug

delivery vehicles that can adequately maintain the intended drug dose in solute form while ensuring the physical stability of the preparation are crucial for the dermatologic utility of cannabinoids.

Nanoformulation to Address Challenges to Cannabinoid Use

Nanotechnology is rapidly becoming instrumental in formulating inflexible actives for both systemic and topical delivery. Mixtures of oils, solvents, and surfactants that produce nano-sized droplets upon contact with aqueous solutions stabilize unfavorable pharmacokinetics. Nanoparticles have been developed for a broad list of volatile active pharmacological ingredients. They have been described extensively in pre-clinical models, and clinical trials for various disease states.[36-39] Nanoformulation can solve the physiochemical constraints outlined above for many dermatologic applications.

By dramatically decreasing droplet size, nanoemulsion boosts the surface-to-volume ratio and increases diffusion and aqueous solubility.[10] Other molecules easily modified by environmental changes and rapid degradation kinetics have successfully been stabilized by nanoencapsulation.[36,37] For topical delivery limited to the skin and targeting skin-specific cell receptors, nanoparticles promote the interaction between the lipid matrix and skin strata and sustain a controlled release of the loaded active molecule.[10] Consequently, nanoformulation may allow penetration into and retention of cannabinoids in the epidermis, allowing interaction with the cutaneous ECS and better exertion of their potential therapeutic effects. Topical delivery of 4% AEA nanoparticles (AEA-np) significantly improved the cutaneous lesions of MRL/lpr lupus-prone mice, a murine model for chronic cutaneous lupus erythematosus (CLE).[40] Mice treated with AEA-np had significantly lower CLE Disease Area and Severity Index (CLASI) scores clinically and histologically than controls,[40] suggesting that the cutaneous ECS can effectively be modulated by nanoformulation, a highly lipophilic endocannabinoid.

Comparing concentrations of AEA-np in pre-clinical data to traditional formulations of AEA from clinical studies is difficult. However, the same nanoparticle platform has been shown under fluorescence microscopy to localize to the skin strata, collect in the hair follicle, and diffuse across the epidermis and base of the hair follicle.[41] Therefore, nanoparticles likely deliver higher effective concentrations than traditional preparations of the same active ingredient, and systemic side effects are likely minimized by the controlled release of the nanoparticles, despite the vasculature of hair follicles. Further proof-of-concept investigations of topical nano-preparations of cannabinoids with abundant clinical and translational evidence are needed to study their potential in skin disease.

Since the FDA approval of Doxil® in 1995, more than 20 nano-formulated, systemic drugs have completed phase III clinical trials, primarily for malignancies and neurologic diseases. The majority aim to target diseased cells via the bloodstream and passively diffuse the active drug at the tumor site, and newer breakthroughs rely on the triggered release of a drug in response to a stimulus, such as heat (ThermoDox®,[42]). Transdermal platforms are beneficial in bypassing first-pass oral metabolism and systemically administer lipophilic molecules less than 500 Da in molecular weight. For larger, hydrophilic macromolecules, nanoformulation and permeation enhancers can overcome the barrier function of the stratum corneum and increase bioavailability.[43] Nagai et al. reported that menthol increased the epidermal and dermal penetration of raloxifene nanoparticles in a rat model of osteoporosis, and the bioavailability from transdermal delivery was five times as from oral administration, with improved therapeutic efficacy.[43] Transdermal technology can also leverage the abundance of cutaneous antigen-presenting cells for a robust immune response. For example, multiple microarray patch platforms encapsulated with inactivated influenza antigens safely generated effective levels of antibodies comparable to intramuscular injection of the vaccine.[44, 45] Although nanomedicine is rapidly transforming systemic drug delivery, widespread systemic access by nano-formulated cannabinoids, mainly due to increased infiltration of nanoparticles through the blood-brain barrier, may drive unwanted psychotropic side effects. Consequently, cannabinoid compounds may be

better suited for topical preparations confining therapeutic activity to cutaneous cells.

Discussion

The extensive endocannabinoid system in the skin is teeming with opportunities for novel treatments in dermatology. Although cannabinoids illustrate therapeutic possibilities in many contexts, the most substantial evidence is their anti-inflammatory properties. Various cell populations express cannabinoid receptors and endocannabinoid regulatory proteins in the skin, and other key receptor families can be targeted by cannabinoid-based drugs to downregulate pro-inflammatory cytokines and hyperactive cell-mediated immune response. The ability to blunt chronic inflammation in the skin translates to clinical significance in an assortment of inflammatory skin diseases, including atopic dermatitis, acne, chronic pruritus, psoriasis, and systemic sclerosis. Unfortunately, the pharmacologic viability of numerous cannabinoids is a significant impediment to effective systemic and topical medications.

Based on our review of other similarly rigid molecules transformed into promising formulations, we propose that nanotechnology can advantageously manipulate challenging physiochemical attributes of cannabinoids and grow their utility in managing inflammatory skin disease and beyond. Encapsulating these lipophilic compounds can provide aqueous solubility, preserve functional integrity despite shifts in the environment, and maintain suitable pharmacokinetics. The need for potentially allergenic additives, ubiquitous in commercial cannabis-derived products,[9] may be lessened with the capability to stabilize the active ingredient. Although some experts express concern that increased bioavailability, particularly in systemic delivery that also activates CB1 receptors, may lead to adverse side effects, we argue that the controlled release characteristic of nanoformulations may mitigate this risk. Additionally, we described evidence that both indirect and direct activation of CB1 in the skin can recalibrate cutaneous immune signalling back to homeostasis. Topical delivery with permeation limited to the epidermis would minimize the unwanted influence on the ECS in other organ systems. Overall, cannabinoids are well suited for nanomedicine to propel encouraging compounds to high-quality, large-scale studies.

Conclusions

The therapeutic potential of cannabinoids for dermatological applications is widely reported. Nanoparticle drug delivery systems are increasingly used for formulating physiochemically prohibitive ingredients for topicals. Novel oral nano-preparations are already improving the pharmacokinetics of cannabis-derived compounds, and topicals would benefit from a similar strategy. With an evolving regulatory landscape and growing evidence for dermatologic value, nanocannabinoids are poised for investigation against cutaneous infection, inflammation, oxidative stress, and UV-induced cellular damage.

Conflict of Interests

The authors declare no conflicts of interest. For a signed statement, please contact the journal office editor@precisionnanomedicine.com

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Abbreviations used:

ECS: endocannabinoid system; CB1: cannabinoid receptor 1; CB2: cannabinoid receptor 2; PPAR-γ: peroxisome-proliferative-activated receptor-γ; AEA: arachidonoylethanolamide; LPS: lipopolysaccharide; TNF: tumor-necrosis factor; IL: interleukin; CXCL8: CXC-chemokine ligand 8; GATA3: GATA-binding protein 3; PEA: N-palmitoylethanolamine; SCORAD: SCORing Atopic Dermatitis; EASI: Eczema Area and Severity Index; VAS: visual analogue itch severity scale; VRS: verbal itching rating scale; FAAH: fatty acid amide hydrolase; TLR: Toll-like receptor; NFκB: nuclear factor kappa B; HSP90: heat shock protein 90; CLE: cutaneous lupus erythematosus; CLASI: Cutaneous Lupus Erythematosus Disease Area and Severity Index

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