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MINI-REVIEW

Cannabinoids in Dermatology: Hope or Hype?

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Abstract

Cannabinoids (CBDs) represent a diverse class of chemicals that may be beneficial in the treatment of various skin diseases due to antipruritic, anti-inflammatory, and antinociceptive properties. Although the legal history of these compounds has previously restricted their use and study, it seems likely that CBDs will gain popularity as they become increasingly available. We examined the mechanisms in which CBDs may have potential in the field of dermatology and reviewed the existing literature. We suggest that dermatologists review the existing evidence for CBD use and be ready to discuss it with their patients. The current literature indicates that CBDs may be beneficial in skin disease, particularly in the treatment of acne, chronic pruritus, and atopic dermatitis. Although there is preliminary evidence to suggest that CBDs are beneficial in these conditions, existing studies tend to be small and lacking rigorous design. There is a clear need for high-quality randomized controlled trials to fully evaluate the efficacy and safety of these compounds before their use can be promoted in the treatment of dermatological diseases.

Keywords: acne; atopic dermatitis; cannabinoids; endocannabinoids; pruritus; skin disease

Introduction

With the recent surge in popularity of cannabinoid (CBD) oil, cannabis-based personal care products are popping up all over the market, from moisturizers and lotions to mascaras and lip balms. This leads to the question of whether CBD use in skin care is simply a trend or is grounded in scientific evidence. The federal government currently lists cannabis as a schedule I controlled substance, creating a considerable hurdle for studying therapeutic properties of CBDs in large randomized controlled trials (RCTs). However, researchers have predicted that cannabis will likely be legalized on a federal level within the next 10 years,[1] opening the doors for the use of CBDs as approved medicines in all 50 states. CBDs may be of particular interest to the field of dermatology due to antipruritic, anti-inflammatory, and antinociceptive properties.[2] To date, applications of CBD therapy have been explored in acne, eczematous disorders, lichen planus, melanoma and nonmelanoma skin cancer, melasma, prurigo, pruritus, psoriasis, scleroderma and systemic sclerosis, and seborrheic dermatitis.[3] Preliminary evidence shows promise for CBDs' potential to treat eczema and other skin conditions with multiple possible routes of administration that can be made to have no psychoactive components.

Background

CBDs are a diverse class of chemical compounds that act on cannabinoid receptors (CBRs). Ligands for these receptors include endogenous endocannabinoids, phytocannabinoids (those produced by plants), and synthetic CBDs. Endocannabinoids include anandamide (AEA), 2-arachidonoyl glycerol (2-AG), *N*-palmitoylethanolamide (PEA), and oleoylethanolamide (OEA). The most commonly used phytocannabinoids are delta-9-tetrahydrocannabinol (THC) and CBD.[4] Notably, THC, the psychoactive component of cannabis, appears to be the only CBD with intoxicating effects. This is particularly important to emphasize to

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health care providers, as a survey of 531 dermatologists found that 64% of respondents did not know that CBD is not psychoactive, and 29% did not know that THC is psychoactive.[5] Most beauty products currently on the market contain hemp seed oil (also known as *Cannabis sativa* seed oil), which contains no THC and trace amounts of CBD. Hemp seed oil is made by pressing hemp seeds in a similar manner to olive oil and is high in omega-6 and omega-3 polyunsaturated fatty acids. Consumers may not understand these differences and the green packaging and "cannabis" labeling on these beauty products can be particularly misleading.

There are two known types of CBRs: CB_1 and CB_2. CBRs have been found on cutaneous nerve fiber bundles, mast cells, and epidermal keratinocytes, potentially explaining the anti-inflammatory and antinociceptive properties of CBR agonists.[6] Some evidence has found that CBDs may directly stimulate keratinocytes and act on other receptors as well, including TPV1, GPR55, PPAR-γ, and PPRAR-α.[7,8] Other CB_1 and CB_2 receptor-independent actions of CBD include its activation of transient potential vanilloid receptor type-1 (TPVR-1),[9] which may mediate inflammation in kidney injury, lung inflammation, arthritis, and encephalomyelitis.[10] TPVR-1 has also been found to be expressed on cutaneous sensory nerve fibers, epidermal keratinocytes, dermal blood vessels, and hair follicles, and may serve a complex role in the pathogenesis of cutaneous pain and pruritus.[11] Furthermore, CBD enhances adenosine A2A receptor activity, which can downregulate over-reactive immune cells and decrease inflammation in surrounding tissue.[12] These findings suggest that CBDs may be used for therapeutic purposes in a number of dermatological conditions.

Clinical and laboratory evidence

Patients with acne are increasingly trying alternative and complementary medicines, including medicinal plants, to treat their condition.[13] Early evidence suggests that CBDs may be helpful in the treatment of acne vulgaris. Oláh et al. administered CBD to cultured human sebocytes and human skin organ culture. They found that CBD inhibited the lipogenic actions of several compounds, including arachidonic acid and a combination of linoleic acid and testosterone. CBD also demonstrated anti-inflammatory actions and inhibition of the NF-κB signaling pathway.[14] In another *in vitro* study using human sebocytes, researchers found that hemp seed hexane extracts showed antimicrobial activity against *Propionibacterium acnes* and exerted anti-inflammatory effects by regulating NF-κB and mitogen-activated protein kinase signaling.[15] Both authors concluded that CBD/hemp seed should further be explored in the treatment of acne, due to antilipostatic, antiproliferative, and anti-inflammatory effects.

Limited clinical data may support their use as well. In a small split-face study, healthy males applied 3% cannabis seeds extract in a base cream on one side of their face and just the base cream to the other side. After 12 weeks of twice-daily application, researchers found that skin sebum production and erythema were significantly decreased on the 3% cannabis seeds extract side compared with the base treated side. Furthermore, the cannabis seed extract was well tolerated with no notable side effects. The study concluded that 3% cannabis seeds extract may be useful in the treatment of acne vulgaris.[16]

Another condition that may benefit from CBDs is chronic pruritus. Chronic pruritus can be a debilitating condition impacting quality of life.[17] Since there are currently no FDA-approved therapies for chronic itch, alternative therapies are often tried.[18] Dvorak et al. found that CB_1 and CB_2 receptors in cutaneous nerves may decrease excitation and histamine-mediated itch. Twelve patients were administered histamine applied by iontophoresis and subsequently received a HU210 (a synthetic CBD agonist) patch. The researchers found that experimentally induced itch was significantly reduced by peripheral administration of HU210 compared with an ethanol control.[19] This finding supports the effectiveness of CBDs to act as an antipruritic compound with potential for treating chronic itch. Specific formulations of CBDs for this purpose are currently being developed.

PEA is an endogenous fatty acid that enhances CBD binding to their receptors. It is not technically a CBD as it does not bind to CBRs itself but is referred to as a cognate.[20] PEA has been known to have emollient and antipruritic effects when applied topically. In an open label study, 22 patients with prurigo, lichen simplex, or pruritus applied an emollient cream containing PEA twice daily. An antipruritic effect was seen in 14 of 22 (63.6%) patients, with 8 of 14 patients reporting a complete cessation (100% reduction) of pruritus. No side effects were observed in any patient. The effectiveness was attributed to PEA's ability to modulate immune cells and inhibit mast cell degranulation.[21] However, Visse et al. found contrary evidence that PEA-enriched lotion was not superior to a base lotion in the treatment of dry itchy skin. In a study of 100

Table 1. Summary of Clinical Studies Using Cannabinoids to Treat Dermatological Conditions

Study	Type of study	*N*	Cannabinoid	Outcome
Acne				
Ali and Akhtar[1]	Single blind compare	11	3% *Cannabis sativa* extract cream	Significant decrease in sebum and erythema ($p < 0.05$)
Aesteatoic eczema				
Yuan et al.[23]	RCT	60	Emollient with PEA/AEA	PEA/AEA associated with improved scaling, dryness, and itching at day 28 ($p < 0.05$), but no difference in transepidermal water loss
Atopic dermatitis				
Callaway et al.[26]	Single blind crossover	20	Dietary hempseed oil	Improvement of skin dryness and itchiness ($p < 0.05$), decrease in dermal medication usage ($p < 0.05$)
Del Rosso[25]	Investigator-blinded compare	43	PEA-containing nonsteroidal cream	Lengthened the mean time to the next flare on an average of 28 days
Eberlein et al.[24]	Cohort	2456	PEA-containing cream	Improvement in symptoms, decreased use of topical steroids, improved sleep ($p < 0.001$)
Chronic pruritus				
Dvorak et al.[19]	Double blinded compare	12	Cannabinoid receptor agonist HU210 by skin patch	Reduced experimentally induced itch ($p < 0.05$), attenuated an increase in blood flow ($p < 0.003$)
Ständer et al.[21]	Cohort	22	Emollient with PEA	Reduced subjective severity of itch ($p \leq 0.05$)
Visse et al.[22]	Single blind compare	100	PEA	No significant differences between PEA and control in itch, quality of life, or cosmetic acceptance

AEA, anandamide; PEA, *N*-palmitoylethanolamide; RCT, randomized controlled trials.

subjects with pruritic dry skin at baseline, patients were randomized to either be treated with a vehicle lotion or a PEA-containing lotion. After 2 weeks of twice-daily treatment, the researchers found that there was no significant difference between the lotion with and without PEA. Improvement of pruritus, scaling, chronic scratch lesions, and quality of life was seen equally in both groups.[22] These findings emphasize the importance of conducting high-quality RCTs to fully evaluate the efficacy of PEA and other CBDs.

PEA-enriched cream has also been studied in treating asteatotic eczema (AE) and atopic dermatitis (AD). Yuan et al. compared PEA/AEA emollient with a traditional emollient in a randomized double-blind comparative trial of 60 patients with AE. They found that the PEA/AEA emollient was associated with improved scaling, dryness, and itching at day 28 ($p < 0.05$), but there was no difference in transepidermal water loss.[23] In a large multinational cohort study of 2,456 patients with AD, Eberlein et al. found that applying a PEA-containing cream resulted in a significant reduction in dryness, excoriation, pruritus, and erythema across the population. Furthermore, sleep quality improved significantly during the study and topical corticosteroids were stopped by 56% of all patients by the end of the study.[24] Although the lotion demonstrated a clear benefit to patients, the lack of a placebo group makes it difficult to draw conclusions on the effectiveness of PEA versus the cream base itself. In another pilot study comparing PEA-containing nonsteroidal cream with a designated moisturizer cream, researchers found that the PEA-containing cream lengthened the mean time to the next flare on an average of 28 days in both children and adults with AD.[25] This finding suggests that PEA may also play a role in the prevention of AD flares. This is a concept that needs to be explored further.

Although the majority of studies examine topical uses of CBDs, oral uses can be explored as well. Callaway et al. found that oral hempseed oil improved AD in a randomized crossover study. The study consisted of 20 adults with AD who consumed either hempseed oil or olive oil. They found that those who consumed hempseed oil showed a significant decrease in skin dryness, itchiness, and use of topical medications when compared with those who consumed olive oil. However, this effect was attributed to and may well be due to the high polyunsaturated fatty acid content in hemp seed oil rather than any CBDs present in the oil.[26] A summary of the clinical studies that have used CBDs to treat dermatological conditions can be found in Table 1.

Conclusions

As alternative and complementary therapies continue to grow in dermatology, CBDs will likely become increasingly popular as they become more readily available. It is important for dermatologists to be knowledgeable about the CBD compounds as the new cannabis-infused products on the market can be

confusing for consumers. Although a few studies have examined CBD use in treating acne, pruritus, and AD, there is a clear need for high-quality RCTs to evaluate their efficacy and safety. Furthermore, the studies have greatly varied in their formulation, route of admission, dosage, and frequency of use. Caution in promoting CBD use is advised until we learn how to effectively use these compounds to treat dermatological conditions and have tested formulations to recommend.

Author Disclosure Statement

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Abbreviations Used

AD = atopic dermatitis
AE = asteatotic eczema
AEA = anandamide
CBD = cannabinoid
CBR = cannabinoid receptor
PEA = N-palmitoylethanolamide
THC = tetrahydrocannabinol