# Cannabinoids in dermatology: a scoping review

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## Abstract

The therapeutic applications of cannabis and cannabinoids are an increasingly conspicuous topic as de-criminalization and legalization of these products continues to expand. A limited number of cannabinoid compounds have been approved for a specific set of conditions. However, the current role of cannabinoids for the treatment of dermatologic conditions remains to be defined. We conducted a review of the current literature to determine the applications of cannabinoids for the therapy of various skin diseases. After conducting our analysis, we found that cannabinoid products have the potential to treat a variety of skin conditions, including acne vulgaris, allergic contact dermatitis, asteatotic dermatitis, atopic dermatitis, hidradenitis suppurativa, Kaposi sarcoma, pruritus, psoriasis, skin cancer, and the cutaneous manifestations of systemic sclerosis. However, the majority of available data on these compounds are pre-clinical and there is a corresponding lack of high-quality randomized, controlled trials that evaluate their effects. Cannabinoids have shown some initial promise as therapy for a variety of skin diseases. However, there is a requirement for thorough pre-clinical research and large-scale, randomized, controlled trials before cannabinoids can be considered safe and effective treatments for these conditions.

*Keywords: cannabinoids, cannabis, skin disease*

## Introduction

The cannabinoids are a diverse class of pharmacologically active compounds that are structurally and biologically similar to the primary psychoactive compound derived from *Cannabis sativa,* Δ(9)-tetrahydrocannabinol (THC), [1-4]. There are three classes of cannabinoids. Endogenous cannabinoids (endocannabinoids) occur naturally/are constitutively produced in the bodies of humans and animals [3, 5, 6]. The most well-known members of this class include 2-arachidonoyl-glycerol (2-AG) and anandamide (AEA), [2-4]. Together, the endocannabinoids, the proteins that regulate their production and degradation, and the cannabinoid receptors comprise the endocannabinoid system (ECS), [4]. Plant-derived cannabinoids (phytocannabinoids) occur exclusively in *Cannabis* plants [2-4, 6]. THC is the most well-known of the phytocannabinoids. Synthetic cannabinoids are developed in laboratories and have chemical and structural similarities to endocannabinoids and phytocannabinoids [3]. Examples of synthetic cannabinoids include WIN-55,212-2, JWH-133, (R)-methanandamide (MET), and CP 55,940 [3, 4]. **Table 1** categorizes several common cannabinoids by class.

The various downstream effects of the cannabinoids are mediated through the cannabinoid receptors, CB1 and CB2. Both CB1 and CB2 are G protein-coupled receptors [1, 3]. CB1 is primarily associated

**Table 1.** *Cannabinoids by class.*

| Cannabinoid Type | Members of Class |
|---|---|
| Endocannabinoids | 2-arachidonoylglycerol (2-AG)<br>Anandamide (AEA)<br>N-arachadonoyl dopamine<br>Homo linoleoyl ethanolamide (HEA)<br>Docosa tetraenyl ethanolamide (DEA)<br>Virodhamine<br>Noladin ether<br>Palmitoyl ethanolamide (PEA)*<br>Oleoylethanolamide (OEA)* |
| Phytocannabinoids | Δ(9)-tetrahydrocannabinol (THC)<br>Cannabidiol (CBD)<br>Cannabidiolicacid (CBDA)<br>Cannabigerol (CBG)<br>Cannabichromene (CBC)<br>Cannabinol (CBN)<br>Cannabidivarin (CBDV)<br>Δ(9)-tetrahydrocannabivarin (THCV)<br>β-caryophyllene<br>Tetrahydrocannibinolic acid (THCA) |
| Synthetic cannabinoids | WIN-55,212-2<br>JWH-133<br>(R)-methanandamide (MET)<br>CP 55,940 |

*Cognate compounds. Not true endocannabinoids. PEA does not bind to CB1 and CB2, but rather enhances endocannabinoid binding to cannabinoid receptors. PEA enhances the action of anandamide at cannabinoid receptors via inhibition of the fatty acid amide hydrolase (FAAH) enzyme

with the psychoactive effects of cannabinoids and is expressed in high levels in the central nervous system [2, 3]. In the brain, CB1 is predominantly pre-synaptic and is responsible for the regulation of memory, mood, sleep, appetite, and the sensation of pain via release of various neurotransmitters [4]. CB1 is also present in lower concentrations in peripheral tissues, including cardiac, testicular, muscular, hepatic, pancreatic, and adipose tissues, among others [2, 4]. CB2 is presumed to be responsible for the immunomodulatory and anti-inflammatory effects of the cannabinoids [4] and is primarily expressed in the spleen and in cells of hematopoietic lineage [2-4]. Recent studies have described the expression of both CB1 and CB2 on cutaneous sensory nerve fibers, mast cells, and keratinocytes [7].

As of August 2017, 29 states, the District of Columbia, Guam, and Puerto Rico have passed legislature allowing for comprehensive public medical marijuana and cannabis programs. Seventeen additional states permit limited medical use of low THC/high cannabidiol products [8]. Approximately 10% of adult cannabis users in the United States report use of cannabis for medical purposes [9].

There is a growing body of literature that describes the potential applications of cannabinoids in the treatment of a wide range of diseases and pathologic conditions [5]. There are numerous studies that describe the uses of cannabinoids for the treatment of chronic pain, spasticity, anorexia, nausea, malignancy [1, 3, 5], asthma [2], intractable epilepsy [6], mood and anxiety disorders, movement disorders, neuropathic pain, multiple sclerosis, spinal cord injury, cancer, atherosclerosis, myocardial infarction, stroke, hypertension, glaucoma, obesity and metabolic syndrome, diabetes mellitus, and osteoporosis [4, 5].

Recently, the literature has begun to describe the promising role of cannabinoids in the treatment of dermatologic conditions, among them skin cancer, inflammatory skin diseases, and pruritus. Herein, we provide a scoping review of the most current literature describing the potential applications of cannabinoids for the treatment of various skin pathologies.

## Body of Article

### Literature Search

Comprehensive literature searches were conducted with EMBASE, Ovid MEDLINE, Ovid MEDLINE Daily, and Ovid MEDLINE In-Process and Other Non-Indexed Citations. Key search terms included "integumentary system," "dermatology," "skin AND ('disease')," "cannabinoids," "cannabis," "endocannabinoid," "phytocannabinoid" and "synthetic cannabinoid." Tables 2 and 3 detail our query strategy for each database in full. At least two reviewers (LE, NK, and/or RP) assessed results for inclusion criteria, and a third reviewer (LE, NK, or RP) was consulted for disagreements. Studies included met criteria for a review or primary article discussing cannabinoid therapies targeting human skin disorders. Both databases were filtered by year. Studies published before 2007 were excluded for the sake of reviewing only the most current literature.

Initial number of articles: Embase (432) + Ovid (18) = 450.

After duplicates removed: 442 (number of duplicates 8).

**Inclusion Criteria**

1. Primary article, systematic review, or meta-analysis
2. Published in last 10 years
3. Involves use of cannabinoids (endocannabinoid, phytocannabinoid, synthetic)
4. Use in dermatological condition

**Exclusion Criteria**

1. Article not in English
2. Opinion Article
3. Article older than 10 years
4. Use not in humans
5. Does not relate to skin disease
6. Does not relate to cannabinoids

## Results

### Study Selection

Our literature search returned 442 non-duplicate articles (432 from EMBASE and 18 from Ovid MEDLINE databases). Of the original 442 records, 244 were not related to dermatology, 64 were not related to treatment but included cannabinoids and skin, 55 were not related to cannabinoids, 12 were abstracts or posters, 12 were non-human studies, 11 involved the anecdotal use of cannabinoids, 4 were opinions or editorials, one was not in English, and one was a duplicate not originally filed. The remaining 38 articles were included in the scoping review [1-7, 10-40]. **Figure 1** depicts our search process and reasoning for exclusion of sources.

Our review indicates that cannabinoids have been investigated for the therapy of multiple skin disorders. **Table 2** describes our findings in detail, including the skin diseases cannabinoids have the potential to treat, the proposed mechanism of treatment, the specific cannabinoid or receptor involved in this mechanism, and the corresponding supporting literature. **Table 3** specifically outlines the details of the randomized controlled trials of cannabinoid-based treatments for skin disorders.

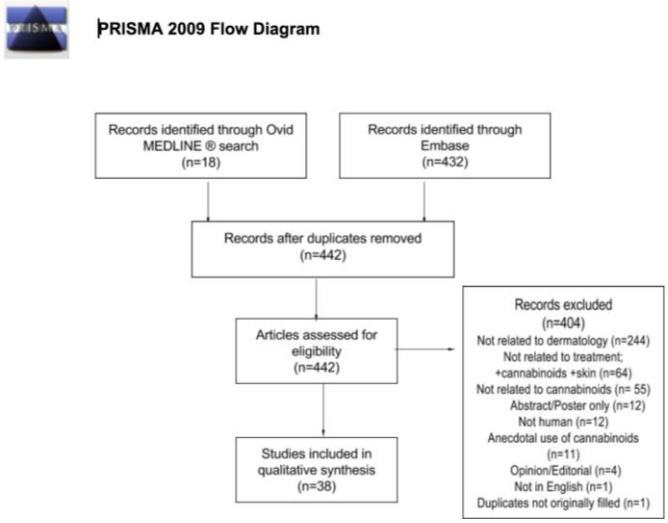


**Figure 1.** *Flow diagram depicting search process and reasons for exclusion; modified from the Preferred Reporting Items for Systematic Reviews and Meta-Analyses.*

## Discussion

### Pathophysiology

It is important to note that, although the potential applications of cannabinoid therapy in the field of dermatology are exciting, the use of cannabinoids is not without risk. The interpretation of potential clinical uses of cannabinoids in the treatment of dermatologic conditions is complex. Cannabinoids bind to multiple cannabinoid receptors with varying affinities. The specificity of these compounds may not be entirely limited to the cannabinoid receptors [34]. It is possible that, at varying doses, they bind to and function through other receptors, or in a receptor-independent manner. Therefore, their biological outcomes cannot be reliably predicted at this time.

### Dermatologic Uses

The available data on the use of cannabinoids for the treatment of dermatologic conditions support a broad spectrum of potentially useful applications. These applications are intrinsically intriguing. However, it is clear that complete investigation of these applications has yet to occur. Much of the data available to us at this time is pre-clinical, and there is a corresponding dearth of large, randomized, controlled trials in this domain. Table 4 provides a summary of skin diseases with potential cannabinoid

**Table 2.** *Search query for Embase.*

| No. | Query | No. of Records |
|---|---|---|
| 1 | 'integumentary system'/exp OR 'integumentary system' OR 'mucosa'/exp OR 'mucosa' OR ('skin'/exp OR skin AND ('disease'/exp OR disease)) OR 'skin cancer'/exp OR 'skin cancer' OR 'dermatology'/exp OR 'dermatology' OR (inflammatory AND ('skin'/exp OR skin) AND ('disease'/exp OR disease)) OR 'pruritis'/exp OR 'pruritis' OR 'itch'/exp OR 'itch' | 1,566,797 |
| 2 | 'cannabinoids'/exp OR 'cannabis' OR 'endocannabinoid' OR 'phytocannabinoid' OR 'synthetic cannabinoid' OR 'mari*uana' | 65,417 |
| 3 | #1 AND #2 | 1,877 |
| 4 | **treatment** | 5,692,499 |
| 5 | #3 AND #5 | 694 |
| 6 | #3 AND #5 AND [humans]/lim AND [english]/lim AND [2007-2017]/py | 432 |

treatment. Table 5 provides a summary of cannabinoid therapy trials.

## Acne Vulgaris

Dobrosi et al. reported human SZ95 sebocytes express CB2, but not CB1. They also found that endocannabinoids are present within these sebocytes and serve to up-regulate lipid synthesis and induce apoptosis-driven cell death via selective CB2-coupled signaling. In SZ95 sebocytes with "silenced" CB2, they observed significant suppression of basal lipid production. Collectively, these findings indicate that both CB2 agonists and antagonists ought to be explored in the context of the management of acne and other skin disorders characterized by sebaceous gland dysfunction [11]. In 2014, Olah et al. described the ability of CBD to inhibit the lipogenic actions of various compounds, including arachidonic acid and a combination of linoleic acid and testosterone, in cultured human sebocytes and human skin organ culture. CBD also suppressed sebocyte proliferation via activation of transient receptor potential vanilloid-4 (TRPV4) ion channels and exerted complex anti- inflammatory effects via A2a adenosine receptor-dependent up-regulation of tribbles homolog 3 (TRIB3) and inhibition of NF-κB signaling [6].

In 2016, Olah et al. found that several phytocannabinoids had the capacity to alter viability of sebocytes at low doses and induce apoptosis of sebocytes at high doses. Cannabichromene (CBC) and tetrahydrocannabivarin (THVC) suppressed basal sebaceous lipid synthesis. Cannabidivarin (CBDV) had only minor effects on suppression of lipid synthesis. The authors found that cannabigerol (CBG) and cannabigerovarin (CBGV) actually increased lipid synthesis. CBC, CBDV, and THCV all

**Table 3.** *Search query for Ovid MEDLINE, Ovid MEDLINE Daily, and Ovid MEDLINE In-Process and other non indexed citations.*

| No. | Query | No. of Records |
|---|---|---|
| 1 | 'integumentary system'/exp or 'integumentary system'.mp. or 'mucosa'/exp or 'mucosa'.mp. or (('skin'/exp or skin.mp.) and ('disease'/exp or disease.mp.)) or 'skin cancer'/exp or 'skin cancer'.mp. or 'dermatology'/exp or 'dermatology'.mp. or (inflammatory.mp. and ('skin'/exp or skin.mp.) and ('disease'/exp or disease.mp.)) or 'pruritis'/exp or 'pruritis'.mp. or 'itch'/exp or 'itch'.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] | 405557 |
| 2 | 'cannabinoids'/exp or 'cannabis'.mp. or 'endocannabinoid'.mp. or 'phytocannabinoid'.mp. or 'synthetic cannabinoid'.mp. or 'mari*uana'.mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept word, rare disease supplementary concept word, unique identifier, synonyms] | 32013 |
| 3 | treatment.mp. | 4129886 |
| 4 | 1 and 2 and 3 | 42 |
| 5 | limit 4 to (english language and humans and yr="2007 - 2017") | 18 |

significantly reduced arachidonic-induced acne-like lipogenesis. All of the phytocannabinoids investigated by this group demonstrated anti-inflammatory actions [13].

Ali et al. [12] evaluated the effects of a 3% cannabis extract cream on sebum level and erythema in 11 patients with acne in a single blinded and comparative study. They found that use of the use of the cannabis extract cream on the right cheek twice per day for 12 weeks resulted in a significant decrease in sebum level in comparison to a control cream ($P<0.05$) that was applied in the same fashion to the left cheek as measured by a photometric device (Sebumeter). They also found that use of the cannabis extract cream resulted in a significant decrease in erythema as measured by a reflectance spectrophotometer (Mexameter), [12].

**Allergic Contact Dermatitis**

Basu et al. described the ability of CB2 to mediate both the exaggeration and inhibition of inflammatory responses in allergic contact dermatitis. Subcutaneous administration of a CB2 antagonist, SR144528, to DFNB mice before and after exposure to triggering allergens resulted in increased inflammatory response. Subcutaneous or topical administration of CB2-selective agonist HU-308 also significantly increased inflammation. However, CB2-selective antagonists/inverse agonists JTE-907 and SR144528 actually *decreased* inflammation. Topical SR144528 also decreased inflammation in oxalozone-induced allergic contact hypersensitivity models [2].

**Asteatotic Eczema/Dermatitis**

Yuan and colleagues conducted a randomized, controlled trial of 60 patients with asteatotic eczema. The patients were instructed to apply an emollient cream to their legs, twice a day, for 28 days. They were randomized to an intervention group that utilized an emollient cream containing N-palmitoylethanolamine (PEA) or N-acetylethanol-amine (NEA) and a control group that used a control emollient cream. The authors found that the PEA and NEA emollient creams were superior in improving skin scaling, dryness, and itching on day 28, as measured by the Eczema Area and Severity Index by two dermatologists ($P<0.05$). They also found that the PEA and NEA creams produced greater change in the hydration and capacitance of the skin surface as measured the by the Corneometer CM820. They did not observe any significant difference between the groups in trans-epidermal water loss as assessed by the TM210 device [26].

**Atopic Eczema/Dermatitis**

Several investigators [15-18, 20] have described the ability of anandamide to exert anti-pruritic effects via activation of TRPV1 ion channels. TRPV1 ion channels co-localize with CB2 on keratinocytes and have been postulated to function as "ionotropic cannabinoid receptors." Anandamide, an endocannabinoid, is normally metabolized by the fatty acid amide hydrolase (FAAH) enzyme. The aforementioned authors describe the ability of PEA to enhance the activity of anandamide at the cannabinoid and vanilloid receptors by inhibiting FAAH. The synthetic FAAH inhibitors, URB597 (KDS-4103) and URB937, and PEA thus have potential utility in treating the itch associated with atopic dermatitis.

In a review on the treatment of pediatric atopic dermatitis, Wollenberg et al. described a study in which topical THC application decreased chemokine ligand 2 (CCL2) production by keratinocytes, interferon gamma (IFN-Y) production by T cells, and myeloid immune cell infiltration in wild-type and CB1/2-deficient mice [23].

PEA itself has also been found to have antipruritic effects [15-19]. Mimyx, a PEA-containing lamellar matrix cream, is a steroid- and calcineurin inhibitor-free barrier repair compound. It was designed to mimic components of the stratum corneum, with the goal of repairing and restoring skin barrier function and decreasing trans- epidermal water loss in conditions including atopic dermatitis, allergic contact dermatitis, and radiation dermatitis. It has been shown to have both anti- inflammatory and anti-pruritic properties, with the former likely due to the ability of PEA to bind CB2 receptors and inhibit mast cell activation. It has also been demonstrated to extend remission of atopic dermatitis, an attribute that adds to the potential cost-effectiveness of the agent in comparison to traditional therapies [14].

Carbone and Ring have also described the utility of PEA in the treatment of atopic dermatitis. In a study

on atopic dermatitis in a pediatric population, twice daily PEA for 4-6 weeks produced a statistically significant difference in physicians' scores of atopic dermatitis severity when compared to baseline and improvement in patient reported pruritus [24]. PEA has also been shown to attenuate histamine-induced responses, including pain, itch, and erythema, in human skin [25].

Eberlein et al. conducted a prospective cohort study involving 2456 patients who were instructed to apply a PEA-containing emollient cream sparingly to problem areas, twice a day, for 4-6 weeks. There was a statistically significant (P<0.001) improvement of patient-reported symptoms, decreased use of topical steroids, and decreased loss of sleep related to itching. Additionally, the authors observed a statistically significant (P<0.001) physician-assessed improvement in symptoms, including dryness, excoriation, pruritus, and erythema [19].

**Hidradenitis Suppurativa**

In a recent review, Scheinfield described the potential efficacy of cannabinoids to treat the pain associated with hidradenitis suppuritiva. In this context, the cannabinoids are thought to act at peripheral sites to produce analgesic effects via CB1 and CB2 receptors. It is possible that this analgesia is produced via inhibition of release of calcitonin gene-related peptide [27].

**Kaposi Sarcoma**

Luca et al. found that the CB1/CB2 agonist WIN-55,212-2 had the capability to induce apoptosis in an HIV+/HHV- cell line derived from Kaposi sarcoma. The investigators described transient increases in phosphorylation of ERK 1 and ERK2 followed by increased phosphorylation of stress kinases p38 and JNK. They also found that Caspase-3 and -6 were activated prior to apoptosis. Selective CB1 and CB2 agonists were not found to induce apoptosis in this cell line [28].

Maor et al. found that CBD was able to induce apoptosis of HIV+/HHV+ Kaposi sarcoma endothelial cells via reduction of vGPCR, a G protein-coupled receptor that is expressed in Kaposi sarcoma epithelium but not in normal epithelium, and its agonist, Gro-α**.** CBD also worked to reduce levels of VEGF-C, a G protein-coupled receptor involved in KSHV-induced transformation and growth of endothelial cells, and its ligand, VEGFR-3 [29].

**Pruritus**

Perhaps the most promising application of cannabinoids in the field of dermatology is in the potential for treatment of itch. Several authors [30-33] have described the ability of CB1 and CB2 agonists to reduce itch via activation of receptors present on cutaneous sensory nerve fibers, mast cells, and keratinocytes. The CB1 agonist anandamide is also capable of suppressing itch by interacting with VR/TRPV-1 receptors present on mast cells and keratinocytes [31].

Peripheral administration of PEA has the capacity to attenuate histamine-induced itch in human subjects. PEA has been incorporated into topical creams with relief of pruritus associated with atopic dermatitis, lichen simplex, prurigo nodularis, and uremic pruritus [30]. Several other studies have described the usefulness of endocannabinoids as therapy for the same conditions [32-34] with additional applications in the treatment of anal pruritus [33].

Dronabinol, a synthetic analog of THC that is already FDA-approved for limited indications (treatment of anorexia associated with weight loss and nausea and vomiting associated with cancer chemotherapy), has shown some success in treating cholestatic pruritus as observed in a handful of small case series and case reports [35].

Visse et al. conducted a single blinded and comparison study of 100 patients to evaluate the ability of a Derma-membrane (DMS)-based dermato-cosmetic lotion containing PEA to reduce pruritus caused by dry skin, pruritus intensity, health- related quality of life, and cosmetic acceptance of dry skin as assessed by the patient. They did not find that use the lotion containing PEA had any significant difference in improving these measures in comparison to a control lotion [40].

**Psoriasis**

Cannabinoids have shown promise in treating psoriasis by several proposed mechanisms. Recently, Derakhshan and Kazemi suggested that cannabinoids offered a therapeutic option for

psoriasis via anti-proliferative effects on human keratinocytes and vagal nerve stimulation leading to enhancement of acetylcholine release and subsequent immunomodulation via inhibition of TNF production by cytokine-producing macrophages. Their review of the literature yielded additional possibilities, including inhibition of antigen processing, macrophage/T-cell interaction, and the release of cytokines, including IL-2, TNF, and nitric oxide [37].

Wilkinson et al. found that cannabinoids have the ability to inhibit keratinocyte proliferation *in vitro*. However, the anti-proliferative effects of selective CB2 receptor agonists and a non-selective CB agonist on keratinocytes was not inhibited by CB1 or CB2 agonists, suggesting that the cannabinoids inhibit keratinocyte proliferation independent of cannabinoid receptor activation. The authors postulate that interactions between cannabinoids and the peroxisome proliferator-activated receptor-gamma (PPARγ) may be the primary mechanism of these anti-proliferative effects [36]. In contrast, Derakhshan and Kazemi describe a study that supported the involvement of CB1 activation in this procession via down-regulation of expression of keratins K6 and K16 within human keratinocytes [37]. Taken in sum, these findings do support a potential role for cannabinoids in the treatment of psoriasis, albeit one that requires further investigation and definition.

**Skin Cancer**

Both melanoma and non-melanoma skin cancer cells express the CB1 and CB2 receptors. These receptors can also be found on benign skin tumor cells, including those of papillomas. The role of CB2 is likely greater than that of CB1 in mediating the anti-malignancy properties of the cannabinoids [38]. Activation of the cannabinoid receptors in this context results in interference with endothelial cell migration [4, 5, 34], inhibition of growth, impaired vascularization [4, 34, 38], and induction of apoptosis in tumorigenic epidermal cells [5, 34] while leaving normal epidermal cells unaffected [34].

Experiments on A353 and MelJuso melanoma cell lines demonstrated that cannabinoids significantly decreased the number of viable cells *in vitro* by inducing apoptosis [34]. CB2 receptor agonists have been found to decrease expression of endothelial growth factor (VEGF) and other pro- angiogenic factors [38], inhibit melanoma progression, and inhibit metastatic spread [34]. Cannabinoid-treated tumors also demonstrated diminished EGF-R function [34].

Activation of the cannabinoid receptors was also shown to decrease tumor growth by impeding melanoma cell proliferation. This effect was postulated to occur through downstream inhibition of the Akt pathway and hypophosphorylation of Rb [4]. An additional study suggested that THC was able to inhibit growth of melanoma cells through antagonistic effects on its characteristic pro-inflammatory microenvironment [4].

Armstrong et al. demonstrated that treatment of melanoma cells with THC resulted in activation of autophagy, loss of cell viability, and induction of apoptosis. The authors found that a Sativex-like compound composed of a 1:1 ratio of THC and cannabidiol has the ability to inhibit melanoma viability, proliferation, and tumor growth, as well as increase autophagy and apoptosis when compared to the standard single-agent treatment (temozolomide). The authors assert that the use of Sativex holds great promise as a cytotoxic agent in the treatment of metastatic melanoma and should be further evaluated in clinical trials [1].

**Systemic Sclerosis**

In SSc models, the CB2-selective agonist JWH-133 had the ability to significantly mitigate clinical disease. The suspected mechanism behind this effect is the restriction of immune responses that typically results in tissue damage. In contrast, CB2(-) models exhibited more severe disease. These findings suggest that CB2-selective agonists could be beneficial for the treatment of SSc [2].

The synthetic cannabinoid receptor agonist WIN55,212-2 was observed to reduce extracellular matrix deposition and counteract several other abnormalities observed in scleroderma fibroblasts, including resistance to apoptosis and trans-differentiation of these cells into myofibroblasts. Interestingly, selective cannabinoid receptor antagonists were not able to revert these anti-fibrogenic effects [39].

### Adverse Effects

We acknowledge that cannabinoid products can also be associated with various adverse reactions. Multiple investigators have reported undesirable, and even dangerous, side effects of cannabis and cannabinoid compounds. Both cannabis and cannabinoids can cause cannabinoid hyperemesis syndrome, a constellation of symptoms including abdominal pain, nausea, and vomiting, with characteristic relief of symptoms during warm bathing or showering. Synthetic cannabinoid use has been associated with anxiety, confusion, agitation, mood dysregulation, paranoia, psychosis (both short- and long-term), perceptual disturbances, suicidal ideation, memory impairment, tremors, seizures, nausea, vomiting, diaphoresis, xerostomia, mydriasis, tachycardia, hypertension, chest pain, acute myocardial infarction, rhabdomyolysis, acute kidney injury, respiratory depression, tachyphylaxis, and death [42]. Exposure to cannabinoids can result in cannabinoid sensitization and/or allergy, the manifestations of which range from mild symptoms to life-threatening reactions. Sensitization to cannabinoids can subsequently lead to cross-reactivity with tobacco, latex, and plant and food-derived alcoholic beverages [43]. There have also been several descriptions of cases of cannabis arteritis, a severe peripheral vascular disease that often leads to limb loss, among young adults who consume cannabis [44]. Few pre-clinical studies have also suggested that, whereas cannabinoids have the potential to exert anti-neoplastic effects, they may also play a role in early stages of malignant transformation [34]. These observations serve to reinforce the great need for careful and comprehensive investigation in order to channel cannabinoid-mediated effects in a specific direction and as a targeted treatment of dermatologic diseases.

### Approved Compounds

A select few compounds based on THC have already received FDA approval for limited indications. Marinol, Cesamet, and Sativex are approved for the treatment of anorexia and weight loss in patients with cancer (via appetite stimulation), chemotherapy- or radiotherapy-induced nausea and vomiting, pain relief, mood amelioration, and insomnia [5]. Unfortunately, there are several foreseeable challenges that researchers may come up against in planning future investigations. Strict regulations, lack of funding, concerns about legal ramifications, and general stigma surrounding cannabinoids all contribute to the current scarcity of studies on therapeutic potential of these compounds [45].

### Federal Regulations

Although many states and other jurisdictions permit the use of cannabis for medical and recreational purposes, marijuana remains a Schedule I substance at the Federal level under the Controlled Substances Act. The process of obtaining approval, funding, and study compounds for research on the therapeutic use of cannabinoids involves an extensive application process involving multiple federal and state organizations, including the Drug Enforcement Administration (DEA), the United States Food and Drug Administration (FDA), the National Institute of Health (NIH), and the National Institute on Drug Abuse (NIDA), [45]. Individual state regulations may vary to complicate this process and this problem may also inhibit the initiation of multi-center investigations. Individual institutional policies and concerns about institutional reputation and stigmatization of the investigator also contribute to the challenges of conducting further high-quality and large-scale studies [45]. Although a complete discussion of the many additional barriers to medical cannabinoid research is beyond the scope of this review, we can conclude that the juxtaposition of federal regulations with state, and even institutional policies with legal, ethical, and social factors is incredibly complex and will require careful navigation by investigators.

## Conclusion

The current literature describes numerous, exciting potential applications of cannabinoids in the treatment of various skin disorders. However, the mechanisms, safety, and efficacy of cannabinoids in the treatment of dermatologic diseases remain to be defined. A greater depth of high-quality, large-scale

investigation is required at both the pre-clinical and clinical levels in order to facilitate safe and effective translation into clinical practice. At this time, large, well-planned, randomized, double-blinded, and placebo-controlled studies are needed to confirm and establish the efficacy and safety profiles of these compounds.

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**Table 4.** *Skin diseases with potential cannabinoid treatment.*

| Disease | Proposed Mechanism | Cannabinoid or receptor | Publication | Type of study |
|---|---|---|---|---|
| **Acne** | Endocannabinoids influence differentiation of sebocytes via CR2 receptors expressed on sebocytes and sebaceous glands | CR2 receptor | Zouboulis, 2008 [10] | Review |
| | Decreased erythema and sebum production | CB1/2 receptor | Ali, 2015 [12] | Single-blinded comparison study |
| | Inhibition of lipogenic compounds, suppression of sebocyte proliferation, inhibition of inflammatory pathways | Cannabidiol (CBD) | Olah, 2014 [6] | Bench Research |
| | Altered viability and apoptosis of sebocytes, reduction of arachidonic acid-induced acne-like lipogenesis, anti-inflammatory actions. | Cannabichromene (CBC), Cannabidivarin (CBDV), cannabigerol (CBG), cannabigerovarin (CBGV), and tetrahydrocannabivarin (THCV) | Olah, 2016 [13] | Bench Research |
| **Allergic Contact Dermatitis** | CB2 antagonists reduce inflammation, but CB2 agonists significantly increase inflammation[i]. | CB2 receptor | Basu, 2011 [2] | Review |
| | PEA thought to have antipruritic and immunomodulatory effects | CB2 | Kircik, 2010 [14] | Review |
| **Atopic Dermatitis** | PEA enhances anandamide, an endocannabinoid, through inhibition of the enzyme fatty acid amide hydrolase (FAAH), FAAH degrades endocannabinoids. PEA thought to have antipruritic effects. | Anandamide | Zhang, 2012 [15] | Review |
| | | | Tey, 2011 [16] | Review |
| | | | Varothai, 2013 [17] | Review |
| | | | Stull, 2016 [18] | Review |
| | | | Eberlein, 2008 [19] | Prospective cohort study |
| | | | Mollanazar, 2016 [20] | Review |
| | PEA is an agonist of CB2 receptors on mast cells and nerve fibers thus inhibiting mast-cell activation and decreasing pruritus and promoting analgesic effect | CB2 Receptor | Kircik, 2010 [14] | Review |
| | | | Hong, 2011 [21] | Review |
| | | | Ständer, 2010 [7] | Review |
| | | | Elias, 2008 [22] | Review |
| | Topical THC decreased chemokine ligand 2 (CCL2) production by keratinocytes and interferon (IFN)-gamma production by T cells | CB1, CB2 | Wollenberg, 2014 [23] | Review |
| | None described | N-palmitoylethanolamide (PEA) | Carbone, 2010 [24] | Review |
| | | | Ring, 2012 [25] | Guidelines |
| **Asteatotic eczema** | Endocannabinoids enhance lipid production in the stratum granulosum | N-palmitoylethanolamine (PEA) and N- | Yuan, 2014 [26] | RCT |

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|---|---|---|---|---|
| | | acetylethanolamine (AEA) | | |
| **Hidradenitis Supprurativa** | Cannabinoids may act by inhibiting release of calcitonin gene-related peptide | CB1/2 | Scheinfeld, 2014 [27] | Review |
| **Kaposi's sarcoma (HHV-, HIV+)** | WIN-55,212-2, a mixed CB1/CB2 agonist, activates caspaces that induce apoptosis of cell line derived from Kaposi's sarcoma. Selective CB1 and CB2 agonists were not able to induce apoptosis. | WIN-55,212-2, CB1/ CB2 | Luca, 2009 [28] | Bench Research |
| **Kaposi's sarcoma (HHV+, HIV+)** | CBD inhibited proliferation and induced apoptosis of Kaposi sarcoma endothelial cells infected with herpes virus | Cannabidiol | Maor, 2012 [29] | Bench Research |
| **Melanoma** | THC initiates apoptosis of melanoma cells by induction of autophagy | Tetrahydrocannabinol (THC) | Armstrong, 2015 [1] | Bench Research |
| **Pruritus** | CB1 and CB2 agonists reduce itch due to receptor expression on cutaneous sensory nerve fibers, mast cells and keratinocytes | CB1/2 | Patel, 2010 [30] | Review |
| | | | Brooks, 2008 [31] | Review |
| | | | Ständer, 2008 [32] | Review |
| | | | Reich, 2011 [33] | Review |
| | Not described | PEA, FAAH inhibitors, CBR agonists | Kupczyk, 2009 [34] | Review |
| | Not described | Dronabinol | Feramisco, 2010 [35] | Review |
| **Psoriasis** | Inhibition of keratinocyte proliferation and anti-inflammatory properties | Unknown[ii] | Wilkinson, 2007 [36] | Bench Research |
| | Several proposed mechanisms: anti-proliferative and immunomodulatory mechanisms | THC, CBD, CBG, CBN | Derakhshan, 2016 [37] | Review |
| **Skin Cancer** | Inhibition of tumor growth, decreased expression of endothelial growth factor (VEGF) when treated with CB2-selective agonists, and induction of apoptosis. Possible THC mediated reduction of inflammation. | CB2 (major role), CB1 (minor role), THC | Bowles, 2012 [38] | Review |
| | | | Pisanti, 2009 [5] | Review |
| | | | Kupczyk, 2009 [34] | Review |
| | | | Nikan, 2016 [4] | Review |
| **Systemic sclerosis (SSc)** | CB2 selective agonists attenuation of immune response | CB2 | Basu, 2011 [2] | Review |
| | Mixed CB1/ CB2 agonist acts by reduction of abnormal fibroblast activity | WIN-55,212-2, CB1/ CB2 | Garcia-Gonzalez, 2009 [39] | Bench Research |

**Table 5.** *Cannabinoid therapy trials.*

| Disease | Publication | Type of Study | Sample Size | Cannabinoid | Treatment, Strength | Length of Treatment, Administration | Quality Control of Product | Outcome Measures | Outcome |
|---|---|---|---|---|---|---|---|---|---|
| Asteatotic eczema | Yuan, 2014 [26] | Randomized controlled trial | 60 | N-palmitoylethanolamine (PEA) and N-acetylethanolamine (AEA) | Emollient PEA/AEA cream (0.3%/0.21%) | PEA/AEA emollient or control cream BID x 28 days on legs | Manufactured by laboratory | 1. Clinical scoring via Eczema Area and Severity Index by two separate dermatologists<br>2. Skin surface hydration using corneometer CM820<br>3. Transepidermal water loss (TEWL) using TM210 device | 1. PEA/AEA associated with improving skin scaling, dryness, and itching on day 28 ($p<0.05$)<br>2. PEA/AEA had greater change in capacitance of the skin surface ($p<0.05$)<br>3. There was no difference in TEWL between PEA/AEA cream and control cream |
| Acne | Ali, 2015 [12] | Single blinded comparison study | 11 | *C. sativa* seeds | *C. sativa* seed extract cream (3%) | *C. sativa* seed extract cream on R cheek, control cream on L cheek BID x 2 weeks | Purchased *C. sativa* seeds identified by by Cholistan Institute of Desert Studies. Extract cream prepared by the authors. | 1. Sebum level using Sebumeter device<br>2. Erythema measurements using Mexameter device | 1. Significant decrease in sebum level ($p<0.05$)<br>2. Significant decrease in erythema ($p<0.05$) |
| Chronic pruritus (secondary to dry skin) | Visse, 2016 [40] | Single blinded comparison study | 100 | N-palmitoylethanolamine (PEA) | Derma-membrane system (DMS)-based dermatocosmetic lotion containing PEA | DMS-based PEA lotion or control lotion BID x 2 weeks | Not reported | 1. Pruritus intensity, as assessed by visual analogue scale (VAS) | 1-4. No significant difference between DMS-based PEA lotion group |

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|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | | 2. Pruritus, as assessed by verbal rating scale (VRS)<br>3. Health-related quality of life as measured with the Dermatology Life Quality Index<br>4. Cosmetic acceptance as reported by patient | and control group |
| Atopic eczema (dermatitis) | Eberlein, 2008 [19] | Prospective cohort study | 2456 | PEA | Emollient cream containing PEA | PEA emollient cream BID x 4-6 weeks | Manufactured by laboratory | 1. Patient self-assessment of symptoms, sleep loss, and frequency of use of topical steroids<br>2. Physician assessment of severity, location, improvement, flare-ups, and tolerance of disease | 1. Improvement of symptoms, decreased use of topical steroids, and decreased loss of sleep ($p<0.001$)<br>2. Decreased severity, flare-ups, increased improvement of symptoms and disease tolerance ($p<0.001$) |

**Supplemental Material**

Cannabinoids in Dermatology: A Scoping Review.
Detailed Results of the Scoping Review of the Uses of Cannabinoids in Dermatology:

Dobrosi et al. reported human SZ95 sebocytes express CB2, but not CB1. They also found that endocannabinoids are present within these sebocytes, and serve to up-regulate lipid synthesis and induce apoptosis-driven cell death via selective CB2-coupled signaling. In SZ95 sebocytes with "silenced" CB2, they observed significant suppression of basal lipid production. Collectively, these findings indicate that both CB2 agonists and antagonists ought to be explored in the context of the management of acne and other skin disorders characterized by sebaceous gland dysfunction [11].

In 2014, Olah et al. described the ability of CBD to inhibit the lipogenic actions of various compounds, including arachidonic acid and a combination of linoleic acid and testosterone, in cultured human sebocytes and human skin organ culture. CBD also suppressed sebocyte proliferation via activation of transient receptor potential vanilloid-4 (TRPV4) ion channels and exerted complex anti- inflammatory effects via A2a adenosine receptor-dependent up-regulation of tribbles homolog 3 (TRIB3) and inhibition of NF-κB signaling [6].

In 2016, Olah et al. found that several phytocannabinoids had the capacity to alter viability of sebocytes at low doses, and induce apoptosis of sebocytes at high doses. Cannabichromene (CBC) and tetrahydrocannabivarin (THVC) suppressed basal sebaceous lipid synthesis. Cannabidivarin (CBDV) had only minor effects on suppression of lipid synthesis. The authors found that cannabigerol (CBG) and cannabigerovarin (CBGV) actually increased lipid synthesis. CBC, CBDV, and THCV all significantly reduced arachadonic-induced acne-like lipogenesis. All of the phytocannabinoids investigated by this group demonstrated anti-inflammatory actions [13].

Ali et al. evaluated the effects of a 3% cannabis extract cream on sebum level and erythema in 11 patients with acne in a single blinded and comparative study. They found that use of the use of the cannabis extract cream on the right cheek twice per day for 12 weeks resulted in a significant decrease in sebum level in comparison to a control cream ($p<0.05$) that was applied in the same fashion to the left cheek as measured by a photometric device (Sebumeter). They also found that use of the cannabis extract cream resulted in in a significant decrease in erythema as measured by a reflectance spectrophotometer (Mexameter)[12].

**Allergic Contact Dermatitis**
Basu et al. described the ability of CB2 to mediate both the exaggeration and inhibition of inflammatory responses in allergic contact dermatitis. Subcutaneous administration of a CB2 antagonist, SR144528, to DFNB mice before and after exposure to triggering allergens resulted in increased inflammatory response. Subcutaneous or topical administration of CB2-selective agonist HU-308 also significantly increased inflammation. However, CB2-selective antagonists/inverse agonists JTE-907 and SR144528 actually decreased inflammation. Topical SR144528 also decreased inflammation in oxalozone-induced allergic contact hypersensitivity models [2].

**Asteatotic Eczema/Dermatitis**
Yuan and colleagues conducted a randomized, controlled trial of 60 patients with asteatotic eczema. The patients were instructed to apply an emollient cream to their legs, twice a day, for 28 days. They were randomized to an intervention group that utilized an emollient cream containing N-palmitoylethanolamine (PEA) or N-acetylethanolamine (NEA) and a control group that used a control emollient cream. The authors found that the PEA and NEA emollient creams were superior in improving skin scaling, dryness, and itching on day 28, as measured by the Eczema Area and Severity Index by two dermatologists ($p<0.05$). They also found that the PEA and NEA creams produced greater change in the hydration and capacitance of the skin surface as measured the by the Corneometer CM820. They did not observe any significant difference between the groups in trans-epidermal water loss as assessed by the TM210 device [26].

**Atopic Eczema/Dermatitis**
Several investigators [15-18, 20] have described the ability of anandamide to exert anti-pruritic effects via activation of TRPV1 ion channels. TRPV1 ion channels co-localize with CB2 on keratinocytes and have been postulated to function as "ionotropic cannabinoid receptors". Anandamide, an endocannabinoid, is normally metabolized by the fatty acid amide hydrolase (FAAH) enzyme. The aforementioned authors describe the ability of PEA to enhance the activity of anandamide at the cannabinoid and vanilloid receptors by inhibiting FAAH. The synthetic FAAH inhibitors, URB597 (KDS-4103) and URB937, and PEA thus have potential utility in treating the itch associated with atopic dermatitis.

In a review on the treatment of pediatric atopic dermatitis, Wollenberg et al. described a study in which topical THC application decreased chemokine ligand 2 (CCL2) production by keratinocytes, interferon gamma (IFN-Y) production by T cells, and myeloid immune cell infiltration in wild-type and CB1/2-deficient mice [23].

PEA itself has also been found to have antipruritic effects [15-19]. Mimyx, a PEA-containing lamellar matrix cream, is a steroid- and calcineurin inhibitor-free barrier repair compound. It was designed to mimic components of the stratum corneum, with the goal of repairing and restoring skin barrier function and decreasing trans- epidermal water loss in conditions including atopic dermatitis, allergic contact dermatitis, and radiation dermatitis. It has been shown to have both anti- inflammatory and anti-pruritic properties, with the former likely due to the ability of PEA to bind CB2 receptors and inhibit mast cell activation. It has also been demonstrated to extend remission of atopic dermatitis, an attribute that adds to the potential cost-effectiveness of the agent in comparison to traditional therapies [14].

Carbone and Ring have also described the utility of PEA in the treatment of atopic dermatitis. In a study on atopic dermatitis in a pediatric population, twice daily PEA for 4-6 weeks produced a statistically significant difference in physicians' scores of atopic dermatitis severity when compared to baseline and improvement in patient reported pruritus [24]. PEA has also been shown to attenuate histamine-induced responses, including pain, itch, and erythema, in human skin [25].

Eberlein et al. conducted a prospective cohort study involving 2456 patients who were instructed to apply a PEA-containing emollient cream sparingly to problem areas, twice a day, for 4-6 weeks. There was a statistically significant ($p<0.001$) improvement of patient-reported symptoms, decreased use of topical steroids, and decreased loss of sleep due to itching. Additionally, the authors observed a statistically significant ($p<0.001$) physician-assessed improvement in symptoms, including dryness, excoriation, pruritus, and erythema [19].

**Hidradenitis Suppurativa**

In a recent review, Scheinfield described the potential efficacy of cannabinoids to treat the pain associated with hidradenitis suppuritiva. In this context, the cannabinoids are thought to act at peripheral sites to produce analgesic effects via CB1 and CB2 receptors. It is possible that this analgesia is produced via inhibition of release of calcitonin gene-related peptide [27].

**Kaposi's Sarcoma**

Luca et al. found that the CB1/CB2 agonist WIN-55,212-2 had the capability to induce apoptosis in a HIV+/HHV- cell line derived from Kaposi's sarcoma. The investigators described transient increases in phosphorylation of ERK 1 and ERK2 followed by increased phosphorylation of stress kinases p38 and JNK. They also found that Caspase-3 and -6 were activated prior to apoptosis. Selective CB1 and CB2 agonists were not found to induce apoptosis in this cell line [28].

Maor et al. found that CBD was able to induce apoptosis of HIV+/HHV+ Kaposi sarcoma endothelial cells via reduction of vGPCR, a G protein-coupled receptor that is expressed in Kaposi's sarcoma epithelium but not in normal epithelium, and its agonist, Gro-α. CBD also worked to reduce levels of VEGF-C, a G protein-coupled receptor involved in KSHV-induced transformation and growth of endothelial cells, and its ligand, VEGFR-3 [29].

**Pruritus**

Perhaps the most promising application of cannabinoids in the field of dermatology is in the potential for treatment of itch. Several authors [30-33] have described the ability of CB1 and CB2 agonists to reduce itch via activation of receptors present on cutaneous sensory nerve fibers, mast cells, and keratinocytes. The CB1 agonist anandamide is also capable of suppressing itch by interacting with VR/TRPV-1 receptors present on mast cells and keratinocytes [31].

Peripheral administration of PEA has the capacity to attenuate histamine-induced itch in human subjects. PEA has been incorporated into topical creams with relief of pruritus associated with atopic dermatitis, lichen simplex, prurigo nodularis, and uremic pruritus [30]. Several other studies have described the usefulness of endocannabinoids as therapy for the same conditions [32-34] with additional applications in the treatment of anal pruritus [33].

Dronabinol, a synthetic analog of THC that is already FDA-approved for limited indications (treatment of anorexia associated with weight loss and nausea and vomiting associated with cancer chemotherapy), has shown some success in treating cholestatic pruritus as observed in a handful of small case series and case reports [35].

Visse et al. conducted a single blinded and comparison study of 100 patients to evaluate the ability of a Derma-membrane (DMS)-based dermatocosmetic lotion containing PEA to reduce pruritus caused by dry skin, pruritus intensity, health- related quality of life, and cosmetic acceptance of dry skin as assessed by the patient. They did not find that use the lotion containing PEA had any significant difference in improving these measures in comparison to a control lotion [40].

**Psoriasis**

Cannabinoids have shown promise in treating psoriasis by several proposed mechanisms. Recently, Derakhshan and Kazemi suggested that cannabinoids offered a therapeutic option for psoriasis via anti-proliferative effects on human keratinocytes and vagal nerve stimulation leading to enhancement of acetylcholine release and subsequent immunomodulation via inhibition of TNF- α production by cytokine-producing macrophages. Their review of the literature yielded additional possibilities, including inhibition of antigen processing, macrophage/T-cell interaction, and the release of cytokines, including IL-2, TNF- α, and nitric oxide [37].

Wilkinson et al. found that cannabinoids have the ability to inhibit keratinocyte proliferation in vitro. However, the anti-proliferative effects of selective CB2 receptor agonists and a non-selective CB agonist on keratinocytes was not inhibited by CB1 or CB2 agonists, suggesting that the cannabinoids inhibit keratinocyte proliferation independent of cannabinoid receptor activation. The

authors postulate that interactions between cannabinoids and the peroxisome proliferator-activated receptor-gamma (PPAR-Y) may be the primary mechanism of these anti-proliferative effects [36]. In contrast, Derakhshan and Kazemi describe a study that supported the involvement of CB1 activation in this procession via down-regulation of expression of keratins K6 and K16 within human keratinocytes [37]. Taken in sum, these findings do support a potential role for cannabinoids in the treatment of psoriasis, albeit one that requires further investigation and definition.

**Skin Cancer**

Both melanoma and non-melanoma skin cancer cells express the CB1 and CB2 receptors. These receptors can also be found on benign skin tumor cells, including those of papillomas. The role of CB2 is likely greater than that of CB1 in mediating the anti-malignancy properties of the cannabinoids [38]. Activation of the cannabinoid receptors in this context results in interference with endothelial cell migration [4,5,34], inhibition of growth, impaired vascularization [4,34,38], and induction of apoptosis in tumorigenic epidermal cells [5,34] while leaving normal epidermal cells unaffected [34].

Experiments on A353 and MelJuso melanoma cell lines demonstrated that cannabinoids significantly decreased the number of viable cells in vitro by inducing apoptosis [34]. CB2 receptor agonists have been found to decrease expression of endothelial growth factor (VEGF) and other pro- angiogenic factors [38], inhibit melanoma progression and metastatic spread [34]. Cannabinoid-treated tumors also demonstrated diminished EGF-R function [34].

Activation of the cannabinoid receptors was also shown to decrease tumor growth by impeding of melanoma cell proliferation. This effect was postulated to occur through downstream inhibition of the Akt pathway and hypophosphorylation of Rb [4]. An additional study suggested that THC was able to inhibit growth of melanoma cells through antagonistic effects on its characteristic pro-inflammatory microenvironment [4].

Armstrong et al. demonstrated that treatment of melanoma cells with THC resulted in activation of autophagy, loss of cell viability, and induction of apoptosis. The authors found that a Sativex-like compound composed of a 1:1 ratio of THC and cannabidiol has the ability to inhibit melanoma viability, proliferation, and tumor growth, as well as increase autophagy and apoptosis when compared to the standard single-agent treatment (temozolomide). The authors assert that the use of Sativex holds great promise as a cytotoxic agent in the treatment of metastatic melanoma, and should be further evaluated in clinical trials.

**Systemic Sclerosis**

In SSc models, the CB2-selective agonist JWH-133 had the ability to significantly mitigate clinical disease. The suspected mechanism behind this effect is the restriction of immune responses that typically results in tissue damage. In contrast, CB2(-) models exhibited more severe disease. These findings suggest that CB2-selective agonists could be beneficial for the treatment of SSc [2].

The synthetic cannabinoid receptor agonist WIN55,212-2 was observed to reduce extracellular matrix deposition and counteract several other abnormalities observed in scleroderma fibroblasts, including resistance to apoptosis and trans- differentiation of these cells into myofibroblasts. Interestingly, selective cannabinoid receptor antagonists were not able to revert these anti-fibrogenic effects [39].