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REVIEW ARTICLE

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Cannabinoids for the treatment of autoimmune and inflammatory skin diseases: A systematic review

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Abstract

In recent years, the medical use of cannabinoids has attracted growing attention worldwide. In particular, anti-inflammatory properties of cannabinoids led to their emergence as potential therapeutic options for autoimmune and inflammatory disorders. Recent studies have also shown that cannabinoid receptors are widely expressed and have endogenous ligands in the skin, suggesting that the skin has its own endocannabinoid system. The aim of this review is to discuss the potential therapeutic effects of cannabinoids in autoimmune and inflammatory skin diseases. Following an overview of cannabinoids and the endocannabinoid system, we describe the cellular and molecular mechanisms of cannabinoids in skin health and disease. We then review the clinical studies of cannabinoids in autoimmune and inflammatory skin diseases including systemic sclerosis (SSc), dermatomyositis (DM), psoriasis (Pso) and atopic dermatitis (AD). A primary literature search was conducted in July 2023, using PubMed and Web of Science. A total of 15 articles were included after excluding reviews, non-human studies and in vitro studies from 389 non-duplicated articles. Available evidence suggests that cannabinoids may be beneficial for SSc, DM, Pso and AD. However, further studies, ideally randomized controlled trials, are needed to further evaluate the use of cannabinoids in autoimmune and inflammatory skin diseases.

KEYWORDS
atopic dermatitis, auto-immune disease, psoriasis

1 | INTRODUCTION

Cannabinoids are biologically active compounds that bind to the cannabinoid receptors in the human body. They are mainly classified as phytocannabinoids (derived from the plant *Cannabis sativa*), endocannabinoids (endogenously produced in the human body) and synthetic cannabinoids.[1] Since ancient times, cannabis derivatives have been used anecdotally for the treatment of various conditions, including pain, anxiety and insomnia.[2] In the late 20th century, the first phytocannabinoids were isolated, followed by the exploration of the endocannabinoid system and the subsequent discovery of cannabinoid receptors and their endogenous ligands.[3–7] Over the past decade, physiological effects of cannabinoids have been extensively studied. In particular, growing evidence supports the immunomodulatory properties of cannabinoids, which led to their emergence as potential therapeutic options for a number of autoimmune and inflammatory disorders.[8–12]

Accumulating evidence shows that cannabinoid receptors are widely expressed and have endogenous ligands in the skin, suggesting that the skin has its own endocannabinoid system.[13–15]

Recent studies have also demonstrated that cannabinoids are involved in skin homeostasis through different mechanisms, such as suppressing the proliferation of epidermal keratinocytes, modulating the production of pro-inflammatory cytokines and regulating the generation of reactive oxygen species.[16–18] In line with these findings, cannabinoids are increasingly used for the treatment of various skin conditions, especially autoimmune and inflammatory ones that are often refractory to conventional therapy, including systemic sclerosis (SSc), dermatomyositis (DM), psoriasis (Pso) and atopic dermatitis (AD).[19–22]

The aim of this review is to discuss the potential therapeutic effects of cannabinoids for autoimmune and inflammatory skin diseases. Initially, we provide an overview of the endocannabinoid system in the skin. We then describe the roles of cannabinoids in skin homeostasis and its breakdown. Lastly, we review the clinical studies of cannabinoids in autoimmune and inflammatory skin diseases with a special focus on SSc, DM, Pso and AD.

2 | CANNABINOIDS, CANNABINOID RECEPTORS AND THE ENDOCANNABINOID SYSTEM

2.1 | Cannabinoids

Cannabinoids are a heterogeneous group of compounds that can be divided into the following three classes according to where they are produced: phytocannabinoids (plant), endocannabinoids (body) and synthetic cannabinoids (chemical synthesis).[1] Representative cannabinoids of each class, along with their mechanisms of actions and biological effects, are provided in Table 1.

Phytocannabinoids are produced by the plant *C. sativa* as secondary metabolites. Over 100 phytocannabinoids have been isolated to date, of which delta-9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) are the most extensively studied. Δ^9-THC is the primary psychoactive constituent of *C. sativa*.[23] Although Δ^9-THC has analgesic, antiemetic and anti-inflammatory effects, its medical use is significantly limited due to the psychotropic properties.[24,25] CBD is a major non-psychoactive constituent of *C. sativa* with beneficial properties including anti-inflammatory, anti-bacterial and antioxidant effects, and attracts much attention for various medical applications.[26–28]

Endocannabinoids are natural ligands of cannabinoid receptors that are produced by the enzymatic cleavage of membrane lipid precursors.[1] N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) are the most abundant endocannabinoids in the human body.[6,29] They are synthesized from arachidonic acid in response to physiological stimuli and are primarily involved in the modulation of inflammation and neurotransmission.[30,31] In addition to these classical endocannabinoids, endocannabinoid-like compounds, such as N-palmitoylethanolamide (PEA) and oleoylethanolamide (OEA), also play an important role in the endocannabinoid system by sharing the synthesis and degradation enzymes with endocannabinoids.[32–34]

Synthetic cannabinoids refer to the laboratory-synthesized analogs of phytocannabinoids or endocannabinoids.[35] Among them, dronabinol, a synthetic Δ^9-THC and nabilone, a synthetic cannabinoid resembling Δ^9-THC, are approved by the United States Food and Drug Administration for the treatment of acquired immunodeficiency syndrome-induced anorexia (dronabinol and nabilone) and chemotherapy-induced nausea and vomiting (nabilone).[36,37] A number of other synthetic cannabinoids, especially non-psychoactive ones, are under clinical trials for different indications.

2.2 | Cannabinoid receptors

There are two types of cannabinoid receptors that have been identified to date: cannabinoid type 1 receptor (CB1R) and cannabinoid type 2 receptor (CB2R).[5,7] They are both members of the G protein-coupled receptor superfamily with seven transmembrane spanning domains. CB1R is mainly expressed in the central and peripheral nervous system, where it regulates the release of neurotransmitters.[38,39] CB2R, on the other hand, is notably expressed in the

TABLE 1 The major cannabinoids and their mechanisms of actions.

Compound	Mechanisms of actions	Potential indications
Phytocannabinoids		
Δ^9-THC	Partial agonist of CB1R and CB2R	Pain; nausea/emesis; inflammation; neurologic disorders
CBD	Inverse agonist and negative allosteric modulator of CB1R and CB2R; agonist of TRPV1 and PPARγ; antagonist of GPR55	Pain; anxiety; epilepsy; inflammation
Endocannabinoids		
AEA	Partial agonist of CB1R and weak agonist of CB2R; activator of TRPV1	Reward pathways; appetite; inflammation
2-AG	Agonist of CB1R and CB2R; additional affinity for TRPV1, PPAR-γ and GPR55	Pain; inflammation
Synthetic cannabinoids		
Dronabinol	Agonist of CB1R and CB2R	Appetite; nausea/emesis
Nabilone	Agonist of CB1R and CB2R	Pain; nausea/emesis

immune system such as spleen, thymus and haematopoietic lineage cells, and modulates immunological responses.[40,41]

Although CB1R and CB2R have been validated as the main receptors in the endocannabinoid system, the presence of other cannabinoid receptors has been widely investigated. Possible candidates for additional cannabinoid receptors include orphan G protein-coupled receptors (GPR18, GPR55 and GPR119), peroxisome proliferator-activated nuclear receptors (PPARα and PPARγ) and transient receptor potential (TRP) receptors (TRPV1, TRPV2, TRPV3, TRPV4, TRPA1 and TRPM8).[42,43] Although these putative receptors are activated by endocannabinoids and/or endocannabinoid-like compounds, their roles in the endocannabinoid system are not fully understood.[44]

2.3 | The endocannabinoid system

The endocannabinoid system consists of endocannabinoids, cannabinoid receptors, endocannabinoid transporters and various enzymes that facilitate the synthesis and degradation of endocannabinoids.[31] Previous studies have shown that AEA acts as a partial agonist at CB1R and a weak agonist at CB2R, while 2-AG is a full agonist at CB1R and CB2R.[45–47] Regarding the metabolism of endocannabinoids, N-acylphosphatidylethanolamine-specific phospholipase D-like hydrolase (NAPE-PLD) are responsible for the synthesis of AEA and other N-acylethanolamines,[48] while diacylglycerol lipases (DAGLα and DAGLβ) catalyse the synthesis of 2-AG and other monoacylglycerols.[49] The degradation of AEA and 2-AG was primarily mediated by fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively.[50,51] N-PEA, a major endocannabinoid-like compound, serves as an alternative substrate to FAAH, thus enhancing the physiological effects of AEA.[51] This mechanism is known as the 'entourage effect'. Although AEA and 2-AG are lipophilic and require inter- and intra-cellular carriers, little is known about their transporter system.[52]

3 | CANNABINOIDS IN SKIN HEALTH AND DISEASE

3.1 | The endocannabinoid system in the skin

Skin homeostasis is regulated by a complex network of different cell types and soluble mediators.[53] Because the breakdown of this fine-tuned balance leads to pathological skin conditions, mechanisms for maintaining skin homeostasis have been rigorously studied. In recent years, there has been a growing interest in the role of the endocannabinoid system in skin homeostasis.[54–56]

It is noteworthy that CB1R and CB2R are widespread in the skin: their expression is observed in various cell types, such as keratinocytes, fibroblasts, sensory neurons and skin immune cells.[13,15] In addition, putative cannabinoid receptors including TRP receptors are detected in keratinocytes, sensory neurons and skin immune cells.[57,58] Regarding their ligands, AEA and 2-AG, the major endogenous ligands of CB1R and CB2R, are detected in multiple cell types, including those from sweat glands and hair follicles.[59,60] PEA, an endocannabinoid-like compound, is also expressed in the skin.[61]

3.2 | Mechanisms of actions of cannabinoids in the skin

3.2.1 | Epidermal proliferation

Multiple members of the endocannabinoid system including CB1R, CB2R, AEA, 2-AG, FAAH, NAPE-PLD and several TRP receptors have been shown to be expressed in human epidermal keratinocytes.[15,54,57,62,63] The activation of CB1R by low concentration of AEA (1 μM) prevents the differentiation of 2D-cultured human keratinocytes.[14] AEA also inhibits the up-regulation of multiple differentiation markers, such as K1 and K10, in a CB1R-dependent manner.[64] Higher concentrations (3–30 μM) of AEA, on the other hand, suppress the proliferation of primary human epidermal keratinocytes while inducing their apoptosis via the sequential activation of CB1R and TRPV1.[65] Interestingly, Δ^9-THC and CBD inhibit the proliferation of HPV-16 E6/E7-transformed human keratinocytes independently of CB1R or CB2R, suggesting the role of non-classical cannabinoid receptors in mediating the anti-proliferative actions of these phytocannabinoids.[16]

Collectively, these data suggest that cannabinoids exert anti-differentiative, anti-proliferative or pro-apoptotic effects on epidermal keratinocytes in a concentration-dependent manner. In line with this, cannabinoids have been investigated as a potential treatment for Pso, a prototypical hyperproliferative skin disease.[16,66–68] Further studies are warranted to understand the exact mechanisms of actions of cannabinoids on human epidermis.

3.2.2 | Inflammation

Since the discovery of CB2R in immune cells, the roles of cannabinoids in inflammation have been extensively studied.[8–10] Karsak et al demonstrated that 2,4-dinitrofluorobenzene (DNFB)-induced allergic inflammation was exacerbated in CB1R and CB2R double knock-out mice, whereas inflammation was attenuated in FAAH knock-out mice with increased levels of AEA.[69] Moreover, DNFB-induced skin inflammation is suppressed by the subcutaneous administration of Δ^9-THC in wild-type mice.[69] These results support a protective role of the endocannabinoid system in allergic inflammation in the skin. Other studies also reported the downregulation of inflammatory cytokines and chemokines by cannabinoids in different models of skin inflammation. For instance, in an in vitro model of allergic contact dermatitis using poly-(I:C)-stimulated human keratinocyte cells, CBD dose-dependently inhibits the release of interleukin (IL)-6, IL-8, tumour necrosis factor (TNF)-α and monocyte chemotactic protein (MCP)-2, while up-regulating AEA levels.[17] These effects are reversed by the antagonists of CB2R and TRPV1.[17] In addition, topical application of CB1R-specific agonist attenuates the skin inflammation in

an oxazolone-induced AD animal model.[70] Another study reported that topical Δ^9-THC therapy effectively suppressed DNFB-induced ear swelling and immune cell infiltration not only in wild-type but also in CB1R and CB2R double knock-out mice, suggesting the anti-inflammatory activity of Δ^9-THC that are independent of CB1R or CB2R.[71] Overall, these studies support the anti-inflammatory effects of cannabinoids as well as the need to further investigate their CB1R/CB2R-dependent and -independent pathways.

3.2.3 | Fibrosis

Fibrosis is a complex process involving inflammatory responses, fibroblast activation and excessive collagen deposition.[72] It is also a hallmark of SSc.[73] Akhmetshina et al reported that bleomycin-induced dermal fibrosis and leukocyte infiltration were exacerbated in CB2R knock-out mice, while a selective CB2R agonist JWH-133 attenuated these changes in bleomycin-treated wild-type mice.[74] Río et al also demonstrated that a CBD quinol VCE-004.8 inhibited transforming growth factor (TGF)-β-induced collagen synthesis in vitro.[75] Importantly, lenabasum, a selective CB2R agonist, has been shown to prevent the progression of bleomycin-induced fibrosis in vivo by stimulating PPAR-γ signalling.[76] These data, along with its favourable safety profile, promote the clinical translation of lenabasum for the treatment of SSc.[77]

4 | EFFICACY OF CANNABINOIDS IN AUTOIMMUNE AND INFLAMMATORY SKIN DISEASES

4.1 | Routes of administration of cannabinoids

Various routes of administration of cannabinoids have been developed to date, including oral, transdermal and transmucosal administration.[78] Although oral administration is the most popular route of cannabinoids, it suffers from low bioavailability due to gastric instability, hepatic degradation and low water solubility.[79,80] In addition, some metabolites can cause psychotropic side effects.[79] To avoid these issues, transdermal administration has been exploited as an ideal route of cannabinoid delivery, especially for skin conditions.[81,82] Indeed, topical cannabinoids have been used in Pso, AD, acne vulgaris and asteatotic dermatitis.[83–85] In recent years, researchers have been trying to further improve the efficacy of topical cannabinoids by utilizing new technologies, such as chemical enhancement, physical enhancement, micro-emulsification and nanoparticle carrier systems.[86–89]

4.2 | A systematic review

A literature search of PubMed and Web of Science was performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines[90] (Figure 1). The search was conducted on 1 July 2023, using the combinations of the following keywords: ('cannabinoid' OR 'cannabis' OR 'cannabidiol') AND ('skin' OR 'cutaneous' OR 'dermatological') AND ('autoimmune' OR 'inflammatory' OR 'systemic sclerosis' OR 'dermatomyositis' OR 'psoriasis' OR 'atopic dermatitis'). Additional relevant publications were selected from the reference lists of the retrieved articles. Only original articles in English evaluating the efficacy of cannabinoids in patients with autoimmune or inflammatory skin diseases were included. Reviews, non-human studies and in vitro studies were excluded.

The initial database search yielded 389 articles after removing the duplicates. Of these, 365 articles were excluded during title and abstract screening. Among the 24 articles that underwent full-text review, 9 articles were excluded for the following reasons: reviews ($n=2$), non-human studies ($n=2$) and in vitro studies ($n=5$). In total, 15 articles were included in the systematic review, of which 5 were clinical trials, 7 were cohort studies and 3 were case reports or case series (Table 2). Consensus was reached between the two researchers (A.K and A.Y) on the inclusion and exclusion of all articles.

4.2.1 | Systemic sclerosis

SSc is a connective tissue disease characterized by autoimmunity, vasculopathy and fibrosis of the skin and internal organs.[73] Although a number of potential therapeutic targets have been identified in SSc, there are few effective treatment options that are validated in randomized controlled trials.[91–94] Based on the encouraging results of preclinical studies using patient fibroblasts and mouse models,[76] a selective CB2R agonist lenabasum has been explored as a potential treatment for SSc.

The first clinical trial of lenabasum in SSc was reported by Spiera et al.[95] In this double-blind, randomized, placebo-controlled phase 2 study (NCT02465437), 42 patients with diffuse cutaneous SSc (dcSSc) on stable medication including immunosuppressants received either oral lenabasum or placebo.[96] Lenabasum dosage was randomized to be 5 mg once daily, 20 mg once daily or 20 mg twice daily for the first 4 weeks, followed by 20 mg twice daily for the next 8 weeks. Safety and efficacy were assessed at Weeks 4, 8, 12 and 16, with the primary endpoint of the American College of Rheumatology (ACR) Combined Response Index in diffuse cutaneous Systemic Sclerosis (CRISS) score.[97] At Week 16, the lenabasum group experienced greater improvement in the ACR CRISS score compared with the placebo group ($p=0.07$ by two-sided mixed-effects model repeated-measures analysis). Adverse events (AEs) occurred in 63% and 60% of the lenabasum and the placebo group, respectively, with no serious AEs related to lenabasum. In an open-label extension, lenabasum continued to show good tolerability, while the ACR CRISS score kept improving.[95]

With the favourable results of the phase 2 trial, the phase 3 trial was undertaken to investigate the safety, efficacy and tolerability of lenabasum in dcSSc (NCT03398837).[98] In this study, 365 patients with dcSSc were randomized and dosed 1:1:1 with lenabasum 20 mg, lenabasum 5 mg or placebo, each twice daily while receiving stable

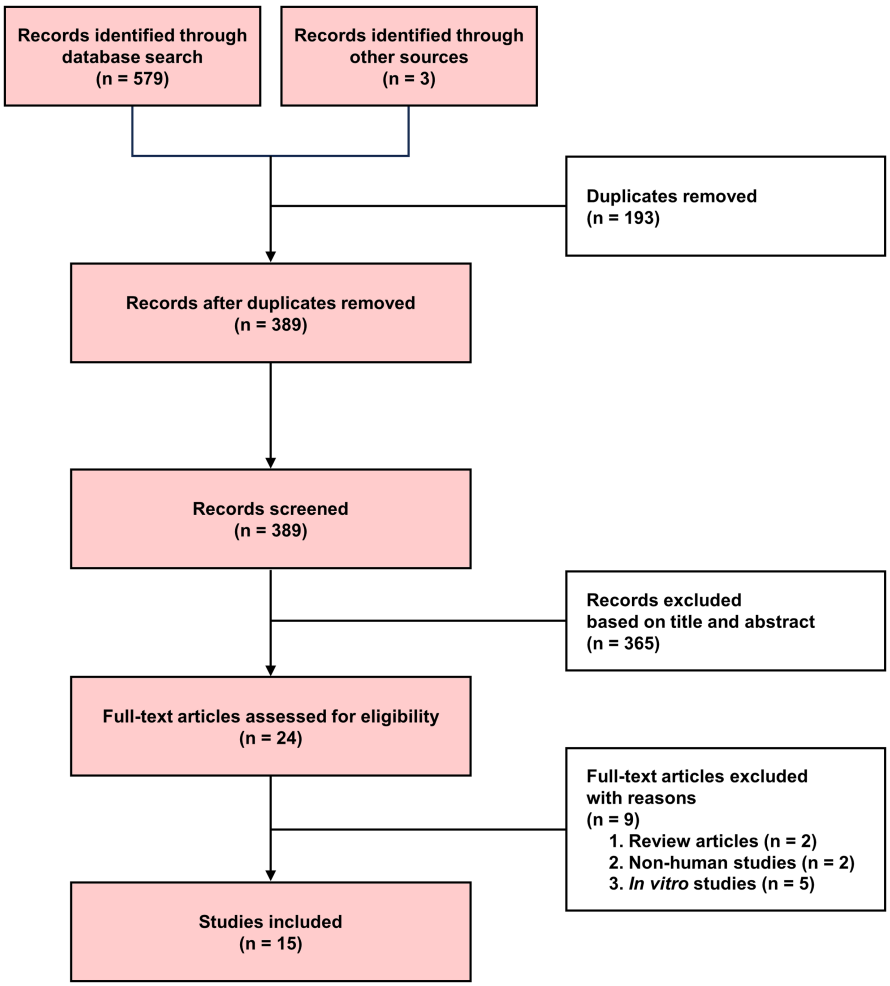

FIGURE 1 PRISMA flow chart.The search process is depicted using a flow diagram adapted from the PRISMA guidelines. PRISMA, preferred reporting items for systematic reviews and meta-analyses.

medication including immunosuppressants. The primary endpoint of the ACR CRISS score was not met (0.888 for lenabasum 20 mg vs. 0.887 for placebo at Week 52; $p=0.497$ by mixed-effects model repeated-measures analysis). This result was attributed to the remarkable improvement of the ACR CRISS score in both lenabasum- and placebo-treated patients, which reflects the efficacy of the background treatment, especially mycophenolate mofetil. In line with other studies, the safety profile of lenabasum was overall acceptable.

Cannabinoids have also been used for the treatment of vasculopathy-associated symptoms that significantly impair the quality of life of patients with SSc. Cocchiara et al showed that the combination of oral (5 drops twice daily) and local (2 drops at the site of ulcers) CBD oil was associated with a significant reduction of the pain related to skin ulcers, suggesting the use of CBD oil as an analgesic for skin ulcers in SSc.[99] Nogueira et al also reported that a male patient with SSc suffering from severe Raynaud's phenomenon and skin ulcers experienced the improvement in and Raynaud's phenomenon and pain after smoking 30 g of *C. sativa* daily.[100] However, no specific metrics were mentioned in this study. In a recent comparative study of SSc patients treated with CBD oil during surgical debridement ($n=25$) and those treated with standard local therapy ($n=20$), the topical CBD therapy was significantly associated with lower pain scores, higher health assessment scores and an increase in total sleep time.[101]

4.2.2 | Dermatomyositis

Dermatomyositis (DM) is an idiopathic inflammatory myopathy with characteristic skin lesions.[102] Skin lesions of DM are associated with pruritus, photosensitivity and visible difference, substantially affecting the quality of life of the patients.[103] Since active skin lesions of DM are often refractory to conventional treatment, more effective therapeutic options are awaited.[104] Recently, anti-inflammatory properties of cannabinoids have attracted much attention in DM. For instance, Robinson et al demonstrated in vitro that lenabasum significantly reduced the production of TNF-α and type I interferons from peripheral blood mononuclear cells in patients with DM.[105]

In the double-blind, randomized, placebo-controlled phase 2 trial (NCT02466243), DM patients with refractory, moderate-to-severely active skin disease were randomized to the lenabasum ($n=11$) or placebo ($n=11$) group.[106] The lenabasum group received 20 mg lenabasum daily for the first 28 days, followed by 20 mg twice daily for the following 56 days. Safety and efficacy were assessed until Day 113, with the primary endpoint of a change in Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI) activity score.[107] On Day 113, the lenabasum group showed greater improvement in CDASI activity score than the placebo group ($p=0.038$

TABLE 2 Published studies of cannabinoids in autoimmune and inflammatory skin diseases.

Author	Year	Study design	Treatment regimen	Results	Adverse events
Systemic sclerosis					
Spiera	2020	RCT ($n=42$)	Oral lenabasum, dose 5 mg once daily, 20 mg once daily or 20 mg twice daily for 4 weeks, followed by 20 mg twice daily for 8 weeks or placebo	The median ACR CRISS score at Week 16 was 0.33 versus 0.00 in placebo ($p=0.07$ by two-sided MMRM)	Lenabasum versus placebo: AEs 63% versus 60%. In lenabasum group, dizziness (22%) and fatigue (19%) were most common
Spiera	2023	RCT ($n=365$)	Oral lenabasum, dose 20 mg, 5 mg, each twice daily or placebo	Primary endpoint of the ACR CRISS at Week 52 for lenabasum 20 mg twice a day versus placebo was not met 0.888 for lenabasum 20 mg versus 0.887 for placebo at Week 52; $p=0.497$ by two-sided MMRM)	No deaths or excess in serious or severe AEs related to lenabasum were reported
Nogueira	2019	Case report ($n=1$)	Inhaled cannabis (30 g/day)	Total resolution of Raynaud's phenomenon and dyspnea	No AEs reported
Cocchiara	2019	Cohort study ($n=25$)	CBD (10%) orally twice daily and topical application.	Significant decrease in pain VAS and HAQ-DI at 2 months	No AEs reported
Spinella	2023	RCT ($n=45$)	Topical CBD or standard local therapy during surgical debridement	Significantly lower pain scores, higher health assessment scores and an increase in total sleep hours	No significant AEs reported
DM					
Werth	2022	RCT ($n=22$)	Oral lenabasum 20 mg daily for 28 days and then 20 mg twice daily for 56 days or placebo	Greater improvement in CDASI activity score than the placebo group on Day 113 ($p=0.038$ by MMRM).	No serious or severe AEs reported related to lenabasum
Werth	2023	RCT ($n=175$)	Oral lenabasum 20 mg twice daily, 5 mg twice daily or placebo	Primary endpoint of TIS were not met (28.3 for lenabasum 20 mg twice daily versus 27.2 for placebo at Week 52; $p=0.331$ by MMRM)	Treatment-emergent AEs in 87.0%, 85.7% and 87.3% of lenabasum 20 mg twice daily, lenabasum 5 mg twice daily and placebo groups, with no deaths
Pso					
Friedman	2020	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 weeks	No AEs reported
Palmieri	2019	Cohort study ($n=5$)	Topical CBD ointment twice daily	Decrease in the number of psoriasis plaques and improved PASI at Day 90 ($p<0.001$)	No AEs reported
Vincenzi	2020	Cohort study ($n=22$)	0.075% CBD in shampoo daily.	Decrease in scaling by Day 14	No AEs reported
AD					
Palmieri	2019	Cohort study ($n=5$)	Topical CBD twice daily	Increased hydration ($p<0.01$) and improved TEWL ($p<0.001$)	No AEs reported
Eberlein	2008	Cohort study ($n=2456$)	Topical N-PEA twice daily	Significant decrease in dryness, scaling, erythema, pruritus, excoriations and lichenification ($p<0.001$)	Pruritus, erythema and/or burning in nine patients

TABLE 2 (Continued)

Author	Year	Study design	Treatment regimen	Results	Adverse events
Pulvirenti	2007	Cohort study ($n=20$)	Topical adelmidrol twice daily	Complete resolution of AD symptoms in 80% patients	No AEs reported
Maghfour	2020	Cohort study ($n=16$)	Topical CBD twice daily	Reduction in POEM ($p<0.0007$)	No AEs reported
Epidermolysis bullosa					
Chelliah	2008	Case series ($n=3$)	Sublingual THC/CBD	Improved pain control and decreased pruritus	Increased appetite ($n=1$)

Abbreviations: HAQ-DI, health assessment questionnaire-disability index; MMRM, mixed-effects model repeated-measures analysis; POEM, patient oriented eczema measure; RCT, randomized controlled trial; TEWL, transepidermal water loss; VAS, visual analog scale.

by mixed-effects model repeated-measures analysis). There were no serious or severe AEs related to lenabasum. In an open-label extension, lenabasum continued to have good tolerability, while the CDASI activity score kept decreasing.[108]

In the double-blind, randomized, placebo-controlled phase 3 study (NCT03813160), patients were randomized 2:1:2 to lenabasum 20 mg twice daily ($n=69$), lenabasum 5 mg twice daily ($n=35$) or placebo twice daily ($n=71$) for 52 weeks.[109] The primary endpoint of Total Improvement Score[110] was not met (28.3 for lenabasum 20 mg twice daily vs. 27.2 for placebo at Week 52; $p=0.331$ by mixed-effects model repeated-measures analysis). In the subgroup analysis of the patients with predominant DM with minimal muscle activity, the improvement in CDASI activity score, which was relegated to a secondary endpoint in the phase 3 study, was significantly greater in the lenabasum 20 mg twice daily group than the placebo group at Week 52 ($p=0.006$).

4.2.3 | Psoriasis

Pso is a common chronic inflammatory skin disease with complex pathogenesis consisting of genetic, epigenetic and environmental factors.[111] Since the skin lesions often develop in highly visible areas such as face, scalp and nails, Pso causes considerable psychosocial disability. The disease burden of Pso further increases with comorbidities such as psoriatic arthritis, cardiovascular diseases and metabolic syndrome.[112,113] However, currently used medications are insufficient to control the disease for some patients. Therefore, there is still an unmet need for the development of new treatments for Pso.[114]

Although preliminary, several case reports and case series assessed the efficacy of cannabinoids in Pso. Friedman et al reported that the use of Δ^9-THC-containing soap and hair oil cleared the scalp lesions after 2 weeks in a male patient with Pso.[66] In a retrospective study of CBD-enriched ointment for chronic inflammatory skin diseases, patients with Pso ($n=5$) showed an improvement in the Psoriasis Area and Severity Index score[115] at Day 90 ($p<0.001$ by the Mann–Whitney test).[83] Vincenzi et al also reported that a shampoo containing 0.075% broad-spectrum CBD significantly improved the severity of scalp inflammation within 2 weeks in patients with mild to moderate scalp Pso ($n=22$).[67] These data suggest that topical CBD is beneficial for Pso skin lesions. However, further studies, especially randomized controlled trials, are needed to further evaluate its safety and efficacy.

4.2.4 | Atopic dermatitis

AD is an allergic inflammatory skin disease characterized by pruritic eruption with a chronic relapsing course.[116] With high prevalence of about 3%–20% worldwide, AD poses a major socioeconomic burden in many countries.[117]

Several studies have evaluated the efficacy of topical cannabinoids for the treatment of AD. Pulvirenti et al showed that twice

daily application of an emulsion containing adelmidrol (2%), an analog of N-PEA, led to the complete resolution of skin lesions in 16 out of 20 paediatric patients with AD after 4 weeks of treatment.[118] Topical CBD-enriched ointment twice daily for 3 months is also associated with the improvement in transepidermal water loss in patients with AD ($n = 5$).[83] In a study by Maghfour et al, twice-daily topical application of CBD significantly improved the Patient Oriented Eczema Measure[119] ($p < 0.0007$) and Quality of Life Hand Eczema Questionnaire[120] ($p < 0.004$) in patients with AD ($n = 16$) after 2 weeks of treatment.[84] Eberlein et al further evaluated the efficacy of topical N-PEA for AD in an observational, non-controlled, prospective cohort study including 2456 patients with a mean treatment duration of 38 days.[121] At the end of the study, intensities of erythema, pruritus and dryness were significantly reduced with a combined score decrease of 58.6%. In addition, earlier-used topical corticosteroids were omitted by 56% of all patients. The tolerance was assessed as very good or good in more than 90% of cases by both patients and physicians. While these data are encouraging and support the use of topical cannabinoids in AD, additional research, ideally randomized controlled trials, are clearly warranted.

4.2.5 | Other diseases

Chelliah et al reported three paediatric cases of topical CBD use in epidermolysis bullosa, where all the patients experienced less blistering, improved wound healing and the decrease in pain.[122]

4.3 | Adverse effects of cannabinoids

Due to the widespread distribution of cannabinoid receptors across multiple organs, various AEs have been reported with the medical use of cannabinoids. In a large systematic review, there was an increased risk of short-term AEs with the use of cannabinoids. Among them, the most frequent AEs were dizziness, nausea, fatigue, somnolence, euphoria, disorientation, drowsiness, confusion, hallucination and loss of balance.[123] It should be noted that the majority of these events are associated with the use of psychoactive cannabinoids such as dronabinol, nabilone and Δ^9-THC. Since non-psychoactive cannabinoids have been mainly used for the treatment of autoimmune and inflammatory skin diseases, we summarize the AEs that were reported in the systematic review in this study (Table 2).

Several AEs were reported in the clinical trials of oral lenabasum for SSc and DM. In the phase 2 study (NCT02465437) of lenabasum in SSc, the most common AE attributed to lenabasum was dizziness (22% for lenabasum vs. 13% for placebo), which led to the study discontinuation in one lenabasum-treated patient.[95] In the phase 3 trial (NCT03398837) of lenabasum in dcSSc, no serious AEs related to lenabasum were observed and the safety profiles were similar to those reported in the phase 2 trial.[98] In the phase 2 trial of lenabasum for DM, no serious or severe AEs occurred in the treatment groups. The most common AEs in the study were mild dizziness (45% for lenabasum vs. 18% for placebo), mild or moderate fatigue (27% vs. 27%), mild dry mouth (36% vs. 18%) and mild diarrhoea (27% vs. 9%).[106] In the phase 3 study of lenabasum in DM, the safety profiles were similar to those in the phase 2 trial.[109] Collectively, these data suggest that lenabasum is well-tolerated and safely administered.

Topical cannabinoids have a significantly favourable safety profile compared with oral cannabinoids. In the study cohort by Eberlein et al, AEs occurred in nine patients receiving topical N-PEA who reported at least one of the following: stinging, erythema and/or burning sensation.[121]

5 | CONCLUSION

This systematic review overviewed the present use of cannabinoids for autoimmune and inflammatory skin diseases (Figure 1, Table 2). The available data support the safety and efficacy of cannabinoids in SSc, DM, Pso and AD, as well as highlight the need for further studies to confirm their therapeutic use.

Clinical trials for cannabinoids in skin disorders have been extensively conducted in SSc and DM, where randomized controlled trials were performed on oral lenabasum (Table 2). Although promising results were obtained from the phase 2 trials, the phase 3 trials failed to meet the primary endpoint in both diseases, which are attributed to the confounding effect of background immunosuppressants in SSc and the change of primary endpoint from CDASI to Total Improvement Score in DM.[98,109] Nonetheless, subgroup analysis suggested that lenabasum was associated with the improvement of several secondary endpoints in both phase 3 trials. In Pso and AD, the included studies, although limited, support the potential therapeutic benefit of topical cannabinoids. In the future, randomized controlled trials are highly warranted to evaluate the clinical efficacy of cannabinoids more rigorously in these diseases.

In conclusion, available evidence suggests that cannabinoids have the potential therapeutic benefit with good tolerability in SSc, DM, Pso and AD. However, there are no sufficient data to validate their clinical efficacy. Randomized controlled trials with appropriate design are needed to further evaluate the use of cannabinoids for the treatment in autoimmune and inflammatory skin diseases.

AUTHOR CONTRIBUTIONS

Conceptualization: AY, SS; Methodology: AK, AY; Literature search: AK, TY, TF, AY-O, AY; Project administration: AY; Supervision: AY, SS; Writing–original draft: AK; Writing–review and editing: AY, SS.

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CONFLICT OF INTEREST STATEMENT

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DATA AVAILABILITY STATEMENT

The data of this study are available from the corresponding author upon reasonable request.

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