WISH Innovations PBC / WISH Skin Labs

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Literature Review. Version 2.0 - 13 October 2022.

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1. Introduction

The current document consists of a literature review and Clinical Trials search on the use of major and minor cannabinoids, i.e., compounds found in the cannabis plant, for the treatment of skin conditions and diseases, with special focus on wound healing.

Part one focus on scientific publications retrieved from the PubMed database of the U.S. National Institutes of Health's National Library of Medicine (NIH/NLM), and part two on clinical trials registered at the clinicaltrials.com website, run by the United States National Library of Medicine at the National Institutes of Health.

2. Data acquisition

2.1. Scientific Publications

Publications for potential inclusion were retrieved via a systematic search of the PubMed database.

The keywords selected for the search were:

- cannabinoids OR cannabis OR hemp OR CBD OR CBN OR CBG OR CBC OR CBDA OR CBGA OR CBDV OR THCV
- AND wound healing OR cicatrization OR skin injury OR laceration OR skin ulcer

The search query used was:

- ((cannabinoids) OR (cannabis) OR (hemp) OR (CBD) OR (CBN) OR (CBG) OR (CBC) OR (CBDA) OR (CBGA) OR (CBDV) OR (THCV)) AND ((wound healing) OR (cicatrization) OR (skin injury) OR (laceration) OR (skin ulcer))

Additionally, a separate search was conducted by adding the following keywords to the search query listed above:

- AND (isolate)
- AND (full spectrum)
- AND (broad spectrum)
- AND ((Cutaneous) OR (Derm))
- AND ((Transdermal) OR (Oral) OR (Transmucosal))
- AND ((proliferation phase) OR (Epithelialization))
- AND ((Biologic) OR (Biosimilar) OR (Liposomal) OR (Exosome) OR (Nanotechnology))
- AND ((Antiseptic) OR (Antimicrobial) OR (Analgesic) OR (Anti-inflammatory) OR (Antiinflammatory))
- AND ((Analgesia) OR (pain))
- AND ((Keratinocyte) OR (Dermato Fibroblast) OR (Peripheral Mononuclear Blood Cell))

Citations were limited to papers published in the past 5 years in the English, Portuguese, Spanish, Italian, French and German languages.

The literature search was completed on October, 2022.

2.2. Clinical Trials

Trials for potential inclusion were retrieved via a systematic search of the ClinicalTrials.gov database using the advanced search with the following search terms:

- Condition or disease: Wound (any condition or disease) OR Skin (any condition or disease)
- Other terms: Cannabinoids OR Cannabis OR Hemp OR Cannabidiol OR Cannabinol
- Study type: Interventional Studies (Clinical Trials)

The search was completed on October, 2022.

3. Results

3.1. Scientific publications

3.1.1. Number of scientific publications retrieved

The total number of scientific publications retrieved was **335 in total.**
The number of relevant publications per type is listed below (Table 1).

Publication Type	Publications of Relevance
In vitro	14
In vivo	12
Clinical trials or Case reports	11
Reviews	15
TOTAL	**52***

Table 1: Number of publication of relevance by type.
* Zheng et al, 2022 conduced both in vitro and in vivo assays.

Additionally, the publications retrieved for each separate search conducted is listed in table 2.

Keyword	Publications Retrieved	Publications of Relevance
isolate	25	2 (Ruhl et al, 2021; Miller et al., 2021)
full spectrum	1	-
broad spectrum	2	-
cutaneous	27	4 (Shao et al, 2021; Correia-Sá et al., 2020; Tóth et al, 2019; Du et al., 2018)
transdermal OR oral OR transmucosal	43	1 (oral) (Klein et al., 2018)

proliferation phase OR epithelialization	16	2 (epithelialization) (Correia-Sá et al, 2022; Zhao et al., 2021)
biologic OR biosimilar OR liposomal OR exosome OR nanotechnology	143	-
antiseptic OR antimicrobial OR analgesic OR anti-inflammatory OR antiinflammatory	80	5 (analgesic) (Makhakhe et al, 2022; Maida & Biasi et al., 2021; Maida et al, 2020; Chelliah et al., 2018; Maida et al, 2017) 10 (anti-inflammatory or antiinflammatory) (Kongkadee et al, 2022; Kibret et al., 2022; Makhakhe et al, 2022; Pryimak et al., 2021; Proksch et al, 2019; Sangiovanni et al, 2019; Klein et al., 2018; Du et al., 2018; Ruhl et al, 2018, Chelliah et al., 2018)
analgesia OR pain	42	2 (analgesia) (Maida et al, 2020; Maida et al., 2017) 12 (pain) (Heath et al, 2022; Tran et al., 2022; Kong et al, 2021; Diaz et al., 2021; Schräder et al, 2021; Shao et al., 2021; Copeland-Halperin et al, 2021; Maida & Biasi et al., 2021; Maida et al, 2020; Chelliah et al., 2018; Dhadwal et al, 2018; Maida et al., 2017)
keratinocyte OR dermato fibroblast OR peripheral mononuclear blood cell	13	3 (keratinocyte) (Weigelt et al, 2021; Proksch et al., 2019; Sangiovanni et al., 2019)

Table 2: Publications retrieved with additional keywords.

3.1.2. Summary of scientific publications of relevance

3.1.2.1. *In vitro* Studies

Gerasymchuk et al, 2022. [in vitro].

Objective: investigate the potential role of **phytocannabinoids** in combination with nutrient signaling regulators in skin rejuvenation. Utilizing CCD-1064Sk skin fibroblasts,

the effect of metformin, triacetylresveratrol, and rapamycin combined with phytocannabinoids on cellular viability, functional activity, metabolic function, and nuclear architecture was tested.
Outcomes: triacetylresveratrol combined with cannabidiol increased the viability of skin fibroblasts, restored wound-healing functional activity, reduced metabolic dysfunction, and ameliorated nuclear eccentricity and circularity in senescent fibroblasts. Conversely, metformin with or without phytocannabinoids did not show any beneficial effects on functional activity, while rapamycin inhibited cell viability and the speed of wound healing.

Monou et al, 2022. [in vitro].
Objective: Study the wound healing activity of drug carrier nanoparticles comprised of Pluronic-F127 and **cannabidiol (CBD) or cannabigerol (CBG)**.
Outcomes: The in vitro wound-healing study (Cell Scratch Assay) showed that the nanoparticles successfully enhanced wound healing in the first 6 h of application, but in the following 6 h they had an adverse effect. MTT assay studies (cytotoxicity) revealed that in the first 24 h, a concentration of 0.1 mg/mL nanoparticles resulted in satisfactory cell viability, whereas CBG nanoparticles were safe even at 48 h. However, in higher concentrations and after a threshold of 24 h, the cell viability was significantly decreased.

Kongkadee et al, 2022. [in vitro].
Objective: To evaluate the anti-inflammatory and gingival wound healing activities of Cannabis sativa L. subsp. sativa **(hemp) extract and cannabidiol (CBD)**.
Outcomes: Our study demonstrates that both hemp extract and CBD can inhibit TNF-α and IL-1β production in LPS-induced RAW 264.7 cells and promote wound healing in HGF-1 cells.

Viereckl et al, 2022. [in vitro].
Objective: Investigate the effect of **Cannabidiol and Cannabigerol** in Inhibiting Cholangiocarcinoma Growth In Vitro via Divergent Cell Death Pathways.
Outcomes: Results indicated that both cannabinoids are effective, yet CBG is more active at lower doses. Overall, CBD and CBG are effective anti-cancer agents against CCA, capable of inhibiting the classic hallmarks of cancer, with a divergent mechanism of action (Type II or Type I respectively) in inducing these effects.

Maia et al, 2022. [in vitro].

Objective: Investigate whether **anandamide (AEA) and 2-arachidonoylglycerol (2-AG)** can modulate the expression of angiogenesis- and invasion-related factors.

Outcomes: Although different angiogenic and migration factors are affected the results obtained in this work showcase the ability of the endocannabinoids to modulate key processes in placental physiology.

Zheng et al, 2022. [in vitro & in vivo].

Objective: Investigate the wound healing effects of a hydrogel dressing (CBD/Alg@Zn) containing **cannabidiol (CBD)** based on the ion crosslinked interaction between Zn2+ ions and the alginate polymer (Alg).

Outcomes: In vitro biological activity experiments indicated that the hydrogel has good biocompatibility, antibacterial activity, and angiogenesis properties. Moreover, it could significantly scavenge DPPH (2,2-diphenyl-1-picrylhydrazyl) free radicals and reduce the inflammatory response. In vivo studies revealed that the CBD/Alg@Zn hydrogel significantly facilitated the wound healing process by controlling the inflammatory infiltration, promoting collagen deposition and the granulation tissue, and benefiting the formation of blood vessels.

Correia-Sá et al, 2022. [in vitro].

Objective: To investigate the effect of the **CB2 selective receptor agonist** (6aR,10aR)-3-(1,1-Dimethylbutyl)-6a,7,10,10a-tetrahydro-6,6,9-trimethyl-6H-dibenzo[b,d]pyran (JWH133) and the **CB2 selective receptor antagonist** (6-Iodo-2-methyl-1-[2-(4-morpholinyl)ethyl]-1H-indol-3-yl)(4-methoxyphenyl)-methanone (AM630), on primary cultures of human fibroblasts.

Outcomes: The CB2 receptor appears to be involved in fibroblast repair during skin wound healing in humans, as TGF-β increases CB2 receptor expression and JWH133 produces an anti-fibrotic effect in human fibroblasts. AM630 also showed an anti-fibrotic effect hypothesizing that other cannabinoid receptors, such as TRPV, may be involved in this response.

Miller et al, 2021. [in vitro].

Objective: Investigate the role of marijuana components (**cannabidiol** (CBD) and **tetrahydrocannabinol** (THC)) on the regenerative ability of stem cells.

Outcomes: Cannabinoids can enhance the regenerative capacity of two major sources of stem cells, adipose- and bone marrow-derived, from human and porcine donors.

Stem cell isolation and expansion is invasive, costly and time consuming. Stem cells with improved regenerative properties may be effective in the treatment of acute or chronic wounds.

Correia-Sá & Carvalho et al, 2021. [in vitro].
Objective: Investigate whether whether CB1 activation or inactivation would change fibroblast differentiation into myofibroblast and collagen deposition in skin human fibroblast.
Outcomes: CB1 inactivation with **AM251** prevents fibroblasts differentiation and collagen deposition, induced by TGF-β in human fibroblasts. The outcome supports that CB1 is a molecular target for wound healing disorders and in vivo and pre-clinical studies should be implemented to clarify this premise.

García-Morales et al, 2020. [in vitro].
Objective: **Cannabidiol (CBD)** has been used to treat a variety of cancers and inflammatory conditions with controversial results. In previous work, we have shown that breast cancer MCF-7 cells, selected by their response to inflammatory IL-1β cytokine, acquire a malignant phenotype (6D cells) through an epithelial-mesenchymal transition (EMT). This study evaluated CBD as a potential inhibitor of this transition and inducer of reversion to a non-invasive phenotype.
Outcomes: CBD reverted the mesenchymal invasive phenotype of breast cancer cells induced by the inflammatory cytokine IL-1β

Al-Eitan et al, 2020. [comparative study].
Objective: To investigate the effects of the synthetic cannabinoid XLR-11 on specific cellular functions such as viability and angiogenesis in vitro.
Outcomes: The current study shows that XLR-11 increases the viability of human brain microvascular endothelial cells and enhances angiogenesis in the brain in vitro, suggesting that XLR-11 could potentially be used as a therapeutic angiogenic drug in human brain injury treatment.

Liu et al, 2019. [in vitro].
Objective: To investigate the effects of **tetrahydrocannabinol** (THC), the major active component in cannabis, on periodontal fibroblast cell adhesion and migration to explore its role in periodontal regeneration and wound healing.

Outcomes: Both CB1 and CB2 were expressed in periodontal tissues but with different expression patterns. Tetrahydrocannabinol promoted periodontal cell wound healing by inducing Human periodontal fibroblast cell adhesion and migration. This was mediated by focal adhesion kinase (FAK) activation and its modulation of MAPK activities. The effect of cannabinoids on periodontal fibroblast cell adhesion and migration was mainly dependent on the CB2.

Sangiovanni et al, 2019. [in vitro].

Objective: To investigate the potential effect of a **Cannabis sativa L. ethanolic extract** standardized in cannabidiol as antiinflammatory agent in the skin, unraveling the molecular mechanisms in human keratinocytes and fibroblasts.

Outcomes: The extract inhibited the release of mediators of inflammation involved in wound healing and inflammatory processes occurring in the skin. The mode of action involved the impairment of the nuclear factor-kappa B (NF-κB) pathway since the extract counteracted the tumor necrosis factor-alpha-induced NF-κB-driven transcription in both skin cell lines. **Cannabis extract** and **cannabidiol** showed different effects on the release of interleukin-8 and vascular endothelial growth factor, which are both mediators whose genes are dependent on NF-κB. The effect of cannabidiol on the NF-κB pathway and metalloproteinase-9 (MMP-9) release paralleled the effect of the extract thus making cannabidiol the major contributor to the effect observed. Down-regulation of genes involved in wound healing and skin inflammation was at least in part due to the presence of cannabidiol.

Luo et al, 2019. [in vitro].

Objective: To evaluate TRPV2 expression and its role on Ca2+ cellular dynamics, trans-endothelial electrical resistance (TEER), cell viability and growth, migration, and tubulogenesis in human primary cultures of BMEC (hPBMEC) or in the human cerebral microvessel endothelial hCMEC/D3 cell line.

Outcomes: **CBD**, at extracellular concentrations close to those observed in plasma of patients treated by CBD, induces proliferation, migration, tubulogenesis, and TEER increase in human brain endothelial cells, suggesting CBD might be a potent target for modulating the human blood-brain barrier.

Guan et al, 2017. [in vitro].
Objective: To investigate the effects of the **CB2R agonists** HU308 and JWH133 on the deposition of newly formed extracellular matrix (ECM) and the contractility of human Tenon's fibroblasts (HTFs).
Outcomes: Agonistic activation of CB2R exerts a protective effect on scarring during the healing of wounds from glaucoma filtration surgery.

3.1.2.2. *In vivo* Studies

Zheng et al, 2022. [in vitro & in vivo].
Objective: Investigate the wound healing effects of a hydrogel dressing (CBD/Alg@Zn) containing **cannabidiol (CBD)** based on the ion crosslinked interaction between Zn2+ ions and the alginate polymer (Alg).
Outcomes: In vitro biological activity experiments indicated that the hydrogel has good biocompatibility, antibacterial activity, and angiogenesis properties. Moreover, it could significantly scavenge DPPH (2,2-diphenyl-1-picrylhydrazyl) free radicals and reduce the inflammatory response. In vivo studies revealed that the CBD/Alg@Zn hydrogel significantly facilitated the wound healing process by controlling the inflammatory infiltration, promoting collagen deposition and the granulation tissue, and benefiting the formation of blood vessels.

Tran et al, 2021. [in vivo].
Objective: to investigate the therapeutic responses of **Δ-9 tetrahydrocannabinol** (a non-selective agonist) and two selective antagonists, **SR141716A** (CB1R antagonist) and **SR144528** (CB2R antagonist), as a topical application using a Dry eye disease (DED) mouse model.
Outcomes: CB1R and CB2R are present at the ocular surface, and desiccating stress increased CBR expressions ($p < 0.05$). After 10 days of DED induction, treated groups demonstrated a reduced CBR expression in the cornea, which was concurrent with improvements in the DED phenotype including fluorescence staining & inflammation. Applying THC protected corneal nerve morphology, thus maintained corneal sensitivity and reduced CD4+ T-cell infiltration. The CB1R antagonist maintained cornea sensitivity without changing nerve morphology.

Ruhl et al, 2021. [in vivo].

Objective: To clarify the role of **CB1 and CB2 receptors** in wound healing trhough excisional wounds on wildtype and CB1 and CB2 knockout mice.

Outcomes: The data indicate that both cannabinoid receptors regulate inflammation, and this study emphasizes the important role of CB1 in wound repair. Furthermore, the findings suggest that the secretome of CB1-deficient MSCs may contribute to the wound healing delay, in vivo.

Zhao et al, 2021. [in vivo].

Objective: To investigate whether **Gp1a-gel (cannabinoid receptor 2 (CB2) agonist**) worked effectively on mouse skin excision wounds

Outcomes: Gp1a-gel might sustainably increase the CB2 for at least 8 days. It decreased inflammation and fibrogenesis while promoting wound enclosure and re-epithelialization.

McIver et al, 2020. [in vivo - equine - n=6]. [NEGATIVE OUTCOME].

Objective: Evaluate the effect of topical 1% **cannabidiol** on second intention wound healing in distal limb wounds of horses.

Outcomes: Irrespective of the treatment, wounds did not retract as expected in the first 7 days after wound creation. There was no difference in wound area, daily healing rate, days to complete healing between treatment groups.

Proksch et al, 2019. [in vivo].

Objective: To explored the influence of **endocannabinoid system** (ECS) modulators on skin permeability barrier repair, epidermal proliferation, differentiation and inflammation in hairless mice.

Outcomes: WOL067-531 (an inhibitor of endocannabinoid reuptake with no relevant FAAH activity, which both signal via cannabinoid receptor-1 and cannabinoid receptor-2 (CB-1R and CB-2R)) exhibits a significant effect on skin barrier repair, epidermal proliferation/differentiation and inflammation.

Kamali et al, 2019. [in vivo].

Objective: To develop a novel scaffold that induces mesenchymal stem cells (MSC) migration towards the defect site, followed by their differentiation into an osteogenic lineage. The authors have fabricated a gelatin/nano-hydroxyapatite (G/nHAp) scaffold

that delivered **cannabidiol** (CBD)-loaded poly (lactic-co-glycolic acid) (PLGA) microspheres to critical size radial bone defects in a rat model.
Outcomes: CBD improved bone healing and showed a critical role for MSC migration in the bone regeneration process.

Murataeva & Daily et al., 2019. [in vivo].
Objective: To examined a potential role for cannabinoid-related **GPR18 receptors** in corneal epithelial chemotaxis and wound healing.
Outcomes: Corneal GPR18 activation induced both chemotaxis and proliferation in corneal epithelial cells in vitro and impacted wound healing. GPR18 may contribute to the maintenance of corneal integrity.

Murataeva & Miller et al, 2019. [in vivo].
Objective: To investigate a potential role of **CB2R receptors** in corneal wound healing. We examined the functional contribution of CB2R receptors to the course of wound closure in an in vivo murine model
Outcomes: CB2R receptor promoter activity is increased by corneal injury and that these receptors are required for the normal course of wound closure, possibly via chemorepulsion.

Du et al, 2018. [in vivo].
Objective: The anti-inflammatory properties of the **cannabinoid 2 receptor (CB2R) i**n injury and inflammatory diseases have been widely substantiated. Specifically, the anti-inflammatory effect of CB2R may be achieved by regulating macrophage polarisation. Several research findings suggested that the activation of CB2R could attenuate inflammation by reducing pro-inflammatory M1 macrophage polarisation and promoting anti-inflammatory M2 polarisation. However, considering CB2R inhibits fibrosis and M2 promotes fibrosis, that the activation of CB2R may lead to an increase in M2 macrophages seems contradictory. Therefore, the authors hypothesised that the activation of CB2R to attenuate inflammation is not achieved by up-regulating M2 macrophages.
Outcomes: The findings suggested that during incised skin wound healing in mice, increased levels of CB2R may affect inflammation by regulating M1 rather than M2 macrophage subtype polarisation. These results offer a novel understanding of the molecular mechanisms involved in the inhibition of inflammation by CBR2 that may lead to new treatments for cutaneous inflammation.

Klein et al, 2018. [in vivo].
Objective: To evaluate the effects of cannabidiol, a Cannabis sativa constituent, on oral wound healing process in rats
Outcomes: CBD exerts an antiinflammatory effect in early phase of wound healing process although it was not sufficient promote clinical improvement of oral traumatic ulcerative lesions.

Ruhl et al, 2018. [in vivo].
Objective: To evaluate whether CBD could influence the inflammatory Multipotent mesenchymal stromal cells phenotype.
Outcomes: Exposure to lipopolysaccharides (LPS) increased the release of IL-6, as well as other soluble factors, and elevated levels of oxidized macromolecules found in cell homogenisates. While the amount of IL-6 was unaffected, co-treatment with CBD reduced the oxidative stress acting on the cells. LPS inhibited adipogenic as well as chondrogenic differentiation, which was attenuated by CBD treatment. In the case of adipogenesis, the disinhibitory effect probably depended on CBD interaction with the peroxisome proliferator-activated receptor-γ. CBD could exert mild immunosuppressive properties on MSCs, while it most effectively acted anti-oxidatively and by restoring the differentiation capacity upon LPS treatment.

3.1.2.3. Clinical Trials and Case Reports

Diaz et al, 2021. [case report].
Objective: To report the case of a patient with a pressure injury (PI) who received cannabis oil treatment for pain management and sleep improvement.
Outcomes: Cannabis oil was effective in treating pain and sleep difficulties. Unexpectedly, during the first 2 weeks of treatment, the PI started to heal and was almost completely closed at the 2-month follow-up.

Schräder et al, 2021. [cross-sectional survey study - 77 patients].
Objective: To evaluate **cannabinoid-based medicines (CBM)** use among Epidermolysis bullosa (EB) patients, including CBM types, effects on symptoms (e.g., pain and pruritus), disease process (e.g., blistering, wounds, and inflammation), well-being (e.g., sleep, appetite) and concomitant medications.

Outcomes: Pain and pruritus were reported retrospectively to decrease by 3 points (scale: 0-10; $p < 0.001$ for both) after CBM use. Most reported that CBM use improved their overall EB symptoms (95%), pain (94%), pruritus (91%) and wound healing (81%). Most participants (79%) reported decreased use of pain medications. The most common side-effect was dry mouth (44%). CBMs improve the perception of pain, pruritus, wound healing, and well-being in EB patients and reduced concomitant medication use. Nevertheless, a direct relation between the use of CBMs and reduction of the above-mentioned symptoms cannot be proven by these data.

Maida & Shi et al, 2021. [open-label trial. Fourteen complex patients with sixteen recalcitrant leg ulcers patients].

Objective: Investigate the effects of **topical cannabis-based medicines** as an adjuvant treatment for venous leg ulcers.

Outcomes: The treatments were well tolerated, and no significant adverse reactions were experienced. The rapid wound closure of previously non-healing venous leg ulcers among elderly and highly complex patients suggests that Topical Cannabis-Based Medicines may become effective adjuvants in conjunction with compression therapy. This may also indicate that they may have an even broader role within integumentary and wound management. Therefore, this treatment paradigm warrants being subjected to controlled trials.

Ruhl et al, 2021. [comparative study].

Objective: To investigate the immunosuppressive influence of the endocannabinoids **anandamide** (AEA) and **2-arachidonoylglycerol** (2-AG) on Macrophages (MPhs) and mesenchymal stromal cells (MSCs) cytokine secretion.

Outcomes: The endocannabinoid system (ECS) down-regulated the inflammatory responses of MPhs and MSCs by decreasing the cytokine release upon LPS treatment, while CB2 appeared to be of particular importance. Hence, stimulating the ECS by manipulation of endo- or use of exogenous cannabinoids in vivo may constitute a potent therapeutic option against inflammatory disorders.

Maida et al, 2020. [open label trial - two elderly Caucasian females with recalcitrant Non-Uremic Calciphylaxis leg ulcers of greater than 6 months duration].

Objective: Investigate the use of **topical cannabis-based medicines** of the treatment for non-uremic calciphylaxis leg ulcers.

Outcomes: Complete wound closure was achieved in a mean of 76.3 days. Additionally, no analgesics were required after a mean of 63 days. The treatments were well tolerated with no adverse reactions.

Correia-Sá et al, 2020. [prospective study with 50 patients who underwent body-contouring surgery].
Objective: To evaluate **systemic and skin endocannabinoid** responses in the wound-healing process in humans.
Outcomes: A positive correlation between plasma and skin AEA concentrations was found in the N group, which was absent in the HT group. Moreover, the AEA concentration was significantly lower in HT scar tissue than in normal scar tissue. Interestingly, in all patients, the surgical intervention produced a time-dependent effect with a U shape for AEA, PEA and OEA plasma concentrations. In contrast, 2-AG plasma concentrations increased 5 days after surgery and were reduced and stabilized 3 months later. These results suggest crosstalk between systemic and local skin endocannabinoid systems during human wound healing.

Palmieri et al, 2019. [spontaneous, anecdotal, retrospective study of 20 patients with two most frequent skin disorders: psoriasis (n: 5 patients), atopic dermatitis (n: 5) and resulting outcome scars (n: 10)].
Objective: To investigate the therapeutic effect of **CBD-ointment** administered on severe skin chronic diseases and/or on their outcome scars.
Outcomes: Based on skin evaluations (hydration, TEWL, elasticity), clinical questionnaires (SCORAD, ADI, PASI), and supported by photographic data and investigators' clinical assessment, the results showed that topical treatment with CBD-enriched ointment significantly improved the skin parameters, the symptoms and also the PASI index score. No irritant or allergic reactions were documented during the period treatment.

Robinson et al, 2018. [20-question online survey].
Objective: To investigate the extent of dermatologists' familiarity with and interest in **cannabinoids** as therapeutics.
Outcomes: Dermatology providers are interested in prescribing cannabinoids and patients are speaking about cannabinoids with their dermatologists. However, providers' fund of knowledge on this subject is lacking. These results highlight the

need for further education and research to detangle the dermatologic benefits and risks of cannabinoids.

Chelliah et al, 2018. [case report].

Objective: To report 3 cases of self-initiated **topical cannabidiol** use in patients with epidermolysis bullosa in an observational study

Outcomes: One patient was weaned completely off oral opioid analgesics. All 3 reported faster wound healing, less blistering, and amelioration of pain with cannabidiol use. Although these results demonstrate promise, further randomized, double-blind clinical trials are necessary to provide scientific evidence of our observed benefits of cannabidiol for the treatment of epidermolysis bullosa.

Maida et al, 2018. [case report].

Objective: To report a prospective case series of three patients with pyoderma gangrenosum that were treated with **topical medical cannabis** compounded in nongenetically modified organic sunflower oil.

Outcomes: Clinically significant analgesia that was associated with reduced opioid utilization was noted in all three cases. Topical medical cannabis has the potential to improve pain management in patients suffering from wounds of all classes.

3.1.2.4. Reviews

Kibret et al, 2022. [review].

Objective: In this review, the authors summarize recent advances on the use of **cannabinoids** to treat skin disorders with an emphasis on wound management.

Conclusion: Despite the promising results of cannabinoids in wound management, further controlled clinical studies are required to establish the definitive role of these compounds in the pathophysiology of wounds and their usefulness in the clinical setting.

Lehlohonolo Makhakhe, 2022. [review].

Objective: Review the effects of **Topical cannabidiol (CBD)** in skin pathology. It comprises a comprehensive review and prospects for new therapeutic opportunities.

Conclusion: Topical cannabis has anti-inflammatory, anti-itching, analgesics, wound healing and anti-proliferative effects on the skin.

Heath et al, 2022. [review].

Objective: Review the effects of **Marijuana** and its chemical constituents on bone health, wound-healing, surgical complications, and pain management.

Conclusion: Current evidence suggests that cannabidiol (CBD) may enhance bone health and metabolism, while Δ9-tetrahydrocannabinol (Δ9-THC), the major psychoactive component in marijuana, has an inhibitory effect. Marijuana users are at higher risk for delayed bone-healing, demonstrate lower bone mineral density, are at increased risk for fracture, and may experience postoperative complications such as increased opioid use and hyperemesis.

Kong et al, 2021. [review].

Objective: To discuss the potential impact of cannabinoid use in dermatologic surgery.

Outcomes: **Cannabinoids** have demonstrated efficacy in wound healing, reducing inflammation, ameliorating pain, and have shown potential as an antitumor agent.

Pryimak et al, 2021. [review].

Objective: To discuss **cannabinoids** and their potential for the prevention and treatment of fibrosis.

Conclusions: Numerous publications suggest that cannabinoids and extracts of Cannabis sativa have potent anti-inflammatory and anti-fibrogenic properties.

Shao et al, 2021. [review].

Objective: To review the current research, possible cutaneous adverse effects, and future directions for **cannabinoids** and their use in skin cancer, acne, psoriasis, pruritus, dermatitis, scleroderma, dermatomyositis, cutaneous lupus erythematous, epidermolysis bullosa, pain, and wound healing.

Conclusions: In vitro and in vivo studies of Cannabis have suggested it has favorable effects on regulating pain, pruritus, and inflammation, making it a potentially attractive therapeutic agent for many dermatologic conditions. The body of literature reporting on the role of cannabinoids in dermatology is in its infancy but growing.

Copeland-Halperin et al, 2021. [review].

Objective: Review the implications of perioperative **cannabis** use.

Conclusion: Surgeons should consider effects of cannabis in the perioperative setting. Little is known about its perioperative effects on wound healing, or on cardiovascular,

pulmonary, and hematologic physiology. Further research should elucidate the effects of administration route, dose, and timing of cannabis use among surgical patients.

Maida & Biasi et al, 2021. [review].

Objective: Review the management of wound-related pain with **cannabis-based medicines**.

Conclusion: Cannabis-based medicines are a prominent prospect under investigation for their potential to reduce dosages of status quo analgesics while effectively reducing pain. The authors propose a new paradigm that emphasizes the use of Cannabis-Based Medicines, delivered through multiple routes, while recommending the need for more foundational scientific investigation into mechanisms, and clinical controlled trials to determine optimal combinations, dosages, and protocols.

Weigelt et al, 2021. [review].

Objective: To review the therapeutic potential of **cannabinoids** for integumentary wound management.

Conclusion: Compelling pre-clinical evidence support the therapeutic potential of CBs to improve wound healing by modulate key molecular pathways.

Raphael-Mizrahi et al, 2020. [review].

Objective: To provide an overview the latest findings from studies investigating the **skeletal endocannabinoid (EC) system** and its involvement in bone formation and resorption

Coclusions: Cannabinoid receptors CB1 and CB2 are expressed in bone and regulate bone homeostasis in rodents and humans. CBD treatment was shown to enhance fracture healing in rats. Recent studies in mice indicate that strain, age, and sex differences dictate the skeletal outcome of the EC activation. CBD treatment was shown to enhance bone healing, but needs validation in clinical trials. While research shows that EC activity protects against bone loss, studies on CB1 and CB2 agonists in bone regeneration models are lacking.

Correia-Sá et al, 2020. [review].

Objective: To find and analyze reported data on compounds acting in the **endocannabinoid system** with significant effect in skin fibrosis.

Outcomes: CB1 receptor inactivation and CB2 receptor activation show anti-fibrotic effects on cellular and animal experimental models of cutaneous fibrosis. CB2 receptor

activation also promotes re-epithelization. Other cannabinoid related receptors, like adenosine A2A receptors and PPAR-γ, are also involved. Their activation lead to a pro-fibrotic and anti-fibrotic effect, respectively.

Miller et al, 2020. [review].

Objective: To review the existing literature related to the effects of **tetrahydrocannabinol (THC)** on inflammation and potentially wound healing, and discuss how this connection may be relevant from a surgical perspective.

Conclusion: A number of studies over the past few decades, both in vitro and in vivo, have demonstrated that THC down-regulates the inflammatory process through various mechanisms.

Tóth et al, 2019. [review].

Objective: To give an overview of the available skin-relevant **endo- and phytocannabinoid** literature with a special emphasis on the putative translational potential, and to highlight promising future research directions as well as existing challenges

Outcomes: Experimental efforts over the last two decades have unambiguously confirmed that cutaneous cannabinoid ("c[ut]annabinoid") signaling is deeply involved in the maintenance of skin homeostasis, barrier formation and regeneration, and its dysregulation was implicated to contribute to several highly prevalent diseases and disorders, e.g., atopic dermatitis, psoriasis, scleroderma, acne, hair growth and pigmentation disorders, keratin diseases, various tumors, and itch.

Del Rio et al, 2018. [review].

Objective: To review the role of the **endocannabinoid system** of the skin as a potential approach for the treatment of skin disorders

Conclusions: The endocannabinoid system (ECS) plays a relevant role in healthy and diseased skin. Specifically, we review how the dysregulation of ECS has been associated to dermatological disorders such as atopic dermatitis, psoriasis, scleroderma and skin cancer.

Dhadwal et al, 2018. [review].

Objective: To review the risks and benefits of **Cannabis** in the dermatology clinic.

Conclusions: In this review, the authors summarize some of the studies and reports regarding the medicinal uses of cannabis in the dermatology clinic and some of the

side effects that might present more often to dermatologists as the use of cannabis increases.

3.1.3. Summary of the main outcomes

A summary of the main outcomes of the publications of relevance is listed on the table below (Table 3 - Main outcomes).

Study Type	Main Outcomes
In vitro	• Triacetylresveratrol combined with cannabidiol increased the viability of skin fibroblasts, restored wound-healing functional activity, reduced metabolic dysfunction, and ameliorated nuclear eccentricity and circularity in senescent fibroblasts. (Gerasymchuk et al, 2022). • Pluronic-F127 and cannabidiol (CBD) or cannabigerol (CBG) nanoparticles successfully enhanced wound healing. (Monou et al, 2022). • Hemp extract and CBD induced anti-inflammatory and gingival wound healing activities. (Kongkadee et al, 2022) • Cannabidiol and Cannabigerol Inhibit Cholangiocarcinoma Growth. (Viereckl et al, 2022). • Cannabinoids can enhance the regenerative capacity of adipose- and bone marrow-derived stem cells which may be effective in the treatment of acute or chronic wounds. (Miller et al, 2021) • Cannabis sativa L. ethanolic extract inhibited the release of mediators of inflammation involved in wound healing and inflammatory processes occurring in the skin. (Sangiovanni et al, 2019). • Agonistic activation of CB2R exerts a protective effect on scarring during the healing of wounds from glaucoma filtration surgery. (Guan et al, 2017).

In vivo	• CBD/Alg@Zn dressing significantly facilitated the wound healing process by controlling the inflammatory infiltration, promoting collagen deposition and the granulation tissue, and benefiting the formation of blood vessels. (Zheng et al, 2022). • CB1 and CB2 receptors regulate inflammation, and their activation contribute to wound repair. (Ruhl et al, 2021). • Gp1a-gel (cannabinoid receptor 2 (CB2) agonist) decreased inflammation and fibrogenesis while promoting wound enclosure and re-epithelialization. (Zhao et al, 2021). • Activation of CB-1R and CB-2R induced a significant effect on skin barrier repair, epidermal proliferation/differentiation and inflammation. (Proksch et al, 2019). • Corneal GPR18 activation impacted wound healing. GPR18 may contribute to the maintenance of corneal integrity. (Murataeva & Daily et al., 2019). • During incised skin wound healing in mice, increased levels of CB2R may affect inflammation by regulating M1 rather than M2 macrophage subtype polarization. CBR2 may be useful for the treatment of cutaneous inflammation. (Du et al, 2018). • CBD exerts an anti-inflammatory effect in early phase of wound healing process. (Klein et al, 2018).
Clinical trials or Case reports	• Cannabis oil was effective in treating pain and sleep difficulties, as well as induced healing of pressure injury (PI). (Diaz et al, 2021). • Cannabinoid-based medicines (CBM) use among Epidermolysis bullosa (EB) patients decreased pain and pruritus, and facilitated wound healing and well-being. (Schräder et al, 2021). • Topical cannabis-based medicines effectively supported wound healing as an adjuvant treatment for venous leg ulcers. (Maida & Shi et al, 2021). (Maida et al, 2020). • Topical treatment with CBD-enriched ointment significantly improved the skin health and induced wound healing in patients with psoriasis. No irritant or allergic reactions were documented during the period treatment. (Palmieri et al, 2019). • Topical cannabidiol use in patients with epidermolysis bullosa induced faster wound healing, less blistering, and amelioration of pain. (Chelliah et al, 2018). • Topical medical cannabis has the potential to improve pain management in patients suffering from wounds of all classes. (Maida et al, 2018).

Reviews	• Cannabinoids present promising results for the treatment of skin disorders with an emphasis on wound management. (Kibret et al, 2022). • Topical cannabis use has anti-inflammatory, anti-itching, analgesics, wound healing and anti-proliferative effects on the skin. (Lehlohonolo Makhakhe, 2022). • Cannabinoids have demonstrated efficacy in wound healing, reducing inflammation, ameliorating pain, and have shown potential as an antitumor agent. (Kong et al, 2021). • Numerous publications suggest that cannabinoids and extracts of Cannabis sativa have potent anti-inflammatory and anti-fibrogenic properties. (Pryimak et al, 2021). • In vitro and in vivo studies of Cannabis have suggested it has favorable effects on regulating pain, pruritus, and inflammation, making it a potentially attractive therapeutic agent for many dermatologic conditions. (Shao et al, 2021). • Compelling pre-clinical evidence support the therapeutic potential of CBs to improve wound healing. (Weigelt et al, 2021). • Cutaneous cannabinoid signaling is deeply involved in the maintenance of skin homeostasis, barrier formation and regeneration, and its dysregulation was implicated to contribute to several highly prevalent diseases and disorders, e.g., atopic dermatitis, psoriasis, scleroderma, acne, hair growth and pigmentation disorders, keratin diseases, various tumors, and itch. (Tóth et al, 2019). • The endocannabinoid system (ECS) plays a relevant role in healthy and diseased skin. Specifically, we review how the dysregulation of ECS has been associated to dermatological disorders such as atopic dermatitis, psoriasis, scleroderma and skin cancer. (Del Rio et al, 2018).

Table 3: Main outcomes.

3.2. Clinical Trials

3.2.1. Number of trials retrieved

The total number of scientific publications retrieved is listed in table 4.

Results	Total Number of Studies	Relevant Studies
Skin	43	13
Wound	75	Zero

Table 4: Clinical Trials involving Cannabinoids OR Cannabis OR Hemp OR Cannabidiol OR Cannabinol for Skin Conditions or Diseases. Number of studies retrieved. Source: ClinicalTrials.gov.

The extended terms and synonyms searched are listed in table 5 below.

Terms	Search Results*	Entire Database**
Synonyms		
Cannabinoids	16 studies	552 studies
Cannabis	17 studies	1,383 studies
Pot	5 studies	120 studies
Marihuana	4 studies	824 studies
Weed	3 studies	34 studies
Hash	1 studies	25 studies
Hemp Plants	--	2 studies
Sativex	--	62 studies
Hemp	4 studies	71 studies
Cannabidiol	14 studies	417 studies
Epidiolex	3 studies	60 studies
Cannabinol	2 studies	15 studies

skin	43 studies	24,884 studies
Cutis	--	99 studies
Integument	--	2 studies
skinned	--	1 studies

Table 5: Clinical Trials involving Cannabinoids OR Cannabis OR Hemp OR Cannabidiol OR Cannabinol for Skin Conditions or Diseases. Terms and Synonyms Searched. -- No studies found; * Number of studies in the search results containing the term or synonym; ** Number of studies in the entire database containing the term or synonym. Source: ClinicalTrials.gov

3.2.2. Summary of clinical trials of relevance

The clinical trials of relevance retrieved are listed with details in table 6.

Status	Study Title	Conditions	Interventions	Phase	Funder Type	Number Enrolled
Not yet recruiting	Topical Cannabidiol Application and Skin Vascular Reactivity	Effect of Drug	Biological: Cannabidiol	Not Applicable	Other	48
Completed	A Study to Investigate the Bioavailability and Skin Absorption of CBD and THC From GT4 Technology in Healthy Adults	Biological Availability; Skin Absorption, CBD, THC	Combination Product: CBD and THC with GT4 technology	Phase 1	Other / Industry	18
Recruiting	INM-755 (Cannabinol) Cream for Treatment of Epidermolysis Bullosa	Epidermolysis Bullosa Simplex, Junctional, Dystrophica; Kindler Syndrome	Drug: INM-755 (cannabinol) cream	Phase 2	Industry	20
Recruiting	Androgenetic Alopecia Treatment Using Varin and Cannabidiol Rich Topical Hemp Oil: A Case Series	Androgenetic Alopecia	Drug: Hemp Oil	Early Phase 1	Other	40
Withdrawn	The Efficacy and Safety of 3% Cannabidiol (CBD) Cream in Patients With Epidermolysis Bullosa: A Phase II/III Trial	Epidermolysis Bullosa; Pain, Ich	Drug: AVCN583601 (3% Cannabidiol cream)	Phase 2; 3	Other / Industry	0
Unknown †	Study to Evaluate the Safety, Tolerability and Efficacy of Cannabidiol (CBD) as a Steroid-sparing Therapy in Chronic Spontaneous Urticaria (CSU) Patients	Chronic Spontaneous Urticaria	Drug: CBD	Phase 2	Industry	20
Recruiting	Impact of Cannabis on Pain and Inflammation Among Patients With Rheumatoid or Psoriatic Arthritis	Rheumatoid Arthritis; Psoriatic Arthritis	Drug: Cannabis: placebo and medium THC/medium CBD	Phase 2	Other	76
Completed	Effect of an Emollient Cream Containing 0.5% Cannabidiol and 1% Hemp Oil in the Hydration and Erythema of the Skin	Cosmetics; Eczema	Other: Topical moisturizer	Not Applicable	Industry	49

Completed	Effect of a Facial Cream Containing Cannabidiol and Hemp Oil on Skin Hydration and Acne-prone Skin	Cosmetic Acne	Other: Topical Moisturizer	Not Applicable	Industry	54
Completed	Myorelaxant Effect of Cannabis Cream Topical Skin Application in Patients With TMD	Temporomandibular Disorder; Myofascial Pain; Cannabis; Electromyography	Combination Product: Cannabis Cream + Placebo Cream	Phase 2; 3	Other	20
Completed	CBD Treatment in Hand Osteoarthritis and Psoriatic Arthritis.	Psoriatic Arthritis; Hand Osteoarthritis	Drug: Cannabidiol + Placebo Oral Tablet	Phase 2	Other	136
Completed	A Phase I, Double Blind, Randomized, Placebo Controlled, Maximal Dose Study to Determine the Safety, Tolerability of Topical Cream Containing MGC (Medical Grade Cannabis) in Healthy Volunteers	Safety Study for Future Treatment of Psoriasis	Drug: OWC MGC cream + OWC Control Cream	Phase 1	Industry	26

Table 6: Clinical Trials involving Cannabinoids OR Cannabis OR Hemp OR Cannabidiol OR Cannabinol for Skin Conditions or Diseases.
Source: ClinicalTrials.gov

4. Conclusions

A similar number of scientific publications of relevance was retried for each type of study, i.e., In vitro, In vivo, Clinical trials or Case reports and Reviews.

Although many of the studies presented in this review do not meet the highest standards of scientific research (randomized, double-blinded, placebo-controlled, large sample size), many were well-designed and reached statistically significant results stating to the benefits of cannabinoids for wound healing.

The clinical trials retrieved are a good indication of the growing interest in the use of cannabinoids for the treatment of skin diseases.

5. Limitations

Primarily, only a few keywords and one database was consulted for this review, i.e., Pubmed. Future updated versions should encompass a revised and extended list of keywords and search terms; and use additional databases, e.g., Directory of Open Access Journals, Goole Scholar, and Embase Database.

Secondly, although publications in any languages were retrieved, in the results only citations in English, Portuguese, Spanish, Italian, French and German were considered in this review, thus, additional data may exist on this topic that may have been overlooked.

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