Journal of Dermatological Treatment

ISSN: 0954-6634 (Print) 1471-1753 (Online) Journal homepage: https://www.tandfonline.com/loi/ijdt20

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**To cite this article:** Tabrez Sheriff, Matthew J. Lin, Danielle Dubin & Hooman Khorasani (2019): The potential role of cannabinoids in dermatology, Journal of Dermatological Treatment, DOI: 10.1080/09546634.2019.1675854

**To link to this article:** https://doi.org/10.1080/09546634.2019.1675854

JOURNAL OF DERMATOLOGICAL TREATMENT
https://doi.org/10.1080/09546634.2019.1675854

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REVIEW ARTICLE

# The potential role of cannabinoids in dermatology

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**ABSTRACT**

Cannabis is increasingly being used world-wide to treat a variety of dermatological conditions. Medicinal cannabis is currently legalized in Canada, 31 states in America and 19 countries in Europe. The authors reviewed the literature on the pharmacology and use of cannabinoids in treating a variety of skin conditions including acne, atopic dermatitis, psoriasis, skin cancer, pruritus, and pain. Cannabinoids have demonstrated anti-inflammatory, antipruritic, anti-ageing, and antimalignancy properties by various mechanisms including interacting with the newly found endocannabinoid system of the skin thereby providing a promising alternative to traditional treatments.

**ARTICLE HISTORY**
Received 12 August 2019
Accepted 23 September 2019

**KEYWORDS**
Cannabinoids in dermatology; cannabis; endocannabinoids; cannabidiol

## Introduction

In Europe, international law permits the use of cannabis-based medicines for a range of symptoms and conditions, including: nausea, chronic pain, anorexia, spasticity, and multiple sclerosis (1–5). Medicinal cannabis is currently legalized in Canada, 31 states in America and 19 countries in Europe (1,2,6). By contrast, no country in Europe authorizes the smoking of cannabis for medical purposes (1).

The last decade has also seen a growing trend in the use of cannabinoids to treat a variety of skin conditions. Herein, the authors review the chemical and pharmacological basis of cannabinoids and the potential utility of cannabinoids for dermatological conditions including pruritus, atopic dermatitis, psoriasis, acne, and skin cancer.

## Study selection

A literature search was performed using the following databases: Pubmed, EMBASE and MEDLINE. Key search terms were: 'cannabinoids', 'cannabis', 'dermatology', 'cannabidiol', and 'endocannabinoid'. Articles were prioritized and selected based on a universally agreed inclusion criteria by the authors:

- Recent publication date (within 15 years)
- Relevance to dermatology and pharmacology
- Original research

Articles were excluded if they:

- Were not in English
- Were older than 15 years
- Not relevant to dermatology
- Were anecdotal

A total of 44 journal articles were included in the review.

## What are cannabinoids?

Cannabinoids are a large group of compounds that are structurally and biochemically similar to the primary psychoactive compound derived from Cannabis sativa delta(9)-tetrahydrocannabinol (THC). Cannabinoids consist of three main classes – endocannabinoids, phytocannabinoids, and synthetic cannabinoids (Table 1).

Endocannabinoids are produced endogenously and together with their receptors, cannabinoid receptor 1 (CB1), and cannabinoid receptor 2 (CB2), comprise the endocannabinoid system (3–5). CB1 and CB2 are G-protein coupled receptors. CB1 is associated with the psychoactive effects of cannabinoids and is highly concentrated in the central nervous system and, to a lesser extent, in peripheral tissues (5,7). CB2 is associated with the immunomodulatory and anti-inflammatory effects of cannabinoids and is expressed mostly in peripheral organs like the spleen and in cells of the hematopoietic lineage (5,7–9). THC is a well-known plant-based cannabinoid that binds strongly to CB1 (Figure 1). Cannabidiol (CBD) is a phytocannabinoid from the cannabis plant that differs slightly from THC structurally and has demonstrated a role in modulating cell-induced death (5). Endocannabinoids or endogenous cannabinoids such as Anandamide (AEA) and 2-arachiodonoylglycerol (2-AG) are derived from cell membrane phospholipids and are the natural ligands for CB1 and CB2 (5).

## The endocannabinoid system and the skin

Recent studies have shown that CB1 and CB2 have endogenous ligands on the skin, suggesting that the skin has its own endocannabinoid system (ECS) (3–5). Cannabinoids exert both agonist and antagonist effects on the ECS, resulting in inhibition or activation of keratinocyte proliferation, sebum production, hair production, and inflammation (5,8). Activation of CB1 in the stratum spinosum and stratum granulosum of the epidermis and CB2 activation in the basal layer may increase DNA methylation in human keratinocytes via a p38 MAP kinase pathway thereby inhibiting keratinocyte proliferation (10). The possibility of a skin ECS suggests a potential use of CB1 and CB2 selective agonists and antagonists to treat a variety of dermatological conditions via manipulation of the cannabinoid receptors.

## Novel cannabinoids

Beyond the endocannabinoid system, exist novel cannabinoid receptors known collectively as the non-CB1/CB2 receptors or

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orphan receptors (11,12). Their definitive nomenclature and exact role in skin disease is yet to be classified however they have been identified as targets for cannabinoids. Novel cannabinoids are also G-protein coupled receptors (GPCR) and over the last few years two important receptors have been identified—GPR55 and GPR18. Expression of GPR18 is concentrated in the testis, spleen, peripheral blood leucocytes, and lymph nodes (11,12). Activation of GPR18 by N-arachidonoylglycine (a metabolite of the endocannabinoid anandamide) leads to apoptosis of inflammatory leucocytes thereby dampening local inflammation (13). GPR55 is expressed in the central nervous system and is activated by plant cannabinoids delta-THC and endocannabinoids (anandamide and 2-AG) (12). It has been identified as a possible target for the treatment of inflammation, pain, and Parkinson's disease (12).

## Eczematous eruptions

Cannabinoids have demonstrated anti-inflammatory and antipruritic properties, highlighting a potential therapeutic role in the management of atopic dermatitis and allergic contact dermatitis. The mechanisms by which cannabinoids decrease inflammation and pruritus are diverse and involve CB1/CB2 receptors, chemokines, and an interplay between the endocannabinoid system and immune system (4).

Karsak et al. (9) found manipulation of CB2 had the potential to both exaggerate and inhibit inflammatory responses in allergic contact dermatitis. When using a 2,4-dinitro-1-fluorobenzene (DFNAB) mouse model, topical application of a CB2 agonist, delta(9)-THC, reduced inflammation in allergic contact dermatitis (4,9). In the same model, subcutaneous administration of a CB2 antagonist, SR144528, increased inflammation. In contrast, however, oral administration of a CB2 selective antagonists/inverse agonists, JTE-907, decreased inflammation as a consequence of CB2 inactivation (7). These diverse findings suggest that CB2 antagonism may be initially beneficial but detrimental upon chronic blockade (4,7). Further *in vivo* and *in vitro* analysis of the specific role of CB2 agonism versus antagonism is therefore needed.

Gaffal et al. (4) also investigated the application of topical THC and the role of CB1 and CB2 receptors in wildtype and CB1/CB2-deficient mice models. Topical application of THC decreased contact allergic inflammation through inhibition of keratinocyte-derived pro-inflammatory mediators (CCL8 and CXCL10) independent of CB1/CB2 receptors (4). This finding was confirmed in humans by Kim et al. (14) who determined topical application of CB1 specific agonists significantly reduced skin fold thickness and enhanced epidermal permeability barrier function.

Leonti et al. (15) also identified CB1's potential capacity to reduce the inflammatory response in dermatitis. Skin prick tests with falcarinol, an irritant found in carrots, parsley and ginseng, provoked histamine-induced edema by acting as a CB1 antagonist in keratinocytes and increasing expression of pro-allergic chemokines like IL-8 and CCL2/MCP-1 (16). Nam et al. (17) found CB1 agonists decreased mast cell recruitment ($p < .01$) and histamine concentration in the bloodstream ($p < .05$). The authors

**Table 1.** Cannabinoid classes.

| Type of cannabinoid | Constituents of class |
|---|---|
| Endocannabinoids | 2-arachidonoylglycerol (2-AG) |
| | Anandamide (AEA) or N-arachidonoylethanolamine |
| | Homo linoleoyl ethanolamide (HEA) |
| | Docosa tetranyl ethanolamide (DEA) |
| | Palmitoylethanolamide (PEA) |
| | Oleoylethanolamide (OEA) |
| Phytocannabinoids | Δ(9)-tetrahydrocannabinol (THC) |
| | Cannabidiol (CBD) |
| | Cannabigerol (CBG) |
| | Cannabinol (CBN) |
| | Cannabidivarin (CBDV) |
| Synthetic | WIN-55,212-2 |
| | JWH-133 |
| | (R)-methanandamide (MET) |
| | CP 55,940 |

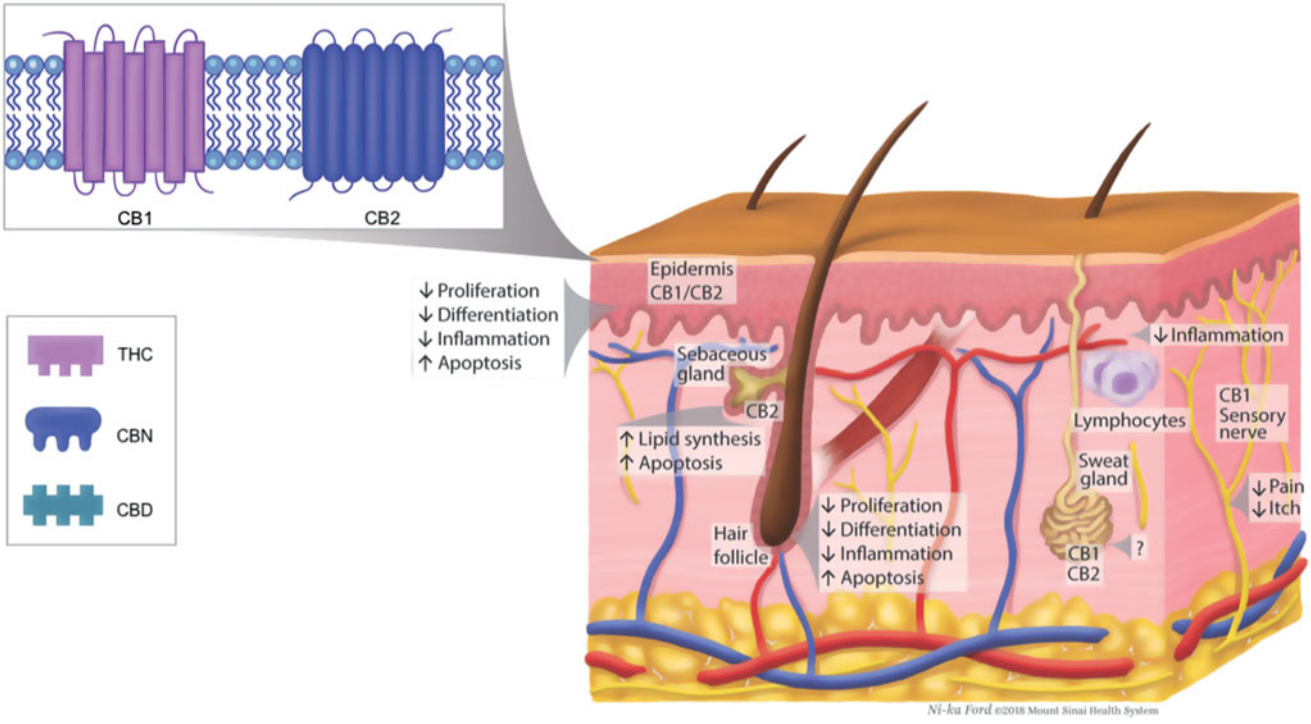


**Figure 1.** The endocannabinoid system. THC binds strongly to CB1 receptors. CBN binds strongly to CB2 receptors. CBD does not fit either CB1 or CB2 but has a role in decreasing activity of T-helper cells, IFN-gamma, IL-17, and keratinocytes.

extrapolated that a reduction in inflammatory mediators may prove beneficial in conditions with mast cell activation, such as contact dermatitis and psoriasis (17).

High concentrations of polyunsaturated fatty acids are thought to reduce itch and inflammation. Callaway et el (18). found that dietary hempseed oil increases the levels of essential fatty acids like linoleic acid and alpha-linoleic acid, which helps improve skin dryness (score $2.25 \pm 1.18$, with $0 =$ no dryness/itching and $5 =$ severe dryness/itching/sleep disturbance) and itching (score $1.56 \pm 1.21$) in patients with atopic dermatitis ($p = .027$ and $p = .024$, respectively).

Furthermore, the literature indicates that CBD has a role in immune pathways involved in atopic dermatitis. Specifically, CBD can potentially inhibit the migration, proliferation and cell maturation processes involved in Th12, Th1, and Th2 immune responses (19,20). CBD has been able to alter gene expression of antigen-primed T-cells to induce a state of anergy via the Erg2 pathway leading to decreased antigen recognition in B-cells with a predominant Th17 response (19). CBD was therefore able to reduce T-cell activity and subsequently also suppress a B-cell mediated response. In addition, CBD has shown to inhibit inflammatory responses due to the addition of IL-17A or IFN-$\gamma$ (16,21). The potential for CBD to decrease IFN-$\gamma$ levels and/or inhibit its effects not only leads to decreased inflammation but also improves skin barrier adherence by reducing IFN-$\gamma$ mediated inhibition of long-chain fatty acid ceramide production in the skin (22).

The above studies suggest a specific anti-inflammatory role of CB1/CB2 and other cannabinoid-mediated inflammatory pathways, highlighting the need for further investigation of CB1/CB2 receptor-dependent and independent effects of cannabinoids.

## Pruritus and cannabinoids

Multiple studies have found that anandamide, an endocannabinoid, possesses antipruritic properties via inhibition of TRPV1 (23,24). TRPV1 is an ion channel expressed mainly in nociceptive neurons of the peripheral nervous system and is responsible for cutaneous induction (burning pruritus). Stander et al. (25) applied palmitoylethanolamide (PEA) with an emollient cream to 22 patients with pruritus, prurigo, and lichen simplex. PEA, which activates anandamide at the cannabinoid receptor by inhibiting the fatty acid amide hydrolase (FAAH) enzyme, decreased itch by 86.4% in these patients. PEA and synthetic FAAH inhibitors, KDS-4103, and URB937, can, therefore, potentially treat itch associated with atopic dermatitis (23,24).

Cannabinoids have also shown to be effective in the treatment of uremic pruritus. Szepietowski et al. (26) evaluated the efficacy of a cream containing lipids and endogenous cannabinoids in 21 patients with uremic pruritus over a 3-week period. Their results showed 38% of patients had complete resolution of itch and 81% had complete reduction of xerosis (26).

A PEA-containing lamellar matrix cream (MimyX ™, Stiefel laboratories, Research Triangle Park, North Carolina) has also been shown to reduce erythema, pruritus, lichenification, and dryness associated with atopic dermatitis by 58.6% (27). With both antipruritic and anti-inflammatory effects, this PEA-containing lamellar matrix cream proposes an alternative to costlier traditional steroids and calcineurin inhibitors. Patients with atopic dermatitis in a pediatric population used the cream for 4–6 weeks. The severity of atopic dermatitis was measured using a four-point analog scale, factoring in lichenification, itching, dryness, and erythema. At the conclusion of the study, patients reported a significant reduction in pruritus compared to baseline (27).

## Psoriasis

Cannabinoids may help inhibit keratinocyte proliferation in psoriasis. Wilkinson et al. (28) proposed that the primary mechanism of THC-mediated inhibition of keratinocyte proliferation is through the peroxisome proliferative-activated receptor gamma (PPAR$\gamma$). A secondary inhibitory mechanism occurs through down-regulation of keratin K6 and K16 expression by CB-1 activation (29,30). Cannabinoids may also exert inhibitory effects on antigen processing and prevent the release of inflammatory cytokines important in the pathogenesis of psoriasis, such as IL-2, TNF-alpha, and interferon gamma (31). Moreover, another synthetic cannabinoid, JWH-133, inhibits other inflammatory cytokines and angiogenic factors involved in psoriasis, such as inducible factor-1 $\alpha$ (HIF-1 $\alpha$), vascular endothelial growth factor (VEGF), basic fibroblast growth factor (bFGF), angiopoitin-2, IL-8, IL-17, and IL-2 *in vivo* and *in vitro* (32). Derakhshan et al. (33) also suggested that the interaction between the immune and nervous system in psoriasis occurs through a cholinergic anti-inflammatory pathway and the endocannabinoid system.

AXIM Biotechnologies began conducting human clinical trials in March 2016 on a topical ointment containing cannabigerol and other cannabinoids of differing concentrations. If successful, their new product, Renecann™, will be the first FDA-approved cannabinoid treatment for psoriasis (34).

## Skin cancer

Cannabinoids may also be useful in the management of both melanoma and non-melanoma skin cancer (NMSC), but further well-designed studies are needed before cannabinoids can be recommended. CB1 and CB2 are expressed by both melanoma and NMSC cell lines. Activation of CB1 and CB2 in mice models has been associated with decreased angiogenesis, growth, proliferation, metastasis, and increased apoptosis within melanoma tumors (35). CB2 in particular appears to have greater antimalignancy properties compared to CB1 (36). A mouse model study compared THC to temozolomide, a chemotherapy control, using immunohistochemical analysis of proliferative activity (Ki67 fluorescence), apoptosis (TUNEL fluorescence), and autophagy (LC3 fluorescence) within skin tumors. The investigators found that, when compared with the chemotherapy control, THC-inhibited melanoma proliferation, growth, and viability while also increasing autophagy and apoptosis (3).

Other animal studies have examined melanoma cell lines (A53 and MelJuSo) and found that CB1 and CB2 activation resulted in increased apoptosis, reduced angiogenesis, and decreased metastases of melanoma (10). The proposed mechanism of these findings involves both cell cycle arrest at the G1-S transition due to hypophosphorylation of the tumor suppressor retinoblastoma protein (Rb) and downstream blockade of the pro-survival Akt pathway (11).

Cannabinoids can also potentially influence NMSC development, although the directionality of this effect is unclear. Long-term ultraviolet B (UVB) light exposure augmented NMSC tumorigenesis in CB1/CB2 $+/+$ mice in comparison to CB1/CB2 $-/-$ mice, suggesting a receptor-dependent relationship with UV-induced neoplasia (37). However, Gegotek et al. found endocannabinoid receptors and endocannabinoids (2-AG and AEA) in keratinocytes and fibroblasts were down-regulated after UVA and UVB radiation, supporting the antitumorigenic properties of cannabinoids (38). This antitumorigenic and pro-tumorigenic paradox is potentially due to the dose-dependent effects of cannabinoids on skin cancer cell viability. Endogenous cannabinoids in the

**Table 2.** Cannabinoid clinical trials.

| Study type and sample size (*n*) | Treatment | Comparison | Outcome(s) measured | Study results | Adverse effects | Study conclusions | Study limitations |
|---|---|---|---|---|---|---|---|
| Randomized, single-blinded comparison study (Ali et al. (8)) $n = 11$ | 3% cannabis seed extract cream applied BID for 12 weeks to right cheek | Base cream applied BID for 12 weeks to left cheek | Sebum production assessed using Sebumeter® device<br>Erythema assessed using Mexameter® device | Significant reduction in erythema and sebum content ($p < .05$) | Nil | Cannabis seed extract cream could treat acne vulgaris, seborrhea, papules and pustules | Small sample size<br>Skin sebum and erythema content not reported |
| Randomized, single blinded controlled study (Callaway et al. (18)) $n = 20$ | 30 mg oral hempseed oil QID for 8 weeks | 30 ml olive oil QID for 8 weeks | Patient-reported questionnaire<br>Trans-epidermal water loss by Vapometer<br>Plasma fatty acid levels | Significant decrease in xerosis, pruritus, and use of TCS after hempseed oil | One participant discontinued due to poor taste | Oral hempseed oil resulted in significant improvement in symptoms of atopic dermatitis a | Small sample size<br>Patient assessment of xerosis |
| Prospective, observational cohort study (Eberlein et al. (27)) $n = 2456$ | Topical PEA emollient (PEACE) cream BID for 4–6 weeks | Nil | Physician assessment of severity, exacerbations, location, improvement and tolerance<br>Patient self-assessment of symptoms using VAS | Reduction in erythema intensity, pruritus, excoriation, scaling, lichenification, and dryness by 58.6% in the study population.<br>Patient assessment: pruritus VAS score reduced from 4.9 to 2.0 and application of TCS decreased by 62% | 1% of participants reported pruritus, erythema and burning | PEACE resulted in improvement of eczematous symptoms, reduced use of TCS and improved quality of life | Absence of control<br>Not randomized |
| Prospective, observational, non-blinded cohort study (Stander et al. (25)) $n = 22$ | Topical emollient cream containing PEA in patients with prurigo, lichen simplex, and pruritus | Nil | Antipruritic effect and itch reduction | 86.4% of participants reported reduction in itch | Nil | Topical cannabinoid agonists are effective and well-tolerated for refractory itch of various origins | Absence of control<br>Not randomized |
| Randomized, double Blinded phase 2 study assessing safety and efficacy of Lenabasum (JBT-101) Open Label Extension (Spiera et al. (44)) $n = 42$ | Cohort 1: oral lenabasum 5 mg QD/20mg BID<br>Cohort 2: oral lenabasum 20 mg QD/20mg BID<br>Cohort 3: oral 20mg BID/ 20mg BID | Placebo pill BID | ACR CRISS<br>PROMIS-29 | Median ACR CRISS score > 95% from 12 to 18months dosing<br>Patient-reported disability, skin symptoms and global health all improved from study start | No serious AEs or deaths. Common AEs were upper respiratory tract infection (28%), skin ulcer (17%), urinary tract infection (14%), arthralgia (14%) and diarrhea (11%) | Positive clinical benefit with acceptable safety and tolerability of lenabasum from Phase 2 results | Valid conclusions can only be determined at trial completion (estimated date of completion: March 2020) |

ACR CRISS: American College of Rheumatology Combined Response Index in Diffuse Cutaneous Systemic Sclerosis Score. Weighted algorithm that includes mRSS (modified rodnan skin score), forced vital capacity, HAQDI (health assessment questionnaire – disability index, physical global assessment and patient global assessment; PROMIS-29: Patient Reported Outcome Modified Measurement Information System; VAS: visual analog scale.

nanomolar range with subsequent UVB exposure increases tumor growth, whereas exogenous administration of cannabinoids in the micromolar range decreases tumor growth (39).

Casanova et al. (40) further investigated the anti-malignancy property of cannabinoids via chemical inoculation of nude mice with epidermal tumor cells(). After local administration of a mixed CB1/CB2 agonist (WIN-55,212–2) or a selective CB2 agonist (JWH-133), considerable growth inhibition of tumor cells was observed due to induction of apoptosis and decreased expression of pro-angiogenic factors (PIGF and Ang2) (40). Soliman et al. (24,41) examined specifically anandamide, a natural ligand for both CB1 and CB2. This ligand is metabolized by cyclooxygenase-2 (COX-2) to J-series prostaglandins, which are known to induce apoptosis via endoplasmic reticulum stress. Elevated levels of COX-2 in tumorigenic keratinocytes, therefore, lent itself to increased anandamide-induced apoptosis (24,41). These findings indicate that the endocannabinoid system may be a useful in the therapeutic induction of tumor cell death.

## Fibrotic skin disease

The CB1 and CB2 receptors may modulate the fibrotic response in conditions such as systemic sclerosis, morphoea, and drug-induced fibrosis. Specifically, CB2 activation in models of fibrotic dermal tissue modulated the immune response, which prevented cutaneous fibrosis and tissue leucocyte infiltration (42). Investigation of a synthetic CB2 agonist in mice with bleomycin-induced fibrosis was also associated with reduced dermal thickening and leucocyte infiltration, suggesting that CB2 receptors may be targeted in the early inflammatory phase of systemic sclerosis (42). This was supported by Gonzalez et al. who identified Ajulemic acid, another nonpsychoactive synthetic analog of THC, which significantly prevented fibrosis in bleomycin exposed mice by stimulating PPARγ signaling. These findings indicate that cannabinoids and PPARγ agonists may be used to target and treat scleroderma, given their ability to modulate fibrosis, inflammation, and vasodilation (43).

Lenabasum (AjA, JBT-101) is a rationally designed oral agonist to CB2 that limits the production of fibrogenic growth factors and extracellular connective tissue, thereby preventing tissue fibrosis. In a randomized, double-blinded phase 2 open label extension study of 42 participants with cutaneous systemic sclerosis, 87% achieved a degree of improvement after 18 months in the Modified Rodnan Skin Score (mRSS). The mRSS has been associated with improved survival in systemic sclerosis (44).

## Acne and seborrhoea

Endocannabinoids have demonstrated utility in the treatment of acne. One study identified CB2 expression on human SZ95 sebocytes (45). Silencing of these CB2 receptors resulted in suppression of basal lipid production, indicating that CB2 antagonists may be useful in the management of skin disorders with sebaceous gland dysfunction (13). Ali et al. investigated the use of 3% cannabis seed extract cream in acne in a single-blinded study of 11 human patients. Participants applied the cream twice daily to the cheek for 12 weeks. Significant improvement in sebum production and erythema was noted at the conclusion of the trial ($p < .05$) (8). Cannabidiol was described by Oláh et al. (46) as a suppressor of sebocyte proliferation via TRPV4 activation. It also inhibits the lipogenic actions of arachidonic acid, linoleic acid and testosterone in cultured human sebocytes (16). Further investigation of the role of specific cannabinoids in the treatment of acne is warranted.

## Skin rejuvenation

Cannabinoids have also demonstrated a role in skin rejuvenation and anti-ageing, due to the ability of the endocannabinoid system to control the proliferation, differentiation and survival of basal cells. Bilkei-Gorzo et al. (47) reported that genetic deletion of CB1 receptors in mice resulted in early onset ageing of the skin. These findings have led to an explosion of non-prescription skin care products that incorporate THC and CBD extracted from hemp plants. Randomized controlled trials are needed to provide scientific evidence in support of these recommendations.

## Conclusion

Patients are increasingly seeking alternative 'natural' treatment options for a range of dermatological conditions. A study in Orlando assessing dermatologists' attitudes to cannabinoids found 86% of respondents believe cannabinoids have medical benefits beyond treating pain and nausea, 68% foresaw using cannabinoids in dermatology and 94% believed it is worthwhile to further research the role of cannabinoids in dermatology ($n = 531$, $p = .018$) (48). The pharmacology of cannabinoids is complex and still not completely understood; however, there appears to be both receptor-mediated and receptor-independent responses that alter immune and cell cycle pathways. Preliminary animal studies do show potential benefits of cannabinoids in the treatment of acne, atopic dermatitis, psoriasis, skin cancer, fibrotic skin diseases, and antiageing, but further well conducted, controlled trials are needed prior to offering definitive recommendations (Table 2).

## Disclosure statement

The authors have no conflict of interest to declare.

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