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Cannabis and cannabinoids in dermatology: protocol for a systematic review and meta-analysis of quantitative outcomes.

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Abstract

Following the discovery of various effects on skin function by modifying endocannabinoid systems, multiple preclinical studies have revealed the promise of cannabis and cannabinoids in the treatment of a variety of skin diseases. However, its clinical efficacy is still debated. This systematic review aims to evaluate the therapeutic efficacy of cannabis and cannabinoids in dermatological conditions and diseases. The protocol has been prepared using the Preferred Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines and has been registered with the International Prospective Register of Systematic Reviews (PROSPERO: CRD42023397189). PubMed, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science will be used for the systemic search. The outcomes will be an improvement in dermatological characteristics, including disease-specific composite scores and objective and subjective outcomes of skin conditions. This systematic review will provide valuable information on dermatological therapy of cannabis and cannabinoids and could be the start of future research and medicinal applications.

Introduction

Skin is the largest human organ and is essential for organism survival. It is the first line of immunological and physical protection against the external environment, including heat control and retention of hydration [1, 2]. A substantial part of the population is affected by skin diseases that have significant effects on the quality of life of sufferers (3-7).

The Endocannabinoid System (ECS), which includes receptors, ligands, and enzymes, is mainly responsible for maintaining homeostasis and the balance of multiple biological functions in the nervous system and peripheral organs [3-5]. Cannabinoids and active components of *Cannabis sativa*, which were found to mimic endocannabinoid signaling and influence receptor expression [6, 7], have gained interest as potential treatment for various diseases [3, 5]. The growing legalization of medicinal cannabis and cannabinoids led to the search for medicinal use in clinical practice. The FDA currently approves the use of cannabinoid to alleviate pain and spasticity in multiple sclerosis and the treatment of chemotherapy-induced nausea and vomiting in cancer patients [8-11].

Modulation of the activity of the endocannabinoid system has been shown to influence several types of skin disease, including atopic dermatitis, psoriasis, acne, and skin tumors, according to the etiology of the diseases [12-15]. Furthermore, cannabis has anti-inflammatory and anti-pruritic properties [10, 16-18]. This makes the cannabinoids and active components of *Cannabis sativa* promising for the therapeutic treatment of the skin disorders mentioned above. Given the insufficient quality clinical studies on this topic, this systematic review aims to examine the efficacy of cannabis and cannabinoids in alleviating dermatological conditions and diseases by highlighting current and historical attempts to collect robust clinical data and identify knowledge gaps.

Material and methods

The systematic review protocol was registered with the International Prospective Register of Systematic Reviews (PROSPERO) on February 17th, 2023 (CRD42023397189). The protocol followed the Preferred Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines.

Study Selection

Any randomized controlled trials and observational studies including cross-sectional studies, case-control studies, or cohort studies that investigate the efficacy or effectiveness of any form of medical cannabis or cannabinoid in alleviating dermatological conditions or diseases will be included. Exclusion criteria are (1) in vitro studies, case report, protocol, review article, guideline, editorial, commentary, and letter to editor (2) non-peer-reviewed studies (3) animal studies (4) studies published in non-English. Human participants of all ages will be included. The intervention includes an application of cannabis or cannabinoids in any preparation through any route. Study with placebo control, active control, or even no control will be assessed.

Study outcome

The efficacy or effectiveness of cannabis and cannabinoids in alleviating dermatological conditions or diseases will be determined based on the followings:

1. Generic outcomes used to assess improvement in skin conditions:
    a. Subjective clinical or patient-reported outcomes such as pruritus score, erythema grade, and quality of life.
    b. Objective evaluation using standard instruments such as transepidermal water loss, lipid analysis, and skin topography evaluation.
2. Disease specific composite scores, mixed subjective and objective outcomes, such as Psoriasis Area Severity Index (PASI) for psoriasis, Eczema Area and Severity Index (EASI), and SCORing Atopic Dermatitis (SCORAD) for atopic dermatitis, etc.

Search strategy

We will search through five databases: PUBMED, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. The search strategy constructed by two health information specialists with systematic review experience will combine search terms and subject headings (MeSH) related to 'cannabis', 'cannabaceae', 'cannabinoids', 'dronabinol', 'dermatology', 'skin', and 'ulcer' (Supplementary 1).

Study records

Data management

After deriving the studies via the mentioned database, we will import them into Covidence systematic review software, which de-duplicates studies and facilitates study selection [19].

Selection process

The titles and abstracts of the identified citations will be evaluated by independent paired reviewers, and initially, the abstracts that do not report the therapeutic effects of cannabis and cannabinoids in dermatological conditions or diseases will be eliminated.

The included studies will then undergo full text review and the final included study will be selected based on all eligibility criteria. Reasons for study exclusion in this step will be recorded. When differences could not be resolved through dialogue, an adjudicator will be brought in to assist. The PRISMA 2020 flow chart will be created to illustrate the workflow.

Data collection and management

The data extraction criteria will be refined prior to data collection to ensure consistency among reviewers. The extracted data includes (1) study characteristics including authors, year of publication, study design, journal, contact information, country and funding (2) participant information including mean age, sex, number of participants, type and baseline severity of skin diseases or conditions (3) treatment details including the kind of medical cannabinoid used, additional constituents of intervention products, route of administration and the length of treatment (4) control preparation , route of administration, and duration of application (5) dermatological improvement incoporating results and time points of reported outcome (6) missing data (7) interpretation and discussion (8) all relevant text, tables, and figures. We will contact the corresponding authors of the included studies to obtain incompletely reported data. If no response is received within 14 days, studies will be carried out using the available data.

Risk of bias

The two reviewers will independently assess the risk of bias. The risk of bias of all randomized controlled studies will be assessed using the Cochrane Risk-of-Bias 2 (RoB2),

including the randomization process, allocation concealment, blinding of participants, outcome evaluation, fully addressed outcome data, selective outcome reporting, and other sources of bias. Using ROBINS-1, bias of all nonrandomized controlled studies was evaluated, including bias due to confounding, selection bias, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. When a dispute between two reviewers cannot be resolved through dialogue, an adjudicator will be called in to aid.

Data synthesis

Qualitative synthesis

We will qualitatively analyze the studies and their results in accordance with Standard 4.2 and Chapter 4 of Finding What Works in Health Care: Standards for Systematic Review [20]. We will analyze the studies following the study outcomes, discuss the details of each performance of cannabis and cannabinoids in alleviating dermatological conditions or diseases, and evaluate the risk of bias.

Quantitative systhesis

If the study includes a control group, we will evaluate the efficacy of medical cannabis or cannabinoids in alleviating skin conditions between case and control, as well as between pre- and post-cannabinoids applications. If the study lacks a control group, we will only compare pre- and post-performance. We will combine the study results for each outcome reported in common by two or more studies using the standard mean difference (SMD) method for continuous outcomes and the relative risk (RR) method for dichotomous outcomes. For continuous outcomes in studies with controls, we will utilize the standard mean difference (SMD) of the difference between the case's pre- and post-performance and the control's pre- and post-performance to eliminate baseline heterogeneity between case and control. To compare findings before and after cannabinoid treatment, we will use the standard mean difference (SMD) of outcomes before and after cannabinoid administration. The pooled effect sizes and 95% confidence intervals (CI) will be calculated using random effects models.

For continuous outcomes measured on different scales, in addition to the standard mean difference (SMD) approach for standardization [21], we will attempt to employ the odd ratio method (OR) by specifying the cutoff of the outcome and converting all continuous measures to binary scale, which are 'improvement' and 'no improvement'. We will seek the raw data from the respective authors by contacting them. If we were unable to get the response within 14 days, we will perform the analysis using only the available data.

RevMan 5.4 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) will be used to perform the meta-analysis.P-value < 0.05 will be considered statistically significant.

Assessment of heterogeneity

Heterogeneity will be determined using the Cochran's Q test [a p-value of 0.10 indicated heterogeneity] and the Higgins' test [I2] [less than 25%: low heterogeneity, 25–75%: moderate heterogeneity, more than 75%: high heterogeneity] [22].

Sensitivity analysis and Publication bias

Sensitivity analyzes will examine redoing the meta-analysis by removing one research at a time to assess the statistical robustness of the primary outcome. The Egger's regression asymmetry test and funnel plots will be considered to assess publication bias using R version 4.0.1 if the number of identified studies is fewer than 10.

Patients and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Discussion

Pathological investigations have suggested that cannabis and cannabinoids may be beneficial in the treatment of dermatological problems. However, there is insufficient agreement on their true therapeutic applicability. Previous scoping studies and systematic reviews may have focused on different types of skin disorders; nevertheless, quantitative meta-analysis and systematic reviews based primarily on skin problems tend to be restricted, particularly when dividing the measured results into subjective, objective and disease-specific composite scores. Reporting the efficacy of the treatment in the aforementioned characteristics can make the findings in this study easier to apply, since this quantitative reporting can be easier to comprehend and reproduce for future extended research and decreases the biased bias of the authors, and because a skin condition is identified in many skin diseases. This systematic review and meta-analysis aims to provide a comprehensive summary of the therapeutic effects of cannabis and cannabinoids on dermatological conditions and diseases. This informs clinicians and patients about the efficacy of cannabis and cannabinoids in skin disorders and identifies information gaps that may lead to the creation of a new alternative therapy for dermatological diseases.

Data Availability

All data produced in the present study are available upon reasonable request to the authors.

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This study did not receive any funding.

Authors' contributions

PS, TN, CS, KC and KP conceived of the study and initiated the study design. PS wrote original draft. KP review and edit the draft. KP supervised. All authors contributed to the refinement of the study protocol.

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Cannabis and cannabinoids in dermatology: A systematic review and meta-analysis of quantitative outcomes

Concept 1: Cannabinoid
Concept 2: Dermatology

Set #	Pubmed (until 9 Nov 2022)
1 Cannabinoids	"cannabis"[MeSH Terms] OR cannabis[tiab] OR canabis[tiab] OR "cannabaceae"[MeSH Terms:noexp] OR cannabaceae[tiab] OR hemp*[tiab] OR marijuana[tiab] OR marihuana[tiab] OR ganja*[tiab] OR hash[tiab] OR hashish[tiab] OR bhang[tiab] OR skunk[tiab] OR sinsemilla[tiab] OR charas[tiab] OR weed*[tiab] OR "cannabinoids"[MeSH Terms] OR cannabinoid*[tiab] OR canabinoid*[tiab] OR cannabidiol*[tiab] OR canabidiol*[tiab] OR cannabinol[tiab] OR cannador[tiab] OR eucannabinolide[tiab] OR "8001-45-4"[tiab] OR "8063-14-7"[tiab] OR "38458-58-1"[tiab] OR "dronabinol"[MeSH Terms] OR dronabinol*[tiab] OR marinol[tiab] OR deltanyne[tiab] OR ea1477[tiab] OR "ea-1477"[tiab] OR tetranabinex[tiab] OR qcd84924[tiab] OR "qcd-84924"[tiab] OR "7663-50-5"[tiab] OR nabidiolex[tiab] OR "13956-29-1"[tiab] OR "nabilone"[Supplementary Concept] OR nabilone[tiab] OR cesamet*[tiab] OR cpd109514[tiab] OR "cpd-109514"[tiab] OR lilly109514[tiab] OR "lilly-109514"[tiab] OR "51022-71-0"[tiab] OR "HU 211"[Supplementary Concept] OR "HU 211"[tiab] OR "HU-211"[tiab] OR hu211[tiab] OR "HU 210"[tiab] OR "HU-210"[tiab] OR hu210[tiab] OR dexanabinol[tiab] OR "112924-45-5"[tiab] OR "tetrahydrocannabinol-cannabidiol combination"[Supplementary Concept] OR "tetrahydrocannabinol-cannabidiol combination"[tiab] OR nabiximol*[tiab] OR sativex[tiab] OR gw1000[tiab] OR "gw-1000"[tiab] OR sab378[tiab] OR "sab-378"[tiab] OR "56575-23-6"[tiab] OR tetrahydrocannabinol*[tiab] OR "tetra-hydrocannabinol"[tiab] OR 9tetrahydrocannabinol[tiab] OR "delta3-THC"[tiab] OR "delta-3-THC"[tiab] OR "delta-3-tetrahydrocannabinol"[tiab] OR sp104[tiab] OR "sp-104"[tiab] OR "1972-08-3"[tiab] OR "delta9-THC"[tiab] OR "delta-9-THC"[tiab] OR "delta-9-tetrahydrocannabinol"[tiab] OR "5957-75-5"[tiab] OR cannabichromene[tiab] OR "521-35-7"[tiab] OR "8-THC"[tiab] OR tetrahydrocannabivarin[tiab] OR anandamide[tiab] OR "n-arachidonoylethanolamine"[tiab] OR nantradol[tiab] OR cp44001[tiab] OR "cp-44001"[tiab] OR cp440011[tiab] OR "cp-44001-1"[tiab] OR "cp44001-1"[tiab] OR "72028-54-7"[tiab] OR endocannabinoid*[tiab] OR phytocannabinoid*[tiab] OR sydros[tiab] OR indica[tiab] OR THC[tiab] OR CBD[tiab] OR AEA[tiab]
2 Dermatology	"dermatology"[MeSH Terms] OR dermatol*[tiab] OR "skin"[MeSH Terms] OR skin[tiab] OR cutaneous[tiab] OR wound*[tiab] OR "ulcer"[MeSH Terms] OR ulcer[tiab]
3	#1 AND #2
4	animals[MeSH Terms] NOT humans[MeSH Terms]
5	#3 NOT #4
6	english[lang]
7	#5 AND #6
8	1945/1/01:2022/11/09[dp]
9	#7 AND #8

Set #	Embase (until 9 Nov 2022)
1 Cannabinoids	'cannabis'/exp OR 'cannabis':ti,ab OR 'canabis':ti,ab OR 'cannabaceae'/de OR 'cannabaceae':ti,ab OR 'hemp*':ti,ab OR 'marijuana':ti,ab OR 'marihuana':ti,ab OR 'ganja*':ti,ab OR 'hash':ti,ab OR 'hashish':ti,ab OR 'bhang':ti,ab OR 'skunk':ti,ab OR 'sinsemilla':ti,ab OR 'charas':ti,ab OR 'weed*':ti,ab OR 'cannabinoid'/exp OR 'cannabinoid*':ti,ab OR 'canabinoid*':ti,ab OR 'cannabidiol*':ti,ab OR 'canabidiol*':ti,ab OR 'cannabinol':ti,ab OR 'cannador':ti,ab OR 'eucannabinolide':ti,ab OR '8001-45-4':ti,ab OR '8063-14-7':ti,ab OR '38458-58-1':ti,ab OR 'dronabinol'/exp OR 'dronabinol*':ti,ab OR 'marinol':ti,ab OR 'deltanyne':ti,ab OR 'ea1477':ti,ab OR 'ea-1477':ti,ab OR 'tetranabinex':ti,ab OR 'qcd84924':ti,ab OR 'qcd-84924':ti,ab OR '7663-50-5':ti,ab OR 'nabidiolex':ti,ab OR '13956-29-1':ti,ab OR 'nabilone'/exp OR 'nabilone':ti,ab OR 'cesamet*':ti,ab OR 'cpd109514':ti,ab OR 'cpd-109514':ti,ab OR 'lilly109514':ti,ab OR 'lilly-109514':ti,ab OR '51022-71-0':ti,ab OR 'HU 211':ti,ab OR 'HU-211':ti,ab OR 'hu211':ti,ab OR 'HU 210':ti,ab OR 'HU-210':ti,ab OR 'hu210':ti,ab OR 'dexanabinol'/exp OR 'dexanabinol':ti,ab OR '112924-45-5':ti,ab OR 'tetrahydrocannabinol-cannabidiol combination':ti,ab OR 'nabiximol*':ti,ab OR 'sativex':ti,ab OR 'gw1000':ti,ab OR 'gw-1000':ti,ab OR 'sab378':ti,ab OR 'sab-378':ti,ab OR '56575-23-6':ti,ab OR 'tetrahydrocannabinol*':ti,ab OR 'tetra-hydrocannabinol':ti,ab OR '9tetrahydrocannabinol':ti,ab OR 'delta3-THC':ti,ab OR 'delta-3-THC':ti,ab OR 'delta-3-tetrahydrocannabinol':ti,ab OR 'sp104':ti,ab OR 'sp-104':ti,ab OR '1972-08-3':ti,ab OR 'delta9-THC':ti,ab OR 'delta-9-THC':ti,ab OR 'delta-9-tetrahydrocannabinol':ti,ab OR '5957-75-5':ti,ab OR 'cannabichromene':ti,ab OR '521-35-7':ti,ab OR '8-THC':ti,ab OR 'tetrahydrocannabivarin':ti,ab OR 'anandamide':ti,ab OR 'n-arachidonoylethanolamine':ti,ab OR 'nantradol':ti,ab OR 'cp44001':ti,ab OR 'cp-44001':ti,ab OR 'cp440011':ti,ab OR 'cp-44001-1':ti,ab OR 'cp44001-1':ti,ab OR '72028-54-7':ti,ab OR 'endocannabinoid*':ti,ab OR 'phytocannabinoid*':ti,ab OR 'sydros':ti,ab OR 'indica':ti,ab OR 'THC':ti,ab OR 'CBD':ti,ab OR 'AEA':ti,ab
2 Dermatology	'dermatology'/exp OR 'dermatol*':ti,ab OR 'skin'/exp OR 'skin':ti,ab OR 'cutaneous':ti,ab OR 'wound*':ti,ab OR 'ulcer'/exp OR 'ulcer':ti,ab
3	#1 AND #2
4	[animals]/lim NOT [humans]/lim
5	#3 NOT #4
6	english:la
7	#5 AND #6
8	[09-11-2022]/sd
9	#7 AND #8

Set #	Scopus (until Nov 2022)
1 Cannabinoids	TITLE-ABS-KEY(cannabis OR cannabis OR cannabaceae OR hemp* OR marijuana OR marihuana OR ganja* OR hash OR hashish OR bhang OR skunk OR sinsemilla OR charas OR weed* OR cannabinoid* OR canabinoid* OR cannabidiol* OR canabidiol* OR cannabinol OR cannador OR eucannabinolide OR "8001-45-4" OR "8063-14-7" OR "38458-58-1" OR dronabinol* OR marinol OR deltanyne OR ea1477 OR "ea-1477" OR tetranabinex OR qcd84924 OR "qcd-84924" OR "7663-50-5" OR nabidiolex OR "13956-29-1" OR nabilone OR cesamet* OR cpd109514 OR "cpd-109514" OR lilly109514 OR "lilly-109514" OR "51022-71-0" OR "HU 211" OR "HU-211" OR hu211 OR "HU 210" OR "HU-210" OR hu210 OR dexanabinol OR "112924-45-5" OR "tetrahydrocannabinol-cannabidiol combination" OR nabiximol* OR sativex OR gw1000 OR "gw-1000" OR sab378 OR "sab-378" OR "56575-23-6" OR tetrahydrocannabinol* OR "tetra-hydrocannabinol" OR 9tetrahydrocannabinol OR "delta3-THC" OR "delta-3-THC" OR "delta-3-tetrahydrocannabinol" OR sp104 OR "sp-104" OR "1972-08-3" OR "delta9-THC" OR "delta-9-THC" OR "delta-9-tetrahydrocannabinol" OR "5957-75-5" OR cannabichromene OR "521-35-7" OR "8-THC" OR tetrahydrocannabivarin OR anandamide OR "n-arachidonoylethanolamine" OR nantradol OR cp44001 OR "cp-44001" OR cp440011 OR "cp-44001-1" OR "cp44001-1" OR "72028-54-7" OR endocannabinoid* OR phytocannabinoid* OR sydros OR indica OR THC OR CBD OR AEA)
2 Dermatology	TITLE-ABS-KEY(dermatol* OR skin OR cutaneous OR wound* OR ulcer)
3	#1 AND #2
4	ALL(animals AND NOT humans)
5	#3 AND NOT #4
6	LANGUAGE(english)
7	#5 AND #6
8	PUBYEAR BEF 2023
9	PUBDATETXT(December 2022)
10	#8 AND NOT #9
11	#7 AND #10

Set #	Web of Science (until Dec 2022)
1 Cannabinoids	TS=(cannabis OR cannabis OR cannabaceae OR hemp* OR marijuana OR marihuana OR ganja* OR hash OR hashish OR bhang OR skunk OR sinsemilla OR charas OR weed* OR cannabinoid* OR canabinoid* OR cannabidiol* OR canabidiol* OR cannabinol OR cannador OR eucannabinolide OR "8001-45-4" OR "8063-14-7" OR "38458-58-1" OR dronabinol* OR marinol OR deltanyne OR ea1477 OR "ea-1477" OR tetranabinex OR qcd84924 OR "qcd-84924" OR "7663-50-5" OR nabidiolex OR "13956-29-1" OR nabilone OR cesamet* OR cpd109514 OR "cpd-109514" OR lilly109514 OR "lilly-109514" OR "51022-71-0" OR "HU 211" OR "HU-211" OR hu211 OR "HU 210" OR "HU-210" OR hu210 OR dexanabinol OR "112924-45-5" OR "tetrahydrocannabinol-cannabidiol combination" OR nabiximol* OR sativex OR gw1000 OR "gw-1000" OR sab378 OR "sab-378" OR "56575-23-6" OR tetrahydrocannabinol* OR "tetra-hydrocannabinol" OR 9tetrahydrocannabinol OR "delta3-THC" OR "delta-3-THC" OR "delta-3-tetrahydrocannabinol" OR sp104 OR "sp-104" OR "1972-08-3" OR "delta9-THC" OR "delta-9-THC" OR "delta-9-tetrahydrocannabinol" OR "5957-75-5" OR cannabichromene OR "521-35-7" OR "8-THC" OR tetrahydrocannabivarin OR anandamide OR "n-arachidonoylethanolamine" OR nantradol OR cp44001 OR "cp-44001" OR cp440011 OR "cp-44001-1" OR "cp44001-1" OR "72028-54-7" OR endocannabinoid* OR phytocannabinoid* OR sydros OR indica OR THC OR CBD OR AEA)
2 Dermatology	TS=(dermatol* OR skin OR cutaneous OR wound* OR ulcer)
3	#1 AND #2
4	ALL=(animal NOT human)
5	#3 NOT #4
6	LA=(English)
7	#5 AND #6
8	PY=2023
9	#7 NOT #8

Set #	CENTRAL (until Nov 2022)
1 Cannabinoids	[mh "cannabis"] OR cannabis:ti,ab,kw OR canabis:ti,ab,kw OR [mh "cannabaceae"] OR cannabaceae:ti,ab,kw OR hemp*:ti,ab,kw OR marijuana:ti,ab,kw OR marihuana:ti,ab,kw OR ganja*:ti,ab,kw OR hash:ti,ab,kw OR hashish:ti,ab,kw OR bhang:ti,ab,kw OR skunk:ti,ab,kw OR sinsemilla:ti,ab,kw OR charas:ti,ab,kw OR weed*:ti,ab,kw OR [mh "cannabinoids"] OR cannabinoid*:ti,ab,kw OR canabinoid*:ti,ab,kw OR cannabidiol*:ti,ab,kw OR canabidiol*:ti,ab,kw OR cannabinol:ti,ab,kw OR cannador:ti,ab,kw OR eucannabinolide:ti,ab,kw OR "8001-45-4":ti,ab,kw OR "8063-14-7":ti,ab,kw OR "38458-58-1":ti,ab,kw OR [mh "dronabinol"] OR dronabinol*:ti,ab,kw OR marinol:ti,ab,kw OR deltanyne:ti,ab,kw OR ea1477:ti,ab,kw OR "ea-1477":ti,ab,kw OR tetranabinex:ti,ab,kw OR qcd84924:ti,ab,kw OR "qcd-84924":ti,ab,kw OR "7663-50-5":ti,ab,kw OR nabidiolex:ti,ab,kw OR "13956-29-1":ti,ab,kw OR nabilone:ti,ab,kw OR cesamet*:ti,ab,kw OR cpd109514:ti,ab,kw OR "cpd-109514":ti,ab,kw OR lilly109514:ti,ab,kw OR "lilly-109514":ti,ab,kw OR "51022-71-0":ti,ab,kw OR "HU 211":ti,ab,kw OR "HU-211":ti,ab,kw OR hu211:ti,ab,kw OR "HU 210":ti,ab,kw OR "HU-210":ti,ab,kw OR hu210:ti,ab,kw OR dexanabinol:ti,ab,kw OR "112924-45-5":ti,ab,kw OR "tetrahydrocannabinol-cannabidiol combination":ti,ab,kw OR nabiximol*:ti,ab,kw OR sativex:ti,ab,kw OR gw1000:ti,ab,kw OR "gw-1000":ti,ab,kw OR sab378:ti,ab,kw OR "sab-378":ti,ab,kw OR "56575-23-6":ti,ab,kw OR tetrahydrocannabinol*:ti,ab,kw OR "tetra-hydrocannabinol":ti,ab,kw OR 9tetrahydrocannabinol:ti,ab,kw OR "delta3-THC":ti,ab,kw OR "delta-3-THC":ti,ab,kw OR "delta-3-tetrahydrocannabinol":ti,ab,kw OR sp104:ti,ab,kw OR "sp-104":ti,ab,kw OR "1972-08-3":ti,ab,kw OR "delta9-THC":ti,ab,kw OR "delta-9-THC":ti,ab,kw OR "delta-9-tetrahydrocannabinol":ti,ab,kw OR "5957-75-5":ti,ab,kw OR cannabichromene:ti,ab,kw OR "521-35-7":ti,ab,kw OR "8-THC":ti,ab,kw OR tetrahydrocannabivarin:ti,ab,kw OR anandamide:ti,ab,kw OR "n-arachidonoylethanolamine":ti,ab,kw OR nantradol:ti,ab,kw OR cp44001:ti,ab,kw OR "cp-44001":ti,ab,kw OR cp440011:ti,ab,kw OR "cp-44001-1":ti,ab,kw OR "cp44001-1":ti,ab,kw OR "72028-54-7":ti,ab,kw OR endocannabinoid*:ti,ab,kw OR phytocannabinoid*:ti,ab,kw OR sydros:ti,ab,kw OR indica:ti,ab,kw OR THC:ti,ab,kw OR CBD:ti,ab,kw OR AEA:ti,ab,kw
2 Dermatology	[mh "dermatology"] OR dermatol*:ti,ab,kw OR [mh "skin"] OR skin:ti,ab,kw OR cutaneous:ti,ab,kw OR wound*:ti,ab,kw OR [mh "ulcer"] OR ulcer:ti,ab,kw
3	#1 AND #2
4	Limit to Jan 1996-Nov 2022

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-2
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	29
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-19
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	203-206
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	201
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	201
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol.	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	38-58
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	58-60
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	68-77
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	93-94, 124-126
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	92-97
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	100-102
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	104-112
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	114-126
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	116-124
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	80-90
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	128-138
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	148-152
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	151-173
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☐	☒	
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	140-145
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	174-179
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	

BMJ Open

Cannabis and cannabinoids in dermatology: protocol for a systematic review and meta-analysis of quantitative outcomes.

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2023-075007.R1
Article Type:	Protocol
Date Submitted by the Author:	08-Aug-2023
Complete List of Authors:	Sermsaksasithorn, Pim; Chulalongkorn University Faculty of Medicine Nopsopon, Tanawin; Brigham and Women's Hospital Department of Medicine Samuthpongtorn, Chatpol; Chulalongkorn University Faculty of Medicine Chotirosniramit, Korn; Chulalongkorn University Faculty of Medicine Pongpirul, Krit; Chulalongkorn University Faculty of Medicine, Center of Excellence in Preventive & Integrative Medicine and Department of Preventive and Social Medicine; Johns Hopkins University Bloomberg School of Public Health, Department of International Health
Primary Subject Heading:	Dermatology
Secondary Subject Heading:	Addiction, Complementary medicine, Pharmacology and therapeutics
Keywords:	Dermatology < INTERNAL MEDICINE, COMPLEMENTARY MEDICINE, Psoriasis < DERMATOLOGY

Cannabis and cannabinoids in dermatology: protocol for a systematic review and meta-analysis of quantitative outcomes.

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Abstract

Introduction: Following the discovery of various effects on skin function by modifying endocannabinoid systems, multiple preclinical studies have revealed the promise of cannabis and cannabinoids in the treatment of a variety of skin diseases. However, its clinical efficacy is still debated.

Methods and analysis: The protocol has been prepared using the Preferred Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines. A systematic search will be conducted using PubMed, EMBASE, SCOPUS, the Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science. We will include randomised controlled trials and observational studies investigating alterations to dermatological characteristics following administration of cannabis and cannabinoids for dermatological diseases and disorders. The two reviewers will perform both the title and abstract and full-text screenings. The Cochrane Risk-of-Bias 2 (RoB2) and ROBINS-1 tools will be used to evaluate the risk of bias. If a group of comparable studies for each quantitative outcome can be discovered, we will conduct a random effects meta-analysis. We will investigate heterogeneity using a combination of visual inspection of the forest plot, the Cochran's Q test and Higgins' test [I2]. Sensitivity analyzes will be performed to assess the statistical robustness of the primary outcome. To evaluate a publication bias, the Egger's regression asymmetry test and funnel plots will be considered.

Ethics and dissemination: This study does not require ethical approval because no original data will be collected. The findings will be presented at conferences and published in peer-reviewed journals.

PROSPERO registration number: CRD42023397189.

Strengths
• Focused on skin issues rather than skin diseases, making it easier to apply because many skin diseases share the same skin problem.
• Quantitative reporting of skin improvement results reduces author bias and simplifies future research.
• Classifying quantitative data as subjective, objective, and disease-related particular composite ratings help readers evaluate outcomes reliability.

Limitations
• Recent interest in cannabis for skin improvement and the restrictions of cannabis legalisation in some countries may limit the amount of studies on this topic, especially randomised controlled trials with large sample sizes.

Introduction

Skin is the largest human organ and is essential for organism survival. It is the first line of immunological and physical protection against the external environment, including heat control and retention of hydration (1, 2). A substantial part of the population is affected by skin diseases that have significant effects on the quality of life of sufferers (3-10).

The Endocannabinoid System (ECS), a complex neuromodulatory signalling network, maintains homeostasis and the balance of multiple biological functions by binding ligands (endocannabinoids) to receptors in the nervous system and peripheral organs (6-8). Cannabinoids and active components of *Cannabis sativa*, which were found to mimic endocannabinoid signaling and influence receptor expression (9, 10), have gained interest as potential treatment for various diseases (6, 8). The growing legalization of medicinal cannabis and cannabinoids led to the search for medicinal use in clinical practice. The FDA currently approves the use of cannabinoid to alleviate pain and spasticity in multiple sclerosis and the treatment of chemotherapy-induced nausea and vomiting in cancer patients (11-14).

Modulation of the activity of the endocannabinoid system may influence several types of skin disease, including atopic dermatitis, psoriasis, acne, and skin tumors, according to the etiology of the diseases (15-18). Furthermore, cannabis has been found to possess anti-inflammatory and anti-pruritic properties (13, 19-21), as well as a few more uncommon ones like anti-hydrosis (22). This makes the cannabinoids and active components of *Cannabis sativa* promising for the therapeutic treatment of the skin disorders mentioned above. Given the insufficient quality clinical studies on this topic, this systematic review aims to examine the efficacy of cannabis and cannabinoids in alleviating dermatological conditions and diseases by highlighting current and historical attempts to collect robust clinical data and identify knowledge gaps.

Material and methods

The protocol followed the Preferred Items for Systematic Review and Meta-analysis Protocols (PRISMA-P) guidelines.

Study Selection

Any randomized controlled trials and observational studies including cross-sectional studies, case-control studies, or cohort studies that investigate the efficacy or effectiveness of any form of medical cannabis or cannabinoid in alleviating dermatological conditions or diseases will be included. Exclusion criteria are (1) in vitro studies, case report, protocol, review article, guideline, editorial, commentary, and letter to editor (2) non-peer-reviewed studies (3) animal studies (4) studies published in non-English.

Study outcome

1. Generic outcomes used to assess improvement in skin conditions:
    a. Subjective clinical or patient-reported outcomes such as pruritus score, erythema grade, and quality of life.
    b. Objective evaluation using standard instruments such as transepidermal water loss, lipid analysis, and skin topography evaluation.
2. Disease specific composite scores, mixed subjective and objective outcomes, such as Psoriasis Area Severity Index (PASI) for psoriasis, Eczema Area and Severity Index (EASI), and SCORing Atopic Dermatitis (SCORAD) for atopic dermatitis, etc.

Search strategy

We will search through five databases: PUBMED, EMBASE, SCOPUS, Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science published from onset until 9 November 2022 which will be updated to prior manuscript submission. The search strategy constructed by two health information specialists with systematic review experience will combine search terms and subject headings (MeSH) related to 'cannabis', 'cannabaceae', 'cannabinoids', 'dronabinol', 'dermatology', 'skin', and 'ulcer' (Supplementary 1).

Study records

Data management
After deriving the studies via the mentioned database, we will import them into Covidence systematic review software, which de-duplicates studies and facilitates study selection (23).

Selection process
The titles and abstracts of the identified citations will be evaluated by independent paired reviewers, and initially, the abstracts that do not report the therapeutic effects of cannabis and cannabinoids in dermatological conditions or diseases will be eliminated.

The included studies will then undergo full text review and the final included study will be selected based on all eligibility criteria. Reasons for study exclusion in this step will be recorded. When differences could not be resolved through dialogue, an adjudicator will be brought in to assist. The PRISMA 2020 flow chart will be created to illustrate the workflow.

Data collection and management
The data extraction criteria will be refined prior to data collection to ensure consistency among reviewers. The extracted data includes (1) study characteristics including authors, year of publication, study design, journal, contact information, country and funding (2)

participant information including mean age, sex, number of participants, type and baseline severity of skin diseases or conditions (3) treatment details including the kind of medical cannabinoid used, additional constituents of intervention products, route of administration and the length of treatment (4) control preparation , route of administration, and duration of application (5) dermatological improvement incoporating results and time points of reported outcome (6) missing data (7) interpretation and discussion (8) all relevant text, tables, and figures. We will contact the corresponding authors of the included studies to obtain incompletely reported data. If no response is received within 14 days, studies will be carried out using the available data.

Risk of bias

The two reviewers will independently assess the risk of bias. The risk of bias of all randomized controlled studies will be assessed using the Cochrane Risk-of-Bias 2 (RoB2), including the randomization process, allocation concealment, blinding of participants, outcome evaluation, fully addressed outcome data, selective outcome reporting, and other sources of bias. Using ROBINS-1, bias of all nonrandomized controlled studies was evaluated, including bias due to confounding, selection bias, bias in classification of interventions, bias due to deviations from intended interventions, bias due to missing data, bias in measurement of outcomes and bias in selection of the reported result. When a dispute between two reviewers cannot be resolved through dialogue, an adjudicator will be called in to aid.

Data synthesis

Qualitative synthesis

We will qualitatively analyze the studies and their results in accordance with Standard 4.2 and Chapter 4 of Finding What Works in Health Care: Standards for Systematic Review (24). We will analyze the studies following the study outcomes, discuss the details of each performance of cannabis and cannabinoids in alleviating dermatological conditions or diseases, and evaluate the risk of bias.

Quantitative systhesis

If the study includes a control group, we will evaluate the outcomes between case and control, as well as between pre- and post-cannabinoids applications. If the study lacks a control group, we will only compare pre- and post-performance. We will combine the study results for each outcome reported in common by two or more studies using the standard mean difference (SMD) method for continuous outcomes and the relative risk (RR) method for dichotomous outcomes. For continuous outcomes in studies with controls, we will utilize the standard mean difference (SMD) of the difference between the case's pre- and post-performance and the control's pre- and post-performance to eliminate baseline heterogeneity between case and control. To compare findings before and after cannabinoid treatment, we will use the standard mean difference (SMD) of outcomes before and after cannabinoid administration. The pooled effect sizes and 95% confidence intervals (CI) will be calculated using random effects models.

For continuous outcomes measured on different scales, in addition to the standard mean difference (SMD) approach for standardization (25), we will attempt to employ the odd ratio method (OR) by specifying the cutoff of the outcome and converting all continuous measures to binary scale, which are 'improvement' and 'no improvement'. We will seek the

raw data from the respective authors by contacting them. If we were unable to get the response within 14 days, we will perform the analysis using only the available data.

RevMan 5.4 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen, Denmark) will be used to perform the meta-analysis.P-value < 0.05 will be considered statistically significant.

Assessment of heterogeneity

Heterogeneity will be determined using the Cochran's Q test [a p-value of 0.10 indicated heterogeneity] and the Higgins' test [I2] [less than 25%: low heterogeneity, 25–75%: moderate heterogeneity, more than 75%: high heterogeneity] (26).

Sensitivity analysis and Publication bias

Sensitivity analyzes will examine redoing the meta-analysis by removing one research at a time to assess the statistical robustness of the primary outcome. The Egger's regression asymmetry test and funnel plots will be considered to assess publication bias using R version 4.0.1 if the number of identified studies is fewer than 10.

Expected dates for research

1 September – 31 November 2023

Ethics and dissemination

Because no original data will be collected, this study does not require ethical approval. The results will be presented at conferences and published in journals with peer review.

Patients and Public Involvement

Patients or the public were not involved in the design, or conduct, or reporting, or dissemination plans of our research.

Implications

This systematic review and meta-analysis aims to provide a comprehensive summary of the therapeutic effects of cannabis and cannabinoids on dermatological conditions and diseases. Previous scoping studies and systematic reviews may have focused on different types of skin disorders; nevertheless, quantitative meta-analysis and systematic reviews based primarily on skin problems tend to be restricted, particularly when dividing the measured results into subjective, objective and disease-specific composite scores. Reporting the efficacy of the treatment in the aforementioned characteristics can make the findings in this study easier to apply, since this quantitative reporting can be easier to comprehend and reproduce for future extended research and decreases the biased bias of the authors, and because a skin condition is identified in many skin diseases. This informs clinicians and patients about the efficacy of cannabis and cannabinoids in skin disorders and identifies information gaps that may lead to the creation of a new alternative therapy for dermatological diseases.

Data Availability

All data produced in the present study are available upon reasonable request to the authors.

Funding Statement

This study did not receive any funding.

Competing interest

None declared.

Authors' contributions

PS, TN, CS, KC and KP conceived of the study and initiated the study design. PS wrote original draft. KP review and edit the draft. KP supervised. All authors contributed to the refinement of the study protocol.

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Cannabis and cannabinoids in dermatology: A systematic review and meta-analysis of quantitative outcomes

Concept 1: Cannabinoid
Concept 2: Dermatology

Set #	Pubmed (until 9 Nov 2022)
1 Cannabinoids	"cannabis"[MeSH Terms] OR cannabis[tiab] OR canabis[tiab] OR "cannabaceae"[MeSH Terms:noexp] OR cannabaceae[tiab] OR hemp*[tiab] OR marijuana[tiab] OR marihuana[tiab] OR ganja*[tiab] OR hash[tiab] OR hashish[tiab] OR bhang[tiab] OR skunk[tiab] OR sinsemilla[tiab] OR charas[tiab] OR weed*[tiab] OR "cannabinoids"[MeSH Terms] OR cannabinoid*[tiab] OR canabinoid*[tiab] OR cannabidiol*[tiab] OR canabidiol*[tiab] OR cannabinol[tiab] OR cannador[tiab] OR eucannabinolide[tiab] OR "8001-45-4"[tiab] OR "8063-14-7"[tiab] OR "38458-58-1"[tiab] OR "dronabinol"[MeSH Terms] OR dronabinol*[tiab] OR marinol[tiab] OR deltanyne[tiab] OR ea1477[tiab] OR "ea-1477"[tiab] OR tetranabinex[tiab] OR qcd84924[tiab] OR "qcd-84924"[tiab] OR "7663-50-5"[tiab] OR nabidiolex[tiab] OR "13956-29-1"[tiab] OR "nabilone"[Supplementary Concept] OR nabilone[tiab] OR cesamet*[tiab] OR cpd109514[tiab] OR "cpd-109514"[tiab] OR lilly109514[tiab] OR "lilly-109514"[tiab] OR "51022-71-0"[tiab] OR "HU 211"[Supplementary Concept] OR "HU 211"[tiab] OR "HU-211"[tiab] OR hu211[tiab] OR "HU 210"[tiab] OR "HU-210"[tiab] OR hu210[tiab] OR dexanabinol[tiab] OR "112924-45-5"[tiab] OR "tetrahydrocannabinol-cannabidiol combination"[Supplementary Concept] OR "tetrahydrocannabinol-cannabidiol combination"[tiab] OR nabiximol*[tiab] OR sativex[tiab] OR gw1000[tiab] OR "gw-1000"[tiab] OR sab378[tiab] OR "sab-378"[tiab] OR "56575-23-6"[tiab] OR tetrahydrocannabinol*[tiab] OR "tetra-hydrocannabinol"[tiab] OR 9tetrahydrocannabinol[tiab] OR "delta3-THC"[tiab] OR "delta-3-THC"[tiab] OR "delta-3-tetrahydrocannabinol"[tiab] OR sp104[tiab] OR "sp-104"[tiab] OR "1972-08-3"[tiab] OR "delta9-THC"[tiab] OR "delta-9-THC"[tiab] OR "delta-9-tetrahydrocannabinol"[tiab] OR "5957-75-5"[tiab] OR cannabichromene[tiab] OR "521-35-7"[tiab] OR "8-THC"[tiab] OR tetrahydrocannabivarin[tiab] OR anandamide[tiab] OR "n-arachidonoylethanolamine"[tiab] OR nantradol[tiab] OR cp44001[tiab] OR "cp-44001"[tiab] OR cp440011[tiab] OR "cp-44001-1"[tiab] OR "cp44001-1"[tiab] OR "72028-54-7"[tiab] OR endocannabinoid*[tiab] OR phytocannabinoid*[tiab] OR sydros[tiab] OR indica[tiab] OR THC[tiab] OR CBD[tiab] OR AEA[tiab]
2 Dermatology	"dermatology"[MeSH Terms] OR dermatol*[tiab] OR "skin"[MeSH Terms] OR skin[tiab] OR cutaneous[tiab] OR wound*[tiab] OR "ulcer"[MeSH Terms] OR ulcer[tiab]
3	#1 AND #2
4	animals[MeSH Terms] NOT humans[MeSH Terms]
5	#3 NOT #4
6	english[lang]
7	#5 AND #6
8	1945/1/01:2022/11/09[dp]
9	#7 AND #8

Set #	Embase (until 9 Nov 2022)
1 Cannabinoids	'cannabis'/exp OR 'cannabis':ti,ab OR 'canabis':ti,ab OR 'cannabaceae'/de OR 'cannabaceae':ti,ab OR 'hemp*':ti,ab OR 'marijuana':ti,ab OR 'marihuana':ti,ab OR 'ganja*':ti,ab OR 'hash':ti,ab OR 'hashish':ti,ab OR 'bhang':ti,ab OR 'skunk':ti,ab OR 'sinsemilla':ti,ab OR 'charas':ti,ab OR 'weed*':ti,ab OR 'cannabinoid'/exp OR 'cannabinoid*':ti,ab OR 'canabinoid*':ti,ab OR 'cannabidiol*':ti,ab OR 'canabidiol*':ti,ab OR 'cannabinol':ti,ab OR 'cannador':ti,ab OR 'eucannabinolide':ti,ab OR '8001-45-4':ti,ab OR '8063-14-7':ti,ab OR '38458-58-1':ti,ab OR 'dronabinol'/exp OR 'dronabinol*':ti,ab OR 'marinol':ti,ab OR 'deltanyne':ti,ab OR 'ea1477':ti,ab OR 'ea-1477':ti,ab OR 'tetranabinex':ti,ab OR 'qcd84924':ti,ab OR 'qcd-84924':ti,ab OR '7663-50-5':ti,ab OR 'nabidiolex':ti,ab OR '13956-29-1':ti,ab OR 'nabilone'/exp OR 'nabilone':ti,ab OR 'cesamet*':ti,ab OR 'cpd109514':ti,ab OR 'cpd-109514':ti,ab OR 'lilly109514':ti,ab OR 'lilly-109514':ti,ab OR '51022-71-0':ti,ab OR 'HU 211':ti,ab OR 'HU-211':ti,ab OR 'hu211':ti,ab OR 'HU 210':ti,ab OR 'HU-210':ti,ab OR 'hu210':ti,ab OR 'dexanabinol'/exp OR 'dexanabinol':ti,ab OR '112924-45-5':ti,ab OR 'tetrahydrocannabinol-cannabidiol combination':ti,ab OR 'nabiximol*':ti,ab OR 'sativex':ti,ab OR 'gw1000':ti,ab OR 'gw-1000':ti,ab OR 'sab378':ti,ab OR 'sab-378':ti,ab OR '56575-23-6':ti,ab OR 'tetrahydrocannabinol*':ti,ab OR 'tetra-hydrocannabinol':ti,ab OR '9tetrahydrocannabinol':ti,ab OR 'delta3-THC':ti,ab OR 'delta-3-THC':ti,ab OR 'delta-3-tetrahydrocannabinol':ti,ab OR 'sp104':ti,ab OR 'sp-104':ti,ab OR '1972-08-3':ti,ab OR 'delta9-THC':ti,ab OR 'delta-9-THC':ti,ab OR 'delta-9-tetrahydrocannabinol':ti,ab OR '5957-75-5':ti,ab OR 'cannabichromene':ti,ab OR '521-35-7':ti,ab OR '8-THC':ti,ab OR 'tetrahydrocannabivarin':ti,ab OR 'anandamide':ti,ab OR 'n-arachidonoylethanolamine':ti,ab OR 'nantradol':ti,ab OR 'cp44001':ti,ab OR 'cp-44001':ti,ab OR 'cp440011':ti,ab OR 'cp-44001-1':ti,ab OR 'cp44001-1':ti,ab OR '72028-54-7':ti,ab OR 'endocannabinoid*':ti,ab OR 'phytocannabinoid*':ti,ab OR 'sydros':ti,ab OR 'indica':ti,ab OR 'THC':ti,ab OR 'CBD':ti,ab OR 'AEA':ti,ab
2 Dermatology	'dermatology'/exp OR 'dermatol*':ti,ab OR 'skin'/exp OR 'skin':ti,ab OR 'cutaneous':ti,ab OR 'wound*':ti,ab OR 'ulcer'/exp OR 'ulcer':ti,ab
3	#1 AND #2
4	[animals]/lim NOT [humans]/lim
5	#3 NOT #4
6	english:la
7	#5 AND #6
8	[09-11-2022]/sd
9	#7 AND #8

Set #	Scopus (until Nov 2022)
1 Cannabinoids	TITLE-ABS-KEY(cannabis OR cannabis OR cannabaceae OR hemp* OR marijuana OR marihuana OR ganja* OR hash OR hashish OR bhang OR skunk OR sinsemilla OR charas OR weed* OR cannabinoid* OR canabinoid* OR cannabidiol* OR canabidiol* OR cannabinol OR cannador OR eucannabinolide OR "8001-45-4" OR "8063-14-7" OR "38458-58-1" OR dronabinol* OR marinol OR deltanyne OR ea1477 OR "ea-1477" OR tetranabinex OR qcd84924 OR "qcd-84924" OR "7663-50-5" OR nabidiolex OR "13956-29-1" OR nabilone OR cesamet* OR cpd109514 OR "cpd-109514" OR lilly109514 OR "lilly-109514" OR "51022-71-0" OR "HU 211" OR "HU-211" OR hu211 OR "HU 210" OR "HU-210" OR hu210 OR dexanabinol OR "112924-45-5" OR "tetrahydrocannabinol-cannabidiol combination" OR nabiximol* OR sativex OR gw1000 OR "gw-1000" OR sab378 OR "sab-378" OR "56575-23-6" OR tetrahydrocannabinol* OR "tetra-hydrocannabinol" OR 9tetrahydrocannabinol OR "delta3-THC" OR "delta-3-THC" OR "delta-3-tetrahydrocannabinol" OR sp104 OR "sp-104" OR "1972-08-3" OR "delta9-THC" OR "delta-9-THC" OR "delta-9-tetrahydrocannabinol" OR "5957-75-5" OR cannabichromene OR "521-35-7" OR "8-THC" OR tetrahydrocannabivarin OR anandamide OR "n-arachidonoylethanolamine" OR nantradol OR cp44001 OR "cp-44001" OR cp440011 OR "cp-44001-1" OR "cp44001-1" OR "72028-54-7" OR endocannabinoid* OR phytocannabinoid* OR sydros OR indica OR THC OR CBD OR AEA)
2 Dermatology	TITLE-ABS-KEY(dermatol* OR skin OR cutaneous OR wound* OR ulcer)
3	#1 AND #2
4	ALL(animals AND NOT humans)
5	#3 AND NOT #4
6	LANGUAGE(english)
7	#5 AND #6
8	PUBYEAR BEF 2023
9	PUBDATETXT(December 2022)
10	#8 AND NOT #9
11	#7 AND #10

Set #	Web of Science (until Dec 2022)
1 Cannabinoids	TS=(cannabis OR cannabis OR cannabaceae OR hemp* OR marijuana OR marihuana OR ganja* OR hash OR hashish OR bhang OR skunk OR sinsemilla OR charas OR weed* OR cannabinoid* OR canabinoid* OR cannabidiol* OR canabidiol* OR cannabinol OR cannador OR eucannabinolide OR "8001-45-4" OR "8063-14-7" OR "38458-58-1" OR dronabinol* OR marinol OR deltanyne OR ea1477 OR "ea-1477" OR tetranabinex OR qcd84924 OR "qcd-84924" OR "7663-50-5" OR nabidiolex OR "13956-29-1" OR nabilone OR cesamet* OR cpd109514 OR "cpd-109514" OR lilly109514 OR "lilly-109514" OR "51022-71-0" OR "HU 211" OR "HU-211" OR hu211 OR "HU 210" OR "HU-210" OR hu210 OR dexanabinol OR "112924-45-5" OR "tetrahydrocannabinol-cannabidiol combination" OR nabiximol* OR sativex OR gw1000 OR "gw-1000" OR sab378 OR "sab-378" OR "56575-23-6" OR tetrahydrocannabinol* OR "tetra-hydrocannabinol" OR 9tetrahydrocannabinol OR "delta3-THC" OR "delta-3-THC" OR "delta-3-tetrahydrocannabinol" OR sp104 OR "sp-104" OR "1972-08-3" OR "delta9-THC" OR "delta-9-THC" OR "delta-9-tetrahydrocannabinol" OR "5957-75-5" OR cannabichromene OR "521-35-7" OR "8-THC" OR tetrahydrocannabivarin OR anandamide OR "n-arachidonoylethanolamine" OR nantradol OR cp44001 OR "cp-44001" OR cp440011 OR "cp-44001-1" OR "cp44001-1" OR "72028-54-7" OR endocannabinoid* OR phytocannabinoid* OR sydros OR indica OR THC OR CBD OR AEA)
2 Dermatology	TS=(dermatol* OR skin OR cutaneous OR wound* OR ulcer)
3	#1 AND #2
4	ALL=(animal NOT human)
5	#3 NOT #4
6	LA=(English)
7	#5 AND #6
8	PY=2023
9	#7 NOT #8

Set #	CENTRAL (until Nov 2022)
1 Cannabinoids	[mh "cannabis"] OR cannabis:ti,ab,kw OR canabis:ti,ab,kw OR [mh "cannabaceae"] OR cannabaceae:ti,ab,kw OR hemp*:ti,ab,kw OR marijuana:ti,ab,kw OR marihuana:ti,ab,kw OR ganja*:ti,ab,kw OR hash:ti,ab,kw OR hashish:ti,ab,kw OR bhang:ti,ab,kw OR skunk:ti,ab,kw OR sinsemilla:ti,ab,kw OR charas:ti,ab,kw OR weed*:ti,ab,kw OR [mh "cannabinoids"] OR cannabinoid*:ti,ab,kw OR canabinoid*:ti,ab,kw OR cannabidiol*:ti,ab,kw OR canabidiol*:ti,ab,kw OR cannabinol:ti,ab,kw OR cannador:ti,ab,kw OR eucannabinolide:ti,ab,kw OR "8001-45-4":ti,ab,kw OR "8063-14-7":ti,ab,kw OR "38458-58-1":ti,ab,kw OR [mh "dronabinol"] OR dronabinol*:ti,ab,kw OR marinol:ti,ab,kw OR deltanyne:ti,ab,kw OR ea1477:ti,ab,kw OR "ea-1477":ti,ab,kw OR tetranabinex:ti,ab,kw OR qcd84924:ti,ab,kw OR "qcd-84924":ti,ab,kw OR "7663-50-5":ti,ab,kw OR nabidiolex:ti,ab,kw OR "13956-29-1":ti,ab,kw OR nabilone:ti,ab,kw OR cesamet*:ti,ab,kw OR cpd109514:ti,ab,kw OR "cpd-109514":ti,ab,kw OR lilly109514:ti,ab,kw OR "lilly-109514":ti,ab,kw OR "51022-71-0":ti,ab,kw OR "HU 211":ti,ab,kw OR "HU-211":ti,ab,kw OR hu211:ti,ab,kw OR "HU 210":ti,ab,kw OR "HU-210":ti,ab,kw OR hu210:ti,ab,kw OR dexanabinol:ti,ab,kw OR "112924-45-5":ti,ab,kw OR "tetrahydrocannabinol-cannabidiol combination":ti,ab,kw OR nabiximol*:ti,ab,kw OR sativex:ti,ab,kw OR gw1000:ti,ab,kw OR "gw-1000":ti,ab,kw OR sab378:ti,ab,kw OR "sab-378":ti,ab,kw OR "56575-23-6":ti,ab,kw OR tetrahydrocannabinol*:ti,ab,kw OR "tetra-hydrocannabinol":ti,ab,kw OR 9tetrahydrocannabinol:ti,ab,kw OR "delta3-THC":ti,ab,kw OR "delta-3-THC":ti,ab,kw OR "delta-3-tetrahydrocannabinol":ti,ab,kw OR sp104:ti,ab,kw OR "sp-104":ti,ab,kw OR "1972-08-3":ti,ab,kw OR "delta9-THC":ti,ab,kw OR "delta-9-THC":ti,ab,kw OR "delta-9-tetrahydrocannabinol":ti,ab,kw OR "5957-75-5":ti,ab,kw OR cannabichromene:ti,ab,kw OR "521-35-7":ti,ab,kw OR "8-THC":ti,ab,kw OR tetrahydrocannabivarin:ti,ab,kw OR anandamide:ti,ab,kw OR "n-arachidonoylethanolamine":ti,ab,kw OR nantradol:ti,ab,kw OR cp44001:ti,ab,kw OR "cp-44001":ti,ab,kw OR cp440011:ti,ab,kw OR "cp-44001-1":ti,ab,kw OR "cp44001-1":ti,ab,kw OR "72028-54-7":ti,ab,kw OR endocannabinoid*:ti,ab,kw OR phytocannabinoid*:ti,ab,kw OR sydros:ti,ab,kw OR indica:ti,ab,kw OR THC:ti,ab,kw OR CBD:ti,ab,kw OR AEA:ti,ab,kw
2 Dermatology	[mh "dermatology"] OR dermatol*:ti,ab,kw OR [mh "skin"] OR skin:ti,ab,kw OR cutaneous:ti,ab,kw OR wound*:ti,ab,kw OR [mh "ulcer"] OR ulcer:ti,ab,kw
3	#1 AND #2
4	Limit to Jan 1996-Nov 2022

PRISMA-P 2015 Checklist

This checklist has been adapted for use with protocol submissions to *Systematic Reviews* from Table 3 in Moher D et al: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Systematic Reviews* 2015 **4**:1

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
ADMINISTRATIVE INFORMATION					
Title					
Identification	1a	Identify the report as a protocol of a systematic review	☒	☐	1-3
Update	1b	If the protocol is for an update of a previous systematic review, identify as such	☐	☒	
Registration	2	If registered, provide the name of the registry (e.g., PROSPERO) and registration number in the Abstract	☒	☐	49
Authors					
Contact	3a	Provide name, institutional affiliation, and e-mail address of all protocol authors; provide physical mailing address of corresponding author	☒	☐	4-20
Contributions	3b	Describe contributions of protocol authors and identify the guarantor of the review	☒	☐	266-270
Amendments	4	If the protocol represents an amendment of a previously completed or published protocol, identify as such and list changes; otherwise, state plan for documenting important protocol amendments	☐	☒	
Support					
Sources	5a	Indicate sources of financial or other support for the review	☒	☐	258-260
Sponsor	5b	Provide name for the review funder and/or sponsor	☒	☐	232-235
Role of sponsor/funder	5c	Describe roles of funder(s), sponsor(s), and/or institution(s), if any, in developing the protocol	☐	☒	
INTRODUCTION					
Rationale	6	Describe the rationale for the review in the context of what is already known	☒	☐	64-92
Objectives	7	Provide an explicit statement of the question(s) the review will address with reference to participants, interventions, comparators, and outcomes (PICO)	☒	☐	90-92
METHODS					

Section/topic	#	Checklist item	Information reported		Line number(s)
			Yes	No	
Eligibility criteria	8	Specify the study characteristics (e.g., PICO, study design, setting, time frame) and report characteristics (e.g., years considered, language, publication status) to be used as criteria for eligibility for the review	☒	☐	99-107
Information sources	9	Describe all intended information sources (e.g., electronic databases, contact with study authors, trial registers, or other grey literature sources) with planned dates of coverage	☒	☐	122-124, 157-160
Search strategy	10	Present draft of search strategy to be used for at least one electronic database, including planned limits, such that it could be repeated	☒	☐	122-128
STUDY RECORDS					
Data management	11a	Describe the mechanism(s) that will be used to manage records and data throughout the review	☒	☐	132-135
Selection process	11b	State the process that will be used for selecting studies (e.g., two independent reviewers) through each phase of the review (i.e., screening, eligibility, and inclusion in meta-analysis)	☒	☐	137-144
Data collection process	11c	Describe planned method of extracting data from reports (e.g., piloting forms, done independently, in duplicate), any processes for obtaining and confirming data from investigators	☒	☐	148-149
Data items	12	List and define all variables for which data will be sought (e.g., PICO items, funding sources), any pre-planned data assumptions and simplifications	☒	☐	149-157
Outcomes and prioritization	13	List and define all outcomes for which data will be sought, including prioritization of main and additional outcomes, with rationale	☒	☐	1079-118
Risk of bias in individual studies	14	Describe anticipated methods for assessing risk of bias of individual studies, including whether this will be done at the outcome or study level, or both; state how this information will be used in data synthesis	☒	☐	162-173
DATA					
Synthesis	15a	Describe criteria under which study data will be quantitatively synthesized	☒	☐	187-189
	15b	If data are appropriate for quantitative synthesis, describe planned summary measures, methods of handling data, and methods of combining data from studies, including any planned exploration of consistency (e.g., I^2, Kendall's tau)	☒	☐	188-198,206-208, 210-214
	15c	Describe any proposed additional analyses (e.g., sensitivity or subgroup analyses, meta-regression)	☒	☐	218-219
	15d	If quantitative synthesis is not appropriate, describe the type of summary planned	☒	☐	177-183, 199-205
Meta-bias(es)	16	Specify any planned assessment of meta-bias(es) (e.g., publication bias across studies, selective reporting within studies)	☒	☐	219-221
Confidence in cumulative evidence	17	Describe how the strength of the body of evidence will be assessed (e.g., GRADE)	☐	☒	