Cannabinoids for the Treatment of Dermatologic Conditions

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In recent years, cannabinoid (CB) products have gained popularity among the public. The anti-inflammatory properties of CBs have piqued the interest of researchers and clinicians because they represent promising avenues for the treatment of autoimmune and inflammatory skin disorders that may be refractory to conventional therapy. The objective of this study was to review the existing literature regarding CBs for dermatologic conditions. A primary literature search was conducted in October 2020, using the PubMed and Embase databases, for all articles published from 1965 to October 2020. Review articles, studies using animal models, and nondermatologic and pharmacologic studies were excluded. From 248 nonduplicated studies, 26 articles were included. There were 13 articles on systemic CBs and 14 reports on topical CBs. Selective CB receptor type 2 agonists were found to be effective in treating diffuse cutaneous systemic sclerosis and dermatomyositis. Dronabinol showed efficacy for trichotillomania. Sublingual cannabidiol and Δ-9-tetrahydrocannabinol were successful in treating the pain associated with epidermolysis bullosa. Available evidence suggests that CBs may be effective for the treatment of various inflammatory skin disorders. Although promising, additional research is necessary to evaluate efficacy and to determine dosing, safety, and long-term treatment guidelines.

INTRODUCTION

For many centuries, at least as early as BC 500, cannabis has been widely used as an herbal medicine for the treatment of insomnia and gastrointestinal disorders, as an anesthetic agent, and for religious practices (Zuardi, 2006).

In the 19th century, investigation into the pharmacokinetics of the active constituents of cannabis, the cannabinoids (CBs), began to shed light on their potential application in modern medicine (Zuardi, 2006). In recent years, there has been an increase in both preclinical and clinical studies exploring the use of CBs for the treatment of dermatologic conditions (Eberlein et al., 2008; Ständer et al., 2006; Yuan et al., 2014).

Given the increasing availability and popularity of CB-containing skincare products and the increase in clinical studies regarding the role of CBs in the treatment of dermatologic conditions, we aimed to review the existing evidence on the use of CBs for the treatment of dermatologic conditions. To orient the reader, we first provide an overview of CB classes, biological pathways, and mechanistic details as follows.

CBs represent a diverse class of chemicals that share structural and biologic similarities with the psychoactive compound delta-9-tetrahydrocannabinol (Δ^9-THC), which is derived from *Cannabis sativa* (Eagleston et al., 2018).

There are three main classes of CBs: phytocannabinoids (derived from the *C. sativa* plant), endocannabinoids (endogenously produced in humans), and synthetic CBs (synthesized in a laboratory) (Eagleston et al., 2018). An introduction to representative CBs from each class, along with their respective mechanisms, is provided in Table 1.

Phytocannabinoids include over 100 compounds; the most notable of these are Δ^9-THC and cannabidiol (CBD) (Eagleston et al., 2018). The most clinically relevant endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Eagleston et al., 2018), whereas the endogenous fatty acid amide N-palmitoyletha-nolamide (N-PEA) is also recognized as an important component of the endocannabinoid system (ECS), acting through multiple pathways (Petrosino and Di Marzo, 2017). Endocannabinoids have been shown to attenuate the production of proinflammatory cytokines and regulate

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Table 1. Biological Activity of Select CB Compounds

Compound	CB Class	Mechanism of Action[1]	Selected Biologic Effects of Interest
2-Arachidonylglycerol	Endocannabinoid (structure: eicosanoid[2])	Agonist of CB1R (primary location: CNS) and primary endogenous agonist of CB2R (PNS and immune cells)[3]; additional affinity for $GABA_a$, TRPV1, PPAR-γ, GPR55	Regulation of circulatory system; emotion; cognition; pain; inflammation (immune cells and neuroinflammation)
Anandamide (N-arachidonoylethanolamine, AEA)	Endocannabinoid (structure: eicosanoid[2])	Partial agonist of CB1R (primary location: CNS) and CB2R (primary location: periphery)[4]; activator of TRPV1 cation channel[2]	Reward pathways; thermoregulation; nociception
CBD	Phytocannabinoid (structure: classical CB[2])	Low affinity for CB1R/CB2R; can act as an antagonist of CB1R/CB2R agonists and inverse agonist of multiple GPRs; $5-HT_{1a}$ partial agonist at low concentration (inverse agonist at higher concentrations); an allosteric modulator of μ and δ opioid receptors; possible PPAR-γ agonist	Epilepsy; movement disorders; inflammation; pain; anxiety
Dronabinol	Synthetic CB (structure: synthetic analog of THC)	Agonist of CB1R and CB2R; complex CNS effects, including central sympathomimetic action; possible agonism of CB1R receptors in vomiting center of the medulla[5]; possible CB receptor–mediated effects in neural tissue; CB1R receptor agonism in hypothalamus stimulating appetite[5]	Appetite; nausea/emesis; sleep apnea; cannabis withdrawal
Nabilone	Synthetic CB (structure: synthetic analog of Δ^9-THC)	Agonist of CB1R and CB2R; possible agonism of CB1R receptors in vomiting center of the medulla[6]	Chemotherapy-induced nausea/emesis; neuropathic pain
N-PEA	Endocannabinoid-like (structure: fatty acid amide)	Agonist of nuclear PPAR-α; agonist of GPR-55; indirect activator of CB1R/CB2R and TRPV1[7]	Pain (particularly neuropathic); inflammation; mast cell degranulation
Δ^9-THC	Phytocannabinoid (structure: classical CB[2])	Partial agonist of CB1R (action in CNS, PNS, and enteric nervous system) and CB2R (PNS)	Neurological disorders; movement disorders; pain; appetite; inflammation

Abbreviations: Δ^9-THC, delta-9-tetrahydrocannabinol; 5-HT, 5-hydroxytryptamine; AEA, anandamide; CB, cannabinoid; CB1R, cannabinoid receptor 1; CB2R, cannabinoid receptor 2; CBD, cannabidiol; GPR, G-protein-coupled receptor; N-PEA, N-palmitoylethanolamide; PNS, peripheral nervous system; PPAR-γ, peroxisome proliferator–activated receptor-γ.

CB1R plays role in anxiety, pain, metabolism, addiction, inflammation; CB2R plays role in inflammation. GPR is a family of transmembrane receptors with signal transduction through cAMP or phosphatidylinositol pathways. γ-Aminobutyric acid $(GABA)_a$ plays a role in mood, sedation, memory, convulsion, and muscle tone. PPAR-γ plays a role in inflammation.

Serotonin, $(5HT1_a)$ plays a role in mood, vascular tone, pain, emesis, and thermoregulation. TRPV1 plays a role in neuropathic pain.

[1]Receptor types.

[2]Console-Bram L, Marcu J, Abood ME. Cannabinoid receptors: nomenclature and pharmacological principles. Prog Neuropsychopharmacol Biol Psychiatry 2012;38:4–15.

[3]Baggelaar MP, Maccarrone M, van der Stelt M. 2-Arachidonoylglycerol: A signaling lipid with manifold actions in the brain. Prog Lipid Res 2018;71:1–17.

[4]Scherma M, Masia P, Satta V, Fratta W, Fadda P, Tanda G. Brain activity of anandamide: a rewarding bliss? Acta Pharmacol Sin 2019;40:309–323.

[5]Prescribers' Digital Reference. Dronabinol mechanism of action. https://www.pdr.net/drug-summary/Marinol-dronabinol-2726#14 (accessed on September 2021).

[6]Prescribers' Digital Reference. Nabilone mechanism of action. https://www.pdr.net/drug-summary/Cesamet-nabilone-692#0 (accessed on September 2021).

[7]Petrosino S, Di Marzo V. The pharmacology of palmitoylethanolamide and first data on the therapeutic efficacy of some of its new formulations Br J Pharmacol 2017;174:1349–65.

keratinocyte (KC) expression (Eagleston et al., 2018). Therefore, it is not surprising that malfunctioning of the ECS has been implicated in a variety of pathologic skin conditions as well as in cutaneous wounds.

Synthetic CBs, first produced in the 20th century, include dronabinol and nabilone, which are approved by the United States Food and Drug Administration for the treatment of acquired immunodeficiency syndrome–induced anorexia and for chemotherapy-induced nausea and vomiting (Taylor et al., 2020).

The physiologic effects of CBs are mediated through CB receptor 1 (CB1R) and CB receptor 2 (CB2R), which are members of the large family of G protein-coupled receptors. Both CB1R and CB2R are expressed on cutaneous nerve fibers, mast cells, and KCs (Ständer et al., 2005). CB1Rs are the predominant CB type in the CNS and appear at lower concentrations in the peripheral nervous system; in the enteric nervous system; as well as in the heart, liver, and muscle tissues (Nikan et al., 2016). CB2R is notable for its presence in the immune system, with expression among cells of the hematopoietic lineage and organs of the immune system, such as the spleen and thymus (Basu et al., 2011).

With regard to binding effects, CB1Rs are primarily responsible for memory, mood, and modulation of pain sensation through the release of neurotransmitters (Nikan et al., 2016). It is thought that CB2Rs are largely responsible for the anti-inflammatory and immunomodulatory effects of CBs (Nikan et al., 2016). CB2R stimulation in KCs has been shown to promote the release of analgesic opioid peptides, which can modulate pain at a local level as well as systemically (through the CNS) (Caterina, 2014).

CBs can interact with transient receptor potential channels, also known as ionotropic CB receptors, which have been shown to modulate pain and itch perception (Caterina, 2014). Transient receptor potential channels are abundant on cutaneous peripheral neurons.

SKIN HEALTH AND THE ECS
The ECS is an integral component of skin homeostasis, comprising CB1R and CB2R, the endogenous CBs 2-AG and AEA, lipid mediators such as N-PEA, and hydrolytic enzymes such as fatty acid amide hydrolase (Eagleston et al., 2018). N-PEA itself has a low binding affinity for CB1Rs and CB2Rs but is able to activate CB receptors indirectly and enhance the effects of endogenous CB compounds such as AEA. N-PEA serves as an alternative substrate to fatty acid amide hydrolase; this in turn potentiates the physiologic effects of AEA. This is known as the entourage effect (Ho et al., 2008). Downstream signaling mediated by AEA leads to the activation of peroxisome proliferator–activated receptor-α. The signaling response is characterized by the inhibition of proinflammatory cytokines, including IL-2; the induction, proliferation, and differentiation of KCs; and increased synthesis of lipids, including fatty acids and ceramides, which play an important role in maintaining skin barrier function and integrity (Kreitzer and Stella, 2009).

Transcription factors such as NF-κB are essential to the pathogenesis of inflammatory skin disorders; NF-κB has been shown to activate downstream molecular signaling pathway, resulting in the upregulation of proinflammatory mediators such as IL-8, matrix metalloproteinase, and VEGF (Hoesel and Schmid, 2013). Results of an in vitro model of human KC cell lines show that CBD is able to inhibit NF-κB transcription and subsequently inactivate the inflammatory cascade (Motwani et al., 2018).

MECHANISTIC ACTION OF TOPICAL CBS
Topical Δ^9-THC and CBD have been shown to suppress the levels of proinflammatory cytokines, including IL such as IL-6 and IL-17, whereas pretreatment with CBD has resulted in an upregulation of IL-10, an anti-inflammatory cytokine (Kozela et al., 2013). These immune-modulating effects appear to be mediated independently of CB signaling pathways.

MECHANISTIC ACTION OF ORAL CBS
Recent studies have illustrated several mechanisms through which oral CBs exert their effects. For example, systemic sclerosis (SSc) fibroblasts are known to possess increased numbers of CB2R, through which oral CB2R agonists act to reduce TGFβ and collagen production and limit the fibrosis characteristic of SSc (Spiera et al., 2020). Modulation of the ECS system by CB2R agonists stimulates the resolution of innate immune responses by activating the production of proresolving lipid mediators, such as lipoxin-A_4 and B_4 and resolvin-D1 and D3. Activation of CB2Rs present in lymphoid tissue has been shown to inhibit cytokine release from immune cells and, therefore, decrease inflammation (Spiera et al., 2020). The marked anti-inflammatory action of CB2R agonists is due in part to inhibition of leukotriene B_4, a neutrophil chemoattractant, and allows for effective clearance of inflammatory stimuli by inhibiting antiphagocytic prostanoids, including prostaglandin E_2, thromboxane B_2, and prostaglandin $F_2\alpha$ (Motwani et al., 2018).

Oral CB2R agonists have also been shown to modulate the immune system in patients with dermatomyositis (DM). A recent study showed a reduction in the production of proinflammatory cytokines, including TNF-α, IFN-α, and IFN-β, among those treated with ajulemic acid/lenabasum, a CB2R agonist (Robinson et al., 2017).

A summary figure illustrating the mechanistic actions and therapeutic effects of CBs as they relate to skin health and the immune system is provided in Figure 1.

A systematic review was conducted, adhering to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Liberati et al., 2009) as illustrated in Figure 2. A search in the Embase and PubMed databases for all peer-reviewed articles in the English language was performed in October 2020, using the following search terms: dermatology, dermatologic conditions, cutaneous, skin, psoriasis, pruritus, and oral, topical, cannabinoids.

The resulting articles were screened on the basis of eligibility criteria. Only articles written in English and discussing the study of CB-based products in humans for treating skin conditions were included. Review articles, studies regarding pharmacology, and in vitro or in vivo studies were excluded. Study design and outcome data were extracted from each included article and are summarized in Tables 2 and 3.

The search criteria identified 270 published articles from 1965 to October 2020. After duplicates were removed, two
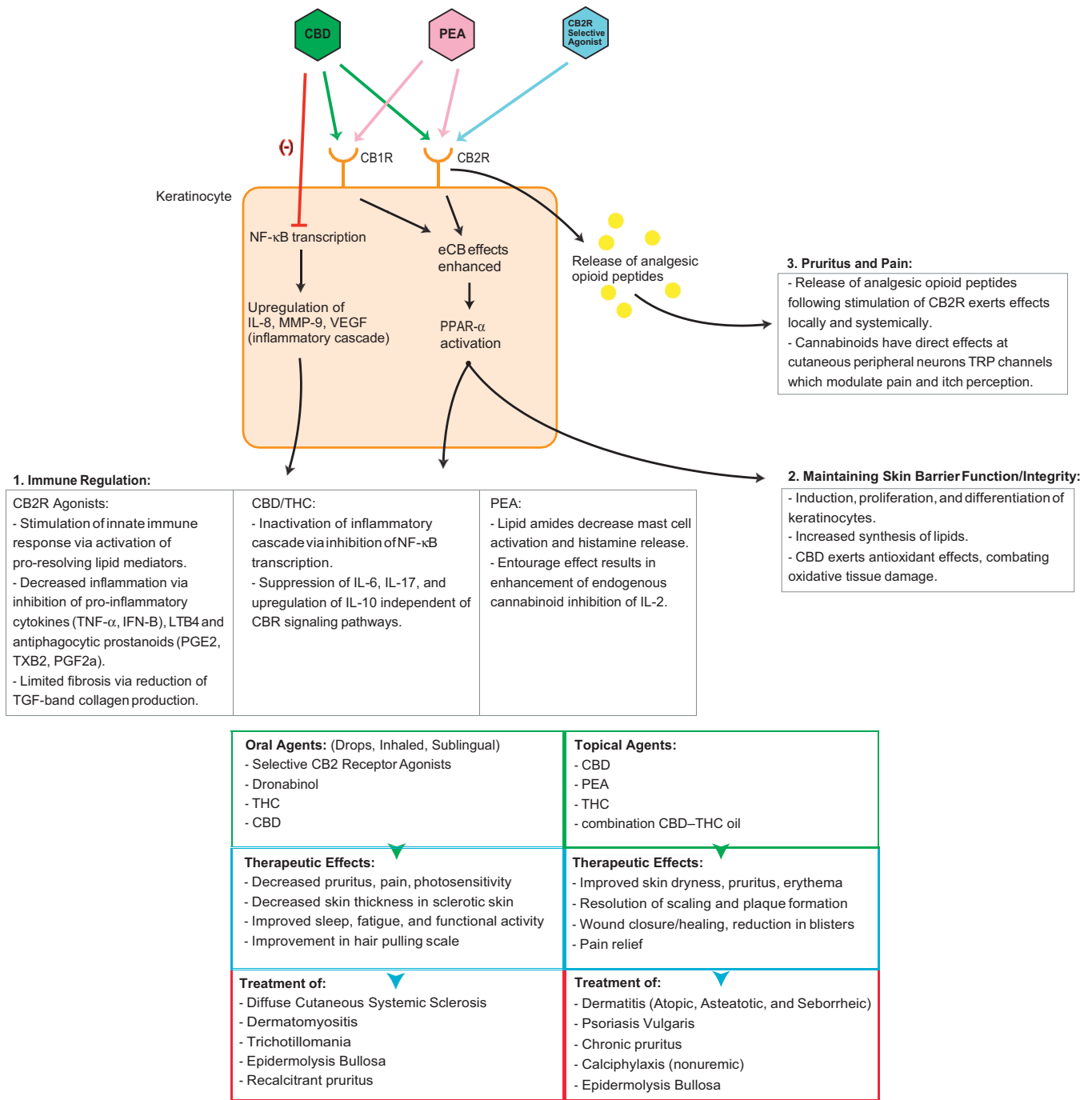
Figure 1. Cannabinoid mechanisms of action. Proposed mechanisms of action of cannabinoids on the immune and cutaneous neuroendocrine system. CB, cannabinoid; CBR, cannabinoid receptor; CB1R, cannabinoid receptor 1; CB2R, cannabinoid receptor 2; CBD, cannabidiol; MMP-9, matrix metalloproteinase 9; PG, prostaglandin; THC, tetrahydrocannabinol; TRP, transient receptor potential; TXB2, thromboxane B2.

reviewers (TES and JM) independently screened articles on the basis of title, abstract, and full-text review to determine eligibility. One article (Maghfour et al., 2020) known to the authors from previous research was also included, with 26 reports eligible for inclusion in this review. Of these, 12 were clinical trials (randomized, open label); six were cohort studies, including one retrospective study; six were case reports or case series; and two were pilot studies. Retrieved articles included assessments of both topical and oral CBs.

There were 13 reports that assessed the effects of systemic CBs (oral, inhalation, or sublingual preparations), of which seven were clinical trials; there were two pilot studies, two case series, one case report, and one experimental study (see Table 2).

There were 13 articles assessing the utility of topical CBs (shown in Table 3). Of these, four were randomized controlled trials (RCTs), five were cohort studies, and four were case reports or case series. Only one article investigated the effects of both topical and oral CBs.
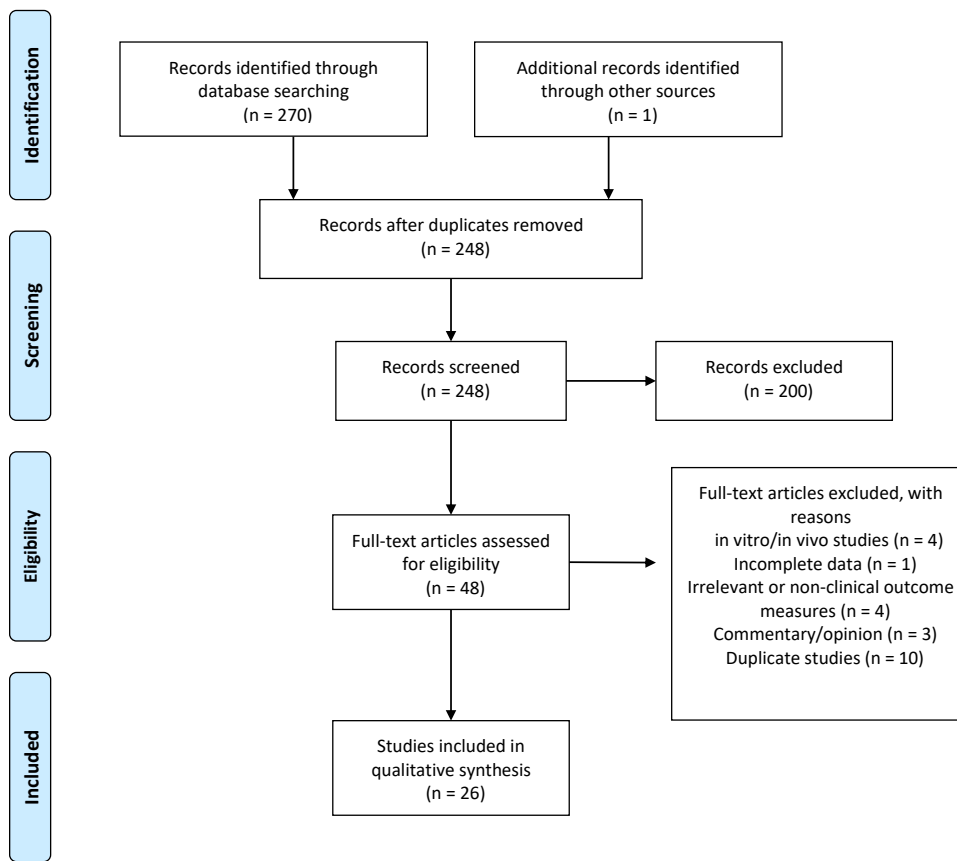
Figure 2. PRISMA flow diagram. The search process is depicted using a flow diagram adapted from the PRISMA guidelines. PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

EFFICACY OF ORAL CBS

Diffuse cutaneous SSc

Current dermatologic literature regarding the use of oral CBs is focused on the treatment of diffuse cutaneous systemic sclerosis. The strongest evidence of safety and efficacy is derived from two RCTs and three open-label extension trials—in these trials, selective CB2R agonists (ajulemic acid; trade name lenabasum, formerly anabasum) were investigated.

Lenabasum is a nonpsychoactive synthetic CB that is a CB2R agonist. Its therapeutic effects occur through the modulation of the immune system and resolution of fibrosis, through two putative molecular mechanisms (Burstein, 2021). After CB2R and phospholipase A2 activation, free arachidonic acid enters one of two pathways: the cyclooxygenase-2− or lipoxygenase-mediated pathway (Burstein, 2021). The cyclooxygenase-2 pathway facilitates caspase production and ultimately apoptosis and resolution of chronic inflammation, whereas the lipoxygenase pathway produces lipoxin A_4 and other proresolving mediators (Burstein, 2021).

Lenabasum was investigated for the treatment of SSc in 42 participants on immunosuppressive therapy, who received either placebo or oral lenabasum for a total duration of 84 days (Spiera et al., 2017: "A phase 2 study…"). After discontinuation of therapy or placebo, all participants were followed from days 85 to 113. Therapeutic dosage was based on randomization and consisted of the following: 5 mg lenabasum daily, 20 mg lenabasum daily, or 20 mg lenabasum twice a day for days 1 to 28, followed by 20 mg twice daily on days 29 to 84, or placebo on days 1 to 84. In the overall disease assessment, the treated group experienced a greater improvement than the placebo group (American College of Rheumatology-combined response index in diffuse cutaneous systemic sclerosis [ACR-CRISS] score: 33 vs. 1% at week 16 in the lenabasum and placebo groups, respectively, $P = 0.044$). There was also a greater reduction in skin thickness and pruritus observed in the lenabasum group. In an open-label extension (Spiera et al. 2017: "Safety and efficacy…"), all participants received lenabasum for a median duration of 194 days, and at 10 weeks, modified Rodnan skin thickness score (MRSS) decreased by 3.2 compared with that at the baseline ($P = 0.0001$).

In a double-blind placebo-controlled RCT (Spiera et al., 2020), the safety and efficacy of oral Lenabasum were explored in 42 subjects (aged 18−69 years) with diffuse cutaneous SSc. This included 32 female participants (9 in the placebo group and 23 in the treatment group). During the initial 4 weeks, participants in the treated group received one of the following: 5 mg or 20 mg of lenabasum once daily. For the remaining treatment period (8 weeks), all subjects in the lenabasum-treated group received a dose of 20 mg twice daily. The control group (n = 12) received placebo throughout the entire study duration (n = 12 weeks). All participants were assessed at weeks 4, 8, 12, and 16.

All participants, including the control group, were receiving background immunosuppressive medications (mycophenolate, etanercept, or hydroxychloroquine). All

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Table 2. Summary of studies investigating oral cannabinoids

Condition, Source	Level of Evidence	Study Design, Number of Participants	Cannabinoid Treatment Regimen	Results	Adverse Events
Diffuse cutaneous SSc					
Spiera et al. 2017	1	RCT, n = 42	Oral lenabasum 5 mg or 20 mg q.d. or 20 mg b.i.d. for 4 wks, then 20 mg b.i.d. for 8 wks; or PBO .	Significant Improvement in ACR-CRISS scores, (including MRSS, PtGA, and PGA) compared with those of the PBO (over 16 wks), $P = 0.044$.	n = 5 (14%), mild fatigue; n = 4 (11%), mild/moderate URI; dizziness occurred in two (6%) subjects.
Spiera et al. 2017	2	OLE, n = 36	Oral lenabasum (20 mg b.i.d.)	Skin induration improved; no withdrawals due to medication	AEs: ≥10% subjects had mild fatigue (14%) and mild/moderate URI (11% of subjects); dizziness in 6%.
Spiera et al. 2018	2	OLE, n = 19	Oral lenabasum (20 mg b.i.d.)	Improvements from study start were ACR-CRISS score = 0.33, MRSS = -8.6 (1.5), HAQ-DI = -0.14 (0.11), PGA = -0.9 (0.5), and 5-D itch = -2.3 (0.8). FVC% predicted was stable from study start.	One subject had a life-threatening AE, 3 (8%) had severe AEs, 21 (58%) moderate, and 8 (22%) mild AEs. Seven (19%) had AEs related to lenabasum; AEs include URI, UTI, diarrhea, and skin ulcers.
Spiera et al. 2019	2	OLE, n = 36	Oral lenabasum (20 mg b.i.d.), assessed at 4 weeks, then every 8 weeks	Compared with the study start, ACR-CRISS median score: 0.99 (0.43 IQR) at wk 76 and MRSS declined by mean (SD) = -10.7 (7.2) points. FVC% predicted decreased by 2.5% from the study start.	At week 92, 97% of subjects had at least 1 AE. 7 (19%) had at least 1 AE considered (fatigue), which was related to lenabasum
Spiera et al. 2020	1	RCT, n = 42	Oral lenabasum, dose 5 mg or 20 mg once a day, or 20 mg b.i.d. for 4 weeks, then 20 mg b.i.d. for 8 weeks, or PBO	Median ACR-CRISS score at wk 16 was 0.33 versus 0.00 in PBO. PtGA treatment differences: 1.2 (0.67) ($P = 0.04$, $P = 0.08$ at wk 16). SSPRO treatment effect (SE) = -16 (6.0) ($P = 0.005$, $P = 0.01$ at wk 12); 5-D itch was -1.8 (1.0) ($P = 0.04$, $P = 0.08$ at wk 12). HAQ-DI at 12 weeks: -0.32 (0.12) ($P = 0.006$, $P = 0.01$).	Lenabasum versus PBO: AEs 63% versus 60%. In lenabasum group, dizziness and nausea were most common. No evidence of toxicity.
Nogueira et al. 2019	5	Case report, n = 1	Inhaled cannabis (30 g/day)	Improvement in all symptoms and total resolution of Raynaud's phenomenon and dyspnea.	No AEs reported
Cocchiara et al. 2019	3	Cohort study, n = 25	CBD (10%) orally b.i.d. and topical application.	Significant reduction in pain VAS and HAQ-DI at 2 months.	No AEs reported
Dermatomyositis (skin predominant)					
Werth et al. 2018	1	RCT, n = 22	Oral lenabasum in escalating doses for 12 weeks.	Mean reduction in CDASI activity by ≥5 points at all visits after 4 weeks ($P = 0.02$); Greater improvement than PBO in PROM of global skin disease and overall disease assessments, skin symptoms[1] ($P ≤ 0.1$) at visits after wk 4.	No AEs reported
Werth et al. 2019	2	OLE, n = 22	Oral lenabasum (20 mg b.i.d.)	At week 28, decrease in CDASI score by 15 points. Physician overall disease VAS = -2.6 (1.90) points, 82.3% of subjects achieving at least 1 point and 20% improvement. Significant improvement in Skindex 29.	≥1 mild AEs in five subjects (25%) Two subjects (10%) experienced DM flare
Trichotillomania					
Grant et al. 2011	3	Pilot study, n = 14	Oral dronabinol (2.5–15 mg/day)	MGH-HPS scores decreased from a mean of 16.5 ± 4.4 at baseline to 8.7 ± 5.5 at study endpoint (mean effective dose = 11.1 ± 4); NIMH-Trichotillomania severity: 11.21 decreased to 4.36 ($P < 0.001$)	No AEs reported

Epidermolysis bullosa					
Schräder et al. 2019	Case Series, n = 3	4	Sublingual THC/CBD (20 mg/mg, CBD; 13 mg/mg,THC)	Improved pain control and decreased pruritus with CBD/THC oil. VAS reduction from 9/10 to 3/10 at 1 month for one subject; 40% reduction in pain reported in one subject; VAS reduction from 9/10 to 1–4/10 at 1 month in one subject.	Increased appetite (n = 1), drug–drug interaction with opioid in one patient (reduced reaction time, altered sense of time)
Pruritus (various causes)					
Neff et al. 2002	Case series, n = 3	4	5 mg Dronabinol nightly	Resolution of pruritus in three of three patients after 4–6 hs of dronabinol dose	Disturbance in coordination, resolved with a decrease in dronabinol (by 2.5 mg)
Dvorak et al. 2003	Pilot study, n = 12	3	HU210 (through a skin patch or microdialysis)	Resolution of pruritus. Skin blood flow and neurogenic-mediated flare responses were reduced ($P < 0.003$ and $P < 0.03$)	AEs not reported

Abbreviations: ACR-CRISS, American College of Rheumatology-Combined Response Index in diffuse cutaneous Systemic Sclerosis; AE, adverse event; b.i.d., twice a day; CBD, cannabidiol; CDASI, Cutaneous Dermatomyositis Disease Area and Severity Index; DM, dermatomyositis; EB, epidermolysis bullosa; HAQ-DI, Health Assessment Questionnaire–Disability Index; IQR, interquartile range; MGH-HPS, Massachusetts General Hospital Hair Pulling Scale; MRSS, Modified Rodnan Skin thickness Score; NIMH, National Institute of Mental Health; OLE, open label extension; PBO, placebo; PGA, Physician Global Assessment; PROM, patient reported outcome measure; ptGA, patient Global-Assessment; q.d., every day; RCT, randomized controlled trial; SSc, systemic sclerosis; SSPRO, Scleroderma Skin Patient-Reported Outcome; THC, Δ[9]-tetrahydrocannabinol; URI, upper respiratory infection; UTI, urinary tract infection; VAS, Visual Analog Score.

[1]Skin symptoms included: pain interfering with activities, fatigue, photosensitivity and itch.

treated subjects experienced an overall improvement as assessed by the ACR-CRISS score. The ACR-CRISS is a validated outcome measure for SSc. It is composed of five core sets of measures, including MRSS, percent predicted forced vital capacity, the health assessment questionnaire disability index, and the patient and clinical global assessments. A score of 0.6 or higher indicates the likelihood that a patient improved with treatment (Khanna et al., 2016). At week 16, the ACR-CRISS score for the treated group was 0.33 (interquartile range: 0.01−0.82), compared with 0.00 (interquartile range: 0.000−0.16) in the placebo group ($P = 0.04$). Participants also experienced improvement in the following domains: scleroderma skin patient-reported outcome ($P < 0.005$), MRSS (mean ± SEM: −2.6 ± 1.9 at week 16, $P < 0.05$), and 5-D itch score (mean ± SEM: −1.8 ± 1.0 at week 12, $P = 0.04$).

Two open-label trials (Spiera et al., 2018, 2019) further explored the safety and efficacy of oral lenabasum among participants who had completed the phase II trial. A total of 25 subjects remained on lenabasum for 52 weeks, with additional improvement in ACR-CRISS score (56%) compared with that at the baseline (before therapy initiation) (Spiera et al., 2017: "Safety and efficacy…"). A reduction in skin thickness (MRSS = −8.6) and decrease in pruritus (5-D itch scale = −2.3) were also observed. In another open-label study (Spiera et al., 2019), participants who remained on lenabasum for >18 months continued to experience clinical improvement in ACR-CRISS score (0.99) and skin thickness reduction (MRSS = −10.2).

It is important to note that although lenabasum appeared to show great promise for the treatment of scleroderma, on the basis of the results of phase II trials and open-label extension studies, it has failed phase III testing, owing to its inability to meet the primary efficacy endpoint of significant ACR-CRISS improvement compared with placebo (Terry, 2020). Notably, ACR-CRISS was the primary outcome measure in the successful phase II trial of lenabasum. However, posthoc analysis of the phase III data showed that participants who received background immunosuppression and were treated with 20 mg lenabasum twice daily had a smaller decline in forced vital capacity at 1 year than those who were treated with placebo (nominal $P = 0.048$). Treatment with lenabasum was also associated with a greater likelihood of a stable forced vital capacity percentage predicted (64% lenabasum vs. 35% placebo).

Both inhaled cannabis and oral formulations of CBD oil have resulted in improvement in the symptoms of SSc. In a study (Cocchiara et al., 2019) on subjects with SSc (n = 25; 22 female) that assessed both oral ingestion of 10% CBD oil (five drops twice daily) and local application of CBD oil to cutaneous ulcers, there was a significant improvement in pain, Visual Analog Score (VAS) improved from 94.8 at baseline to 40.9 after treatment ($P < 0.0001$), and the health assessment questionnaire disability index decreased from 1.1 to 0.46 after a 2-month course of therapy.

In a previous study (Nogueira et al., 2019), a patient with SSc who smoked 30 g of *C. sativa* daily experienced an improvement in dyspnea, Raynaud's phenomenon, and pain. However, there were no specific metrics measured in this study.

Table 3. Summary of Studies Investigating Topical Cannabinoids

Condition, Source	Level of Evidence	Study Design	Cannabinoid Treatment Regimen	Results	Adverse Events
Atopic dermatitis					
Yuan et al. 2014	1	RCT, n = 60	Topical N-PEA/AEA	Reduction in skin scaling, dryness, and itching ($P < 0.05$)	AEs not reported
Palmieri et al. 2019	3	Retrospective cohort, n = 5	Topical CBD, twice daily, for 3 months	Hydration increased ($P < 0.01$); TEWL improved ($P < 0.001$); improvement in SCORAD index score	AEs not reported
Eberlein et al. 2008	3	Cohort, n = 2,456	Topical N-PEA, b.i.d. for 6 wks	Significant reduction in dryness, excoriations, lichenification, scaling, erythema, and pruritus ($P < 0.001$).	Pruritus, burning, and erythema
Pulvirenti et al. 2007	3	Cohort study, n = 20	Topical adelmidrol	16 (80%) experienced complete resolution of AD symptoms	AEs not reported
Maghfour et al. 2020)	3	Cohort study, n = 16	Topical CBD, b.i.d. for 2 wks	Reduction in POEM: (16 ± 1.35) to (8.25 ± 1.80), $P < 0.0007$. QOLHEQ from a mean score of 20.9 ± 2.06 to 8.375 ± 1.609 ($P < 0.004$)	AEs not reported
Pruritus (various causes)					
Szepietowski et al. 2005	3	OLE, n = 21	Topical AEA/N-PEA	Reduction in xerosis in 80% of Pts; decrease in pruritus ($P < 0.001$); n = 8 experienced resolution of itch	AEs not reported
Visse et al. 2017	3	Cohort, n= 100	Topical N-PEA, twice daily, for 2 wks	Pruritus VAS decreased after 2-wk treatment ($P < 0.001$).	12 subjects experienced the following AEs: pruritus, stinging, scaling, and erythema)
Ständer et al. 2006	3	Observational, n = 7	Topical N-PEA, daily, 2 wks for 6 months	Improvement in pruritus, unspecified. No changes in the intensity of pruritus due to aquagenic and/or cholestasis	AEs not reported
Prurigo nodularis					
Ständer et al. 2006	3	Observational, n = 13	Topical N-PEA, daily for 7.6 wks	Reduction in pruritus in nine subjects	AEs not reported
Lichen simplex chronicus					
Ständer et al. 2006	3	Observational, n = 2	Topical N-PEA, daily for 3 wks	(VAS: 8.5 vs. 0; $P < 0.05$) in both Pts	AEs not reported
Psoriasis vulgaris					
Friedman et al. 2020	5	Case report, n = 1	THC soap infused with hemp 5 mg/mL, hair oil with THC distillate dissolved oil 5 mg/mL	Lesion clearance after 2 wks. At 2 months, Pt started using product as maintenance therapy (once a wks)	AEs not reported
Palmieri et al. 2019	3	Retrospective cohort, n = 5	Topical CBD ointment, b.i.d. for 3 months	A decrease in the number of psoriasis plaques. Improved PASI at day 90 ($P < 0.001$).	AEs not reported
Scalp psoriasis and seborrheic dermatitis					
Vincenzi et al. 2020	3	Observational study, n = 50	0.075% CBD in shampoo, daily	Reduction in arborizing vessel/twisted capillary inflammation and scaling by day 14 in both scalp psoriasis and seborrheic dermatitis.	AEs not reported
Epidermolysis bullosa					
Chelliah et al. 2018	4	Case Series, n = 3	Topical CBD, daily	Decreased pain, faster wound healing	AEs not reported

(continued)

Table 3. Continued

Condition, Source	Level of Evidence	Study Design	Cannabinoid Treatment Regimen	Results	Adverse Events
Wounds (pyoderma gangrenosum, calciphylaxis)					
Maida and Corban 2017	4	Case series, n = 3, Pyoderma Gangrenosum	THC 7 mg/ml + CBD 9 mg/ml). Route: 0.5-1mL to wound bed.	Daily pain score decreased (P <0.05) (n = 2). All cases had pain reduction of 30% or greater. Average daily opioid dose was reduced	Onset of analgesia 3–5 min after application of topical CBD/THC
Maida et al. 2020	2	Multicohort open-label trial, n = 33, calciphylaxis	Topical THC and CBD	Wound closure in up to 90% of cases in nonuremic Pts.	AEs not reported

Abbreviations: AD, atopic dermatitis; AE, adverse event; AEA, anandamide; b.i.d., twice a day; CBD, cannabidiol; N-PEA, N-palmitoylethanolamide; PG, pyoderma gangrenosum; Pt, Patient; sig, significant; POEM, patient-oriented eczema measure; QOLHEQ, Quality of Life Hand Eczema Questionnaire; RCT, randomized controlled trial; SCORAD, scoring atopic dermatitis; TEWL, transepidermal water loss; THC, tetrahydrocannabinol; VAS, Visual Analog Score.

DM

The role of lenabasum was investigated in a study of 22 participants with DM: 11 subjects received 20 mg oral lenabasum twice daily, whereas the remaining half of participants were in the placebo group for a total duration of 16 weeks (Werth et al., 2018). Compared with placebo, a five-point reduction in cutaneous disease activity severity index score (CDASI) was observed at 16 weeks ($P < 0.05$). Patient-reported metrics of global skin disease, including photosensitivity and itch, were significantly improved at week 4. Treated participants also experienced an improvement in fatigue, sleep, and functional activity.

Of the 22 participants in the study, 20 were eligible for an open-label extension (Spiera et al., 2019, 2017; Werth et al., 2019), in which all subjects received oral lenabasum for 28 weeks. A 15.4-point reduction in CDASI, a reduction in VAS results for itch and pain, and QOL improvement measured through Skindex-29 were noted after treatment completion. There were two serious adverse events reported (fatigue and metastatic prostate cancer), which were considered unrelated to lenabasum; no serious events related to lenabasum were reported, and no subjects discontinued the open-label extension owing to adverse events related to the drug (Spiera et al., 2019). With regard to DM, lenabasum also failed to meet its primary endpoint in phase III: total improvement score at week 28. Of note, regulatory mandates prompted the change from CDASI to total improvement score as the primary outcome for the phase III trial, whereas the validated CDASI scale was downgraded to a secondary endpoint. Nonetheless, posthoc analysis of phase III data revealed that participants with skin predominant DM (minimal muscle activity) experienced a significant improvement in CDASI score ($P = 0.016$) (Global Newswire, 2021).

Trichotillomania

The effect of oral dronabinol was investigated in 14 female patients (mean age = 33.3 years) with trichotillomania for a period of 12 weeks (Grant et al., 2011). The mean effective dose of dronabinol was 11.6 mg (range: 2.5−15 mg). At the end of the study, there was an improvement in the Massachusetts General Hospital Hair Pulling Scale from 16.5 ± 4.4 at baseline to 8.7 ± 5.5 ($P = 0.001$).

Epidermolysis bullosa

Phytocannabinoids (Δ^9-THC and CBD) were explored as a therapeutic option among three patients with epidermolysis bullosa (aged 36−61 years) (Schräder et al., 2019). Sublingual delivery of Δ^9-THC (13 mg/ml) and CBD (20 mg/ml) was provided to all participants. The main outcome measured was an improvement in pain and pruritus; improvement was noted after only 1 month of treatment.

In one patient, after 2 years of treatment with the sublingual CB regimen, the addition of topically applied Δ^9-THC−CBD oil (1 mg CBD with 0.65 mg Δ^9-THC) enabled the cessation of topical morphine and amitriptyline; the patient also continued on the sublingual CB regimen. A patient with recessive dystrophic epidermolysis bullosa (generalized severe) continued to experience severe pain despite being on a regimen of multiple opioids; after 1 week of sublingual CBD−Δ^9-THC combination oil, the patient reported a 40% reduction in pain (Schräder et al., 2019).

Pruritus secondary to systemic diseases

In this review, one report (Neff et al., 2002) assessed the efficacy of oral Δ^9-THC for the treatment of recalcitrant pruritus secondary to cholestatic liver disease. All three patients in the report were unresponsive to doxepin, naltrexone, cholestyramine, UV therapy, and plasmapheresis; they experienced severe and debilitating pruritus that resulted in impaired QOL, depression, and suicidal ideation. Patients were started on 5 mg of Δ^9-THC at bedtime and experienced a decrease in pruritus, along with improvements in sleep and functional activities, with treatment effects lasting from 4 to 6 hours. One patient developed disturbance in coordination, which improved after a dose reduction to 2.5 mg at night (Neff et al., 2002).

Histamine-induced pruritus

In an experimental study (Dvorak et al., 2003), pruritus was induced in 18 participants and was successfully treated with peripheral administration (dermal patch) of HU210, a CB2R agonist. Skin blood flow and neurogenic-mediated flare responses were the major outcome measures; both were reduced from baseline ($P < 0.003$ and $P < 0.03$, respectively).

EFFICACY OF TOPICAL CBS

The effectiveness of topical CBD, N-PEA, and Δ^9-THC was reported for the following conditions: chronic and uremic pruritus, postinflammatory scars, ulcers secondary to pyoderma gangrenosum and calciphylaxis (uremic and nonuremic types), epidermolysis bullosa, psoriasis vulgaris, and dermatitis (atopic, asteatotic, and seborrheic).

Atopic dermatitis

The efficacy of topical CBs for dermatitis treatment was reported six times (Cocchiara et al., 2019; Eberlein et al., 2008; Maghfour et al., 2020; Palmieri et al., 2019; Pulvirenti et al., 2007; Yuan et al., 2014). A total of 60 female participants with asteatotic eczema experienced an improvement in scaling, dryness, and itch ($P < 0.05$) after the use of topical N-PEA and AEA (Yuan et al., 2014). Similar findings were reported among 21 subjects (Maghfour et al., 2020; Palmieri et al., 2019) with atopic dermatitis when treated with a 1% CBD infusion gel and ointment. There was an improvement in transepidermal water loss ($P < 0.001$) and PASI score ($P < 0.001$) after a treatment period of 3 months (Palmieri et al., 2019) and in the patient-oriented eczema measure score from 16 to 8.1 ($P < 0.007$) (Maghfour et al., 2020) at 2 weeks. In the same study (Maghfour et al., 2020) in which authors assessed the emotional burden of atopic dermatitis using the Quality of Life Hand Eczema Questionnaire (QOLHEQ), a significant reduction in the emotional domain of the QOL-HEQ was noted after treatment completion (20.9 ± 2.06 vs. 8.37 ± 1.609, $P < 0.004$)

Topical adelmidrol, an analog of N-PEA, appeared effective for the treatment of pediatric atopic dermatitis (Pulvirenti et al., 2007). After a treatment course of 4 weeks, all participants experienced a significant improvement in pruritus and erythema; 16 (80%) experienced clinical resolution.

Eberlein et al. (2008) assessed the efficacy of topical N-PEA in a large dataset of 2,456 patients (aged 21.2 ± 17.8 years; 65% female). Participants from various geographic locations received topical N-PEA with a mean treatment duration of 38 days. All subjects experienced symptom improvement of at least 70% in the following domains: dryness, excoriation, lichenification, scaling, erythema, and pruritus ($P < 0.01$).

Psoriasis vulgaris

Six patients with psoriasis (Friedman et al., 2020; Palmieri et al., 2019) were treated with topical CBD (n = 5) or Δ^9-THC (n = 1). All patients had a resolution of psoriasis plaques. Patients treated with topical CBD had an overall improvement in PASI score on day 90 ($P < 0.001$).

Scalp psoriasis and seborrheic dermatitis

Vincenzi et al. (2020) investigated CBD oil (0.075%) as a treatment for scalp psoriasis (n = 22) and scalp seborrheic dermatitis (n = 28). Efficacy was assessed using trichoscopy at baseline and on day 14. There was a reduction in arborizing vessel/twisted capillary inflammation and scaling by day 14 (2.3 vs. 0.5, $P < 0.001$). Symptoms of itching and burning were also reduced from 6.9 to 1.3 for scalp psoriasis and from 4.5 to 1.0 for seborrheic dermatitis (both with $P < 0.0001$).

Calciphylaxis

In a multicohort open-label trial (Maida et al., 2020), 32 participants with calciphylaxis, not caused by uremia, received topical CBD (3.75 mg/ml) and minimal Δ^9-THC (<1 mg per day), which was applied to wound beds and peri-wound tissues. Wound closure was achieved in 90% of cases after 1 year of treatment. There was only one patient in the trial with uremic calciphylaxis located on the bilateral lower legs; this patient experienced an increase in granulation tissue (58% on the left and 78% on the right leg wound) with an overall reduction in wound size by 9% on the left and 5% on the right. No localized or systemic effects were reported; however, the patient expired owing to coexisting heart disease.

Pyoderma gangrenosum

Topical combined CBD$-\Delta^9$-THC appears to be effective for pain relief in patients with pyoderma gangrenosum. Three patients achieved symptomatic relief of pain ($P < 0.05$), with an overall pain reduction of 30% (Maida and Corban, 2017).

Idiopathic pruritus

Topical N-PEA solution was assessed as a therapy for chronic pruritus secondary to xerosis in 100 participants (mean age = 56 years; range = 18−83 years; 56 female subjects) (Visse et al., 2017). After 2 weeks of twice-daily use, there was a significant improvement in VAS-measured pruritus ($P < 0.001$). However, in both the treated and control groups, 13 individuals reported worsening of pruritus, stinging, scaling, and erythema.

Pruritus secondary to systemic disease

Uremic pruritus secondary to renal disease can be debilitating and often represents a therapeutic challenge. In a trial conducted by Szepietowski et al. (2005), 21 subjects were instructed to apply topical N-PEA/AEA cream twice a day. After a 3-week course of treatment, there was a significant reduction in pruritus ($P < 0.0001$); eight subjects (38.1%) had complete resolution of pruritus (Szepietowski et al., 2005).

Topical N-PEA was also explored for pruritus secondary to the following conditions: cholestasis due to hepatitis C (n = 1), pruritus due to limited scleroderma (CREST [calcinosis, Raynaud phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia] syndrome) (n = 1), and aquagenic pruritus (n = 2) (Ständer et al., 2006). Subjects were instructed to apply the N-PEA test product on a daily basis, with treatment ranging from 2 weeks to 6 months. No improvement was noted among patients with cholestasis or aquagenic pruritus.

Prurigo nodularis and lichen simplex chronicus

Prurigo nodularis and lichen simplex are chronic skin conditions in which pruritus is the hallmark symptom. In a study on these conditions (Ständer et al., 2006), topical N-PEA was used for an average of 7.6 weeks among participants with prurigo nodularis (n = 13, VAS: 6.6 for baseline vs. 3.3 after treatment). However, four (30.7%) subjects were unresponsive to topical N-PEA. Two patients with lichen simplex chronicus were instructed to apply topical N-PEA for a 3-week course; subjects achieved a significant improvement in pruritus (VAS = 8.5 at baseline, VAS = 0 at end of treatment) (Ständer et al., 2006).

Epidermolysis bullosa

Topical CBD was investigated in two reports (Chelliah et al., 2018; Eberlein et al., 2008) with six pediatric patients (aged 6 months to 10 years). All patients experienced a reduction in blisters by at least 50%, with improved wound healing and decreased use of opioid analgesics.

ADVERSE EFFECTS OF TOPICAL CBS

Topical CBs have shown a significantly lower side effect profile than oral CBs. For topical CBs, adverse events were reported in nine subjects receiving topical N-PEA who experienced at least one of the following: stinging, erythema, and/or burning after application.

ADVERSE EFFECTS OF ORAL CBS

All patients treated with lenabasum experienced at least one adverse event, including mild fatigue, dizziness, and upper respiratory tract infection. DM flare was reported in two participants. One patient experienced a disturbance in co-ordination after administration of oral 5 mg dronabinol, which resolved with a 50% dose reduction.

This systematic review sought to examine the present use of CB-based products in dermatology. Analysis of the included research revealed that the application of CBs has been studied for 13 different dermatologic conditions, with systemic sclerosis and DM investigated most extensively.

Current evidence highlights the use of topical CBs in the treatment of pruritus, reduction of erythema, and enhanced wound healing. These clinical effects rely on CBs ability to inhibit the production of proinflammatory cytokines and modulate the immune system.

Findings from the available published data, although relatively scarce, highlight the promising results of CBs for the treatment of various dermatologic conditions. Despite the expanding body of evidence relating to the applicability and efficacy of CBs, there continue to be significant knowledge gaps. This review confirmed that existing evidence from high-quality studies (particularly RCTs) remains limited. Further clinical studies pertaining to the therapeutic dosage and long-term safety of both topical and oral CBs are highly warranted. Physicians who prescribe CBs should be aware of the systemic effects reported in the literature and bear in mind that long-term safety data exist primarily for the selective CB2R agonists only.

In addition, clinical trials investigating autoimmune skin conditions such as scleroderma and DM should be mindful of the necessity for ongoing immunosuppression in potential study participants and ethical implications related to the fact that systemic disease negates the possibility of a placebo-only group. Such trials should be designed with an eye toward including outcomes that allow for tapering of prednisone and the inclusion of participants who are on stable background doses of immunosuppressive medications.

LIMITATIONS

A significant limitation of our review is the small number of RCTs available for inclusion, resulting in a greater proportion of lower-level evidence obtained from case reports or case series. Selection bias may also have affected this review because positive outcomes are more likely to be published.

In conclusion, both oral and topical CBs appear to be promising therapies for the treatment of various inflammatory and autoimmune skin disorders. Despite limited studies, the compilation of current evidence from the published literature supports the utility of topical and systemic CBs for the treatment of primary inflammatory skin disorders such as DM, diffuse cutaneous systemic sclerosis, atopic dermatitis, leg ulcers, and epidermolysis bullosa. In addition, thoughtfully designed RCTs are warranted to provide the necessary evidence base to support the use of CBs for the treatment of these dermatologic conditions. Studies should aim to control for confounders that may affect outcomes, such as the use of ongoing immunosuppressive agents and the potential anxiolytic properties of CBs, which could influence patient-reported outcomes. The minimal side effect profiles associated with CBs, particularly with topicals, are an important attribute and further encourage additional studies to support the application of CBs in dermatology practice.

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