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Cannabis and the skin

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AbstractUniversity of Conneticut School of Medicine The public and health care providers are increasingly curious about the potential medical benefits of *Cannabis. In vitro* and *in vivo* studies of *Cannabis* have suggested it has favorable effects on regulating pain, pruritus, and inflammation, making it a potentially attractive therapeutic agent for many dermatologic conditions. The body of literature reporting on the role of cannabinoids in dermatology is in its infancy but growing. We review the current research, possible cutaneous adverse effects, and future directions for cannabinoids and their use in skin cancer, acne, psoriasis, pruritus, dermatitis, scleroderma, dermatomyositis, cutaneous lupus erythematous, epidermolysis bullosa, pain, and wound healing.

Introduction

With its growing popularity and accessibility, *Cannabis* has become more available throughout the United States in various formulations and methods of delivery. It is regularly used for both medicinal and recreational purposes. A recent survey of dermatologists found that, although providers are interested in prescribing cannabinoids, their knowledge of the subject is limited.[1] The literature reports promising results for the role of cannabinoids in skin cancer, acne, psoriasis, pruritus, dermatitis, scleroderma, dermatomyositis, cutaneous lupus erythematous, epidermolysis bullosa, pain, and wound healing. We review potential therapeutic uses, current research, potential cutaneous adverse effects, and the need for additional research regarding *Cannabis* and its effect on dermatologic disorders.

Cannabinoids are a class of compounds similar to or derived from *Cannabis* (Figure 1). Cannabinoids can be grouped as endocannabinoids, phytocannabinoids, and synthetic cannabinoids (Table 1).[2] Endocannabinoids are produced endogenously. Phytocannabinoids are those derived from plants, with the two major phytocannabinoids being tetrahydrocannabinol (THC) and cannabinol (CBD). THC is the main psychoactive cannabinoid and causes the sensation of getting "high," but CBD is not psychoactive. Synthetic cannabinoids are created in a laboratory.

Researchers have identified two G protein–coupled cannabinoid receptors in mammalian tissue—cannabinoid receptor 1 (CB1R) and cannabinoid receptor 2 (CB2R).[3,4] These receptors are present in the skin and serve various functions.[5-7] Through these receptors, cannabinoids affect the growth, proliferation, differentiation, and apoptosis of keratinocytes, melanocytes, adnexal structures, and fibroblasts.[8-10] Cannabinoid receptors also exist in cutaneous nerve fibers and immune cells. Cannabinoids can act independently of formal cannabinoid receptors through transient receptor potential (TRP) ion channels. Overall, cannabinoids' influence on skin homeostasis supports their therapeutic potential in dermatology.

Nonmelanoma skin cancer

In the epidermis, activation of CB1Rs and CB2Rs may increase DNA methylation and inhibit keratinocyte proliferation.[11] Independent of the CB1R/CB2R system, endocannabinoids can inhibit keratinocyte proliferation through peroxisome proliferator-activated receptor gamma (PPAR-

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Fig. 1 Leaves and flower of the *Cannabis* plant. Source: https://libreshot.com/marijuana/.

γ) or G-protein couple receptor GPR55 activity.[12] Given these roles, cannabinoids may reduce the development of squamous and basal cell carcinomas.

Animal studies report paradoxic findings. Endocannabinoid agonists of both CB1Rs and CB2Rs and synthetic agonists selective to only CB2Rs have been associated with cancer cell apoptosis and impaired tumor vascularity.[13,14] Some endocannabinoids may also have apoptotic effects on nonmelanoma skin cancer (NMSC) tumor cells but work independently of CB1Rs and CB2Rs. For example, N-arachidonoyl ethanolamide is an endocannabinoid that induces apoptosis in NMSC of murine cell lines. When CB1Rs and CB2Rs were pharmacologically blocked, N-arachidonoyl ethanolamide–induced apoptosis was not inhibited.[15] In contrast, mice who lack CB1Rs/CB2Rs exhibit decreased tumorigenesis after exposure to ultraviolet B light compared with mice who have these receptors.[16] These results suggest the cannabinoid receptor stimulation, such as by ultraviolet B, may promote tumor development, but giving exogenous endocannabinoids or synthetic cannabinoids may induce tumor cell death via both independent and dependent cannabinoid receptor mechanisms. In addition, cannabinoids seem to have concentration-dependent effects. One study demonstrated that nanomolar concentration of endocannabinoids incited tumor development, but that high concentrations 1,000-fold greater diminished NMSC growth.[17] *In vivo* human studies of phytocannabinoids like THC or CBD have not been completed for NMSC.

Melanoma

Melanocytes produce the endocannabinoid anandamide, and melanoma cells express CB1Rs/CB2Rs.[18] As with NMSC, there are conflicting results regarding the relationship of cannabinoids to melanoma. When compared with a chemotherapy control, THC inhibited melanoma proliferation and viability.[5] Another study demonstrated that the antigrowth effect of THC on melanoma cells may be through hampering its characteristic proinflammatory microenvironment.[19] Some researchers suggest that CBD relies on CB2R-mediatied activity, whereas THC may have both CB1R- and CB2R-mediated effects.[5,20,21] Two synthetic cannabinoids that are CB2R agonists, WIN-55,212-2 and JWH-133, decreased cell proliferation and caused cell cycle arrest in murine models with melanoma.[9]

In contrast, gene activation of CB1Rs alone stimulated tumor growth and neural metastasis compared with gene silencing.[22,23] One study reported that *Cannabis* may lower the response rate of nivolumab, a programmed cell death protein-

Table 1 Examples of cannabinoids

Cannabinoid type	Example compounds
Endocannabinoid	2-arachidonoylglycerol (2-AG)
	Anandamide (AEA)
	N-arachidonoyl dopamine
	Palmitoylethanolamide (PEA)
Phytocannabinoids	Δ(9)-tetrahydrocannabinol (THC)
	Cannabidiol (CBD)
	β-caryophyllene
	Cannabidiolic acid (CBDA)
	Cannabigerol (CBG)
	Cannabichromene (CBC)
	Cannabinol (CBN)
	Cannabidivarin (CBDV)
	(9)-tetrahydrocannabivarin (THCV)
	Tetrahydrocannabinolic acid (THCA)
Synthetic cannabinoids	WIN-55,212-2 (mixed CB1/CB2 agonist)
	JWH-133 (selective CB2 agonist)
	CP 55,940
	5-thienyl pyrazole (CB1 antagonist)
	Arachidonoyl-chloro-ethanolamide (ACEA)
	S-777469 (selective CB2 agonist)
	HU210 (synthetic THC)
	Dronabinol (synthetic THC)
	JTE-907 (CB2 antagonist)
	α-OOS (synthetic AEA)
	JBT-101, ajulemic acid, lenabasum, anabasum (synthetic THC)
	VCE-004.8
	G1pa (CB2 agonist)

1 inhibitor used in the treatment of melanoma.[24] Additional research is needed to better define the role of cannabinoids in melanocyte biology and melanoma.

Kaposi sarcoma

The synthetic cannabinoid WIN-55,212-2 is effective in causing apoptosis of cell lines derived from Kaposi sarcoma (KS).[25] In KS-affected endothelial cells, CBD-inhibited viral G-protein couple receptors and vascular endothelial growth factor–receptors, which inhibit tumor cell growth and angiogenesis.[26] Paradoxically, low-dose THC promoted KS-associated herpes virus by facilitating viral replication and viral transmission.[27] The role of cannabinoids in KS may also be dose dependent and depend on the form of cannabinoid used.

Psoriasis

Cannabinoids may be promising in the treatment of psoriasis owing to their potential inhibitory effects on keratinocyte proliferation.[28-30] In human skin models, a synthetic CB1R agonist inhibited keratinocyte cell proliferation and reduced expression of K6 and K16.[28] Another study observed that the effect of cannabinoids on psoriasis may act independently of CB1Rs and CB2Rs.[12] Of note, a patent was filed in 2019 for a topical-containing CBD and cannabigerol, another phytocannabinoid, for the treatment of psoriasis. Instructions are to apply twice daily for 6 weeks to the affected areas. The patent claims that a concentration of 15% demonstrated a 16% to 33% improvement, based on 2 subjects who served as their own unblinded controls.[31] More extensive clinical studies are needed to better understand the role of cannabinoids in psoriasis.

Acne vulgaris and seborrhea

Cannabinoids may have a multifactorial impact on acne and sebaceous disorders. The expression of CB1Rs and CB2Rs in human sebaceous glands has been demonstrated.[32] Key enzymes that synthesize and degrade endocannabinoids are also expressed in human sebocytes.[33-35] Cannabinoids may influence sebocytes via activation of the CB2Rs to inhibit lipogenic actions of arachidonic acid, linoleic acid, and testosterone. This signaling results in decreased lipid production, sebum secretion, and sebocyte growth.[10,36-38]

Dysregulation of this pathway may contribute to both acne and seborrhea,[39] and a better understanding of it could lead to novel targeted therapies. CBD and THC were observed to have anti-acne and anti-sebocyte proliferative effects[10,36]; however, cannabigerol and cannabigerovarin, also both phytocannabinoids, increased sebocyte viability.[36] The sebocyte response is likely dependent on the type of cannabinoid used.

Major phytocannabinoids and hemp seed hexane extracts have exhibited anti-microbial activity, including against *Propionibacterium acnes*,[40,41] providing an additionally therapeutic application for acne. In addition, in a split-face study, 3% topical *Cannabis* seed extract decreased erythema and skin sebum.[37] There is also a phase 2 clinical trial of a 5% CBD topical for acne (BTX1503), but results have not yet been published.[42] Conversely, recreational synthetic cannabinoid addiction and the smoking of *Cannabis* have been associated with acne vulgaris, acne excoriée, acne keloidalis, and acne conglobata.[43,44] The majority of patients denied acne complaints before synthetic cannabinoid use, whereas 28% described worsening of existing acne.[43] Patients were not followed over time to assess whether acne lessened when stopping the synthetic cannabinoid. These conflicting results further exemplify the complex relationship between cannabinoids and the skin.

Alopecia and hair growth disorders

Cannabinoids, especially those targeting CB1R or TRP channels as antagonists, may have therapeutic potential in hair growth disorders. Agonists could have benefits for hirsutism or hypertrichosis. CB1Rs are expressed in human hair follicles.[32] Both CB1Rs and cannabinoid-responsive receptors, like TRP ion channels, promote the onset of the catagen phase and suppress hair shaft elongation when they are activated.[45-48]

A survey and examination of patients abusing synthetic cannabinoids found hair loss was a frequent dermatologic complaint. Clinical manifestations included telogen effluvium, androgenic alopecia, trichotillomania, and alopecia areata.[43] Preliminary data suggest that cannabinoid dysregulation may play a role in alopecia areata. A mutation in a tyrosine phosphatase involved in synthetizing the endocannabinoid anandamide that normally suppresses cytotoxic T-cell proliferation was found to be linked to alopecia areata.[49,50]

During a study of cannabinoids' anti-obesity potential, researchers observed that an oral CB1R antagonist promoted hair growth in mice. The same results were not obtained when used topically.[51] A single-case report presented at an international conference observed hair growth in intractable alopecia areata with 1.0% CBD ointment.[52] To our knowledge, no human clinical trial examining the use of oral or topical cannabinoids in alopecia has been performed.

Pruritus

The relationship between cannabinoids and itch is multifactorial.[53] Cannabinoids may inhibit mast cell degranulation and histamine release.[29,54-59] In skin prick tests, an irritant (ie, falcarinol) found in ginseng, carrots, and parsley, caused histamine-induced edema by acting as an antagonist of CB1R on keratinocytes and increasing proinflammatory cytokines like interleukin (IL)-8 and monocyte chemotactic protein-1.[59] Cutaneous nerve fibers contain CB1R/CB2R that—when bound by ligands—may decrease excitation of the nerve fibers and thus may diminish pruritus.[60] CB1Rs in the central nervous system are a main locus of action for antipruritic effects.[61,62] Independent of cannabinoid receptors, cannabinoids may modulate pruritus through TRP ion channels, such as TRPV1, a capsaicin receptor whose blockage is known to reduce itch.[63,64]

Investigators reported that, in mouse models, fatty acid amide hydrolase, an enzyme involved in pruritus, could be suppressed by THC or by an endocannabinoid CB1R activation (N-arachidonoyl ethanolamide).[61,65] An orally available selective synthetic CB2R agonist was found to inhibit scratching in animal models[66]. In contrast, a synthetic CB2R antagonist, JTE-907, resulted in suppressed scratching in mice.[67] THC given systemically to mice reduced scratching.[65]

In humans, a synthetic cannabinoid receptor agonist (ie, HU210) similar in structure to THC, relieved histamine-induced itch.[60] A topical emollient containing the endocannabinoid palmitoylethanolamide (PEA) resulted in significant lessening of itch in patients with prurigo nodularis, lichen simplex, atopic dermatitis, asteatotic dermatitis, and unspecified pruritus.[68-70] Even hemodialysis patients demonstrated a reduction in uremic pruritus with the use of topical PEA.[56] Patients with chronic liver disease reported relief of intractable pruritus with oral dronabinol, a synthetic THC; however, this was a case series of only three patients.[71] High levels of polyunsaturated fatty acids derived from dietary hempseed oil, an oil from the seed of a *Cannabis* plant containing no CBD or THC, have also demonstrated to decrease itch and inflammation.[72]

Atopic dermatitis

In addition to the potential effect cannabinoids have on pruritus, cannabinoids may produce anti-inflammatory effects that can aid in the management of atopic dermatitis.[73,74] Mice that lack CB1Rs have an impaired ability to repair their epidermal barrier. These animals had elevated levels of IL-4 and CCL8, suggesting CB1Rs may help to maintain the barrier function of the epidermis and accentuate a T helper 2 (Th2) cell response.[75]

In human models, CB1R agonists markedly enhanced epidermal barrier function and decreased skinfold thickness.[76,77] CB2Rs are also present on B, T, and antigen-presenting cells. When activated, Th1-cell immunity is inhibited and Th2-cell immunity is promoted.[74] WIN-55,212-2, a synthetic mixed CB1 and CB2 agonist, has been demonstrated to lower levels of tumor necrosis factor (TNF), IL-12, IL-1β, and IL-8 .[29] THC when coadministered with lipopolysaccharides decreased TNF and IL-6. This agonist also decreases levels of TNF and IL-6.[74]

Topical PEA decreases pruritus in patients with atopic dermatitis.[68] Studies also have reported less dryness, scaling, lichenification, excoriation, erythema, topical steroid use, and mean time to flare.[66,78] The combination of a topical steroid and topical PEA resulted in quicker clearance of atopic dermatitis.[78] Systemic hempseed oil compared with olive oil lessened skin dryness and pruritus, as well as decreased the use of prescribed medications.[72]

Allergic contact dermatitis

The antipruritic and anti-inflammatory effects of cannabinoids could theoretically lessen findings associated with allergic contact dermatitis. CBD reduced inflammation in polyinosinic:polycytidylic acid-induced allergic contact dermatitis in human keratinocytes.[79] In animal studies, topical THC inhibited keratinocyte-derived proinflammatory mediators, such as C-C motif chemokine ligand 8 and C-X-C

motif chemokine ligand 10, which reduced allergic contact-associated findings in mice.[6] Mice who did not have CB1Rs or CB2Rs were more likely to develop cutaneous contact hypersensitivity when exposed to either nickel or 2,4-dinitrofluorobenzene.[80] Additional studies, however, demonstrated that the effects may differ, if CB1Rs and CB2Rs are targeted separately. Mice deficient in fatty acid amide hydrolase, an enzyme that could be suppressed by CB1R activation, had decreased allergic responses.[80] Other studies demonstrated that, although CB2R activation can initially lower inflammation, chronic CB2R blockade is proinflammatory.[80,81] Overall, the true relationship between cannabinoids and allergic contact dermatitis needs to be further elucidated.

Systemic sclerosis

Based on their potential role in regulating inflammation, cannabinoids could also be used to prevent tissue thickening and fibrosis in sclerosing disorders. In addition, both CB1Rs and CB2Rs are found in dermal fibroblasts.[82] The synthetic cannabinoid WIN55, 212-2 limited dermal fibrosis in scleroderma mice modeled by bleomycin-induced dermal fibrosis.[83] Ajulemic acid (ie, lenabasum, anabasum or JBT-101) is a synthetic analogue of THC that binds to the CB2R. In mice, it similarly lowered the risk of bleomycin-induced dermal fibrosis.[84] This synthetic cannabinoid is believed to inhibit growth factor expression including TGF-β, platelet-derived growth factor, and connective tissue growth factor. Published phase 2 data of patients with diffuse cutaneous systemic sclerosis concluded that those who took oral lenabasum showed improvement in their symptoms index scores.[85] A phase 3 clinical trial has been initiated.[86] VCE-004.8 is another synthetic cannabinoid associated with lower vascular collagen deposits, macrophage infiltration, and fibroblast proliferation in mice models of scleroderma.[87]

Dermatomyositis

Similar to the results observed with systemic sclerosis, a phase 2 trial of patients with skin-predominant dermatomyositis demonstrated symptom severity index scores markedly improved with oral lenabasum.[88] The pathogenesis may be explained by lenabasum's ability to significantly suppress secretions of TNF-α, Interferon-α-(IFN-α), and IFN-β in peripheral mononuclear cells of patients with dermatomyositis.[89] Another randomized control trial demonstrated that lenabasum administered over 12 weeks decreased IFN levels and T-helper cell inflammation in skin lesions of dermatomyositis.[90] There is an ongoing phase 3 study of lenabasum in dermatomyositis that was begun in 2019.[91]

Cutaneous lupus erythematosus

One study reported that plasma levels of 2-arachidonoylglycerol (2-AG), also an endocannabinoid, were significantly higher in patients with systemic lupus erythematosus compared with healthy patients.[92] The highest levels of 2-arachidonoylglycerol were found in those with lower disease activity, implying a potential, yet complex, role of the endocannabinoid system and lupus. In animal models of cutaneous lupus, topical anandamide, an endocannabinoid, showed improvement and even reversal of classic symptoms.[93] As with systemic sclerosis and dermatomyositis, an investigation of lenabasum and cutaneous lupus erythematosus is also underway.[151]

Epidermolysis bullosa

The use of CBD oil in patients with epidermolysis bullosa has been proposed for its potential to relieve pain, reduce pruritus, and decrease inflammation. There are anecdotal reports of pain relief using topical CBD oil in epidermolysis bullosa patients.[95] In a case series of three pediatric patients whose families had initiated topical CBD oil, familiesreported fewer blisters, improved wound healing, and reduced need for analgesics; however, these perceived benefits could be confounded by spontaneous resolution attributable to older age, better skin care, and vehicle/placebo effects. Each patient also used a different formulation of CBD, making accurate quantitative outcome measurement challenging.[96] Another case series of adult patients reported that pharmaceutical-grade sublingual cannabinoid oil, containing both THC and CBD, resulted in less itch and lower opioid use.[97] The literature detailing the role of cannabinoids and epidermolysis bullosa has been anectodical, and randomized controlled studies are needed.

Pain

In 2017, the Health and Medicine Division of the US National Academies of Sciences, Engineering, and Medicine concluded that enough evidence substantiated the claim that *Cannabis* can improve chronic pain, especially neuropathic pain.[98] Most early research studied smoked *Cannabis*. Studies on topical cannabinoid applications for pain are limited but becoming more frequent.[99,100] In animal models, an intraplantar injection of a CB2R-agonist alleviated capsaicin-induced pain.[101] A topical mixed CB1R/CB2R agonist was observed to have a dose-dependent antinociceptive effect.[102] The same agonist was observed to have a synergistic effect with topical morphine compared with topical morphine alone.[103]

Human studies are in their preliminary stages. *Cannabis* in many forms (eg, oral, topical, and inhaled) have been studied for the management of cancer-associated pain, chronic neuropathic pain, and arthritis with varying concentration of THC and CBD.[100,104-107] Epidermolysis bullosa patients have reported pain relief with topical CBD oil.[95] An observational study of eight patients with facial postherpetic neuralgia reported significant pain reduction with a topical cream containing the cannabinoid PEA.[108] A case series of three patients with pyoderma gangrenosum reported clinically significant analgesia with reduced opioid use after the application of topical *Cannabis* oil.[109] Large-scale clinical trials have not yet been performed.

Wound healing and skin aging

Selective CB2R agonists and antagonists were found to affect inflammation in incised wounds of mouse skin by regulating M1 and M2 macrophage infiltration.[110] CB2R activation also reduced neutrophil infiltration, and promoted keratinocyte migration, fibroblast accumulation, and fibroblast to myofibroblast transformation.[111] These findings support the proposal that cannabinoids may accelerate wound re-epithelization and scar formation. A deletion of CB1Rs in mouse models, on the other hand, resulted in less skin rejuvenation and early-onset aging.[112] Last, a flax fiber-derived "CBD-like" compound may promote wound healing by enhanced collagen production.[113,114] Additional research is needed to fully comprehend the role of cannabinoids in wound healing.

Adverse effects

Common systemic side effects of inhaled *Cannabis* use include dry mouth, dry eyes, and disturbed coordination. More serious harm includes its influence on mood states and mental health disorders, due to the psychoactive compound THC.[115] Studies of oral medical *Cannabis* have reported dizziness, sedation, and nausea.[116] Common side effects from CBD alone include nausea, vomiting, sedation, and decreased appetite.[117] Cutaneous adverse effects of cannabis remain rarely reported. Those that have been published are largely anecdotal or observational. Possible dermatologic risks include acne, hair abnormalities, oral cancers, oral stomatitis and candidiasis, *Cannabis*-induced arteritis, and allergy or hypersensitivity.

Certain cannabinoids have the potential to aid in the management of acne. Conversely, the regular smoking of *Cannabis* and use of synthetic cannabinoids have been associated with acne flares[43,44] Other dermatologic findings include periorbital hyperpigmentation, premature aging, hair loss, and gray hair.[43] In addition to its possible premature aging effects on hair, THC and the endocannabinoid anandamide were found to inhibit hair-shaft elongation and hair-matrix keratinocytes proliferation via CB1Rs.[118] Using scanning electron microscopy, one report noted that chronic *Cannabis* users had enlarged, node-shaped areas on their hair shafts, which were not present on normal controls.[119]

Oral findings immediately after the use of inhaled *Cannabis* include xerostomia, anesthesia, and erythema due to mucosal irritation.[120,121] Long-term inhaled use can cause chronic inflammation, hyperkeratosis, leukoplakia, gingivitis, dental caries, oral candidiasis, and oral carcinoma.[120-125] The relationship between oral cancer and *Cannabis* use remains controversial. Studies have quantified a 1.2- to 2.6-fold greater risk of head and neck cancers in patients who smoked *Cannabis*.[124,126] This risk is significantly worsened by concomitant use of tobacco.[127] Other reports have found low to no risk of oral cancer with *Cannabis* use.[128,129] One analysis even concluded a decreased risk of tongue cancer among *Cannabis* users.[130]

Several cases of *Cannabis* arteritis have been reported since 1960; however, it is still considered an infrequent adverse effect.[131] Patients present with peripheral claudication, Raynaud phenomenon, and eventually digital necrosis and ulceration, usually of the lower extremities.[131-133] Venous thrombosis has also been associated with *Cannabis* use.[132] Unlike peripheral artery disease that shows calcified plaques or atherosclerosis, patients with *Cannabis* arteritis present with complete peripheral artery occlusion on ultrasound.[134] The majority of cases occurred in young men who smoked at least one joint per day and reported concomitant tobacco use.[131,133] Complete peripheral artery occlusion is reversible with the cessation of *Cannabis* and tobacco, as well as beginning to take daily aspirin. In severe cases, iloprost may be used.[134,135] Without treatment, more than 50% of patients with complete peripheral artery occlusion progressed to requiring amputation.[131]

Cannabis allergy may present as urticaria, pruritus, or angioedema.[99,136-138] *Cannabis* allergy has been confirmed by scratch testing, skin prick testing, and IgE antibody testing.[139-141] Because the majority of recreational *Cannabis* is consumed by inhalation, respiratory symptoms are a frequent manifestation of allergy,[142-144] with nearly one-third of patients having a positive *Cannabis* bronchial challenge.[139] Anaphylaxis has also occurred from oral ingestion.[144] *Cannabis* may also cross react with other allergens such as tomatoes, tobacco, peach, kiwi, banana, cherry, apple, or citrus.[139,142,145] One case report described a woman who had a urine toxicology that tested positive for cocaine and *Cannabis* who then developed a hypersensitivity reaction that presented as acute generalized exanthematous pustulosis and eosinophilia.[146]

Allergy to additive ingredients in unregulated over-the-counter *Cannabis* products should be considered as well. A study of California dispensaries found 1 or more allergens from the North American Contact Dermatitis Group were listed in 84% of the products.[147] The most common allergens were tocopherol, peppermint/menthol,

Table 2 Skin conditions and potential cannabinoid treatments

Disease	Cannabinoid	Delivery	Effect
Nonmelanoma skin cancer	AEA	*In vitro*	Cancer cell apoptosis and impaired tumor vascularity
	WIN-55,212-2	Mouse injection	
	JWH-133	Mouse injection	
Melanoma	THC	*In vitro*	Cancer cell apoptosis, slowed proliferation, and reduced inflammation
	WIN-55,212-2	Mouse injection	Decreased cancer cell proliferation
	JWH-133	Mouse injection	
Kaposi sarcoma	WIN-55,212-2	*In vitro*	Cell cancer apoptosis
	CBD	*In vitro*	Inhibited tumor cell growth and angiogenesis
	THC	*In vitro*	Promoted Kaposi sarcoma–associated herpes virus replication and transmission
Psoriasis	ACEA	*In vitro*	Inhibited keratinocyte cell proliferation
	CBD + cannabigerol	Human topical (n = 2)	Lesion improvement
Acne/seborrhea	CBD	*In vitro*	Decreased sebocyte proliferation, lipogenesis, and inflammatory pathways
		Human topical	Phase 2 clinical trial without published results
	THCV	*In vitro*	Decreased lipogenesis
	Cannabigerol	*In vitro*	Increased lipogenesis, apoptosis of sebocytes, and decreased inflammation
	Cannabigerovarin	*In vitro*	Increased lipogenesis, apoptosis of sebocytes, and decreased inflammation
	Recreational synthetic cannabinoids	Human inhaled	Observational study with development or worsening of acne
	Cannabis seed extract	Human topical	Decreased erythema and skin sedum
Alopecia/hair growth	Synthetic cannabinoids	Human inhaled	Observational study with increased reports of telogen effluvium, androgenic alopecia, trichotillomania, and alopecia areata
	5-thienyl pyrazole	Human oral	Hair growth promoted
		Human topical	No effect
	CBD	Human topical (n = 1)	Hair growth in alopecia areata
Pruritus	AEA	Mouse injection	Suppressed FAAH (an enzyme involved in pruritus)
	THC	Mouse injection	Suppressed FAAH and reduced scratching, but also caused hypomotility
	S-777469	Human oral	Reduced itch
	HU210	Human topical	Reduced itch
	PEA	Human topical	Reduced itch
	Dronabinol	Human oral	Reduced itch (n = 3)
Atopic dermatitis	WIN-55,212-2	*In vitro*	Lowered TNF, IL-12, IL-1β and IL-8
	THC	*In vitro*	Lowered TNF and IL-6
	α-OOS	Human topical	Improved epidermal barrier function
	PEA	Human topical	Enhanced lipid production, reduced itch, less dryness, scale, lichenification, excoriation, erythema, and topical steroid use
	Hempseed oil	Human oral	Reduced itch, dryness, and the use of prescribed medications
Allergic contact dermatitis	CBD	*In vitro*	Reduced inflammation initially, but increased inflammation over time
	JTE-907	Mouse topical	Proinflammatory when used chronically
	THC	Mouse topical	Inhibited CCL8 and CXCL10
Systemic sclerosis	WIN-55,212-2	Mouse injection	Lowered risk of bleomycin-induced dermal fibrosis (scleroderma mouse models)
	Lenabasum	Mouse oral	Lowered risk of bleomycin-induced dermal fibrosis (scleroderma mouse models)
		Human oral	Phase 2 clinical trial with improvement in symptom severity. Phase 3 ongoing.

(*continued on next page*)

Table 2 (*continued*)

Disease	Cannabinoid	Delivery	Effect
	VCE-004.8	Mice oral	Lower vascular collagen deposits, macrophage infiltration, and fibroblast proliferation
Dermatomyositis	Lenabasum	Human oral	Decreased IFN levels and T-helper cell inflammation. Phase 2 clinical trial with improvement in symptom severity. Phase 3 ongoing.
Cutaneous lupus erythematosus	Anandamide	Mouse topical	Symptom improvement
	Lenabasum	Human oral	Phase 1 clinical trial with unpublished results
Epidermolysis bullosa	CBD	Human topical	Fewer blisters, improved wound healing, and less analgesic use
	THC+CBD	Human sublingual	Less itch and lower opioid use
Pain	β-caryophyllene	Mouse injection	Alleviated capsaicin-induced pain
	WIN-55,212-2	Mouse topical	Dose-dependent reduction of tail-flick pain
	THC+CBD	Human inhaled, topical, oral	Reduction in cancer-associated pain, chronic neuropathic pain, and arthritis
	PEA	Human topical	Reduction in facial postherpetic neuralgia
	Cannabis oil	Human topical (n = 3)	Reduced pain and opioid use in pyoderma gangrenosum
Wound healing and skin aging	Flax fiber "CBD-like" compound	*In vitro*	Enhances collagen production
	JWH-133	Mouse injection	Reduce macrophage infiltration
	Gp1a	Mouse injection	Reduce neutrophil infiltration, promote keratinocyte migration, fibroblast accumulation, and fibroblast to myofibroblast transformation

Abbreviations: α-OOS, synthetic anandamide; ACEA, arachidonoyl-chloro-ethanolamide; AEA, anandamide; CBD, cannabinol; FAAH, Fatty acid amide hydrolase; IFN, Interferon; IL, interleukin; PEA, palmitoylethanolamide; THC, tetrahydrocannabinol; THCV, (9)-tetrahydrocannabivarin; TNF, tumor necrosis factor.

lavender oil, and fragrance mix. Most unregulated over-the-counter *Cannabis* products have not been tested for their safety or efficacy by the US Food and Drug Administration. Caution should be taken with the use of commercial, unregulated topical cannabinoids on active wounds, which may increase the risk for contamination and infection.[148]

Conclusions

Medical providers and patients share an interest in the potential therapeutic benefits of cannabinoids.[1] Because numerous states have legalized *Cannabis*, there has been increased widespread use of the drug and its associated products, both medically and recreationally, and it is increasingly incorporated into many over-the-counter products.[149] Encouraging data suggest possible therapeutic roles for cannabinoids in dermatology as anti-inflammatory and antiproliferative agents (Table 2). Much of the literature regarding the health effects of *Cannabis* is in its infancy at this time.

The relationship between cannabinoids and the skin is complex and is further complicated by the heterogeneity of the cannabinoid family and its family of receptors. With the exception of phase 2 and 3 trials of oral synthetic cannabinoids for select autoimmune conditions, claims of benefits have likely outpaced sound available data. Dermatologists should also be aware of potential adverse effects of cannabinoids and the risk of potential allergenicity of unregulated topical products.

Declaration of Competing Interest

The authors declare no conflict of interest.

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