Health Effects of High-Potency Cannabis Products: A Scoping Review Protocol

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1. Background

1.1 Introduction and context

The potency, or concentration, of cannabis products, often measured as a percentage of tetrahydrocannabinol (THC), has been increasing over the last decade.[1] Concerns about the adverse health effects of using these high-potency products has also been on the rise.[2-4] However, there has been no up-to-date and rigorous systematic review of the health effects of high-potency cannabis to inform policy recommendations on regulating marijuana concentrates.

Colorado House Bill 1317 [5] requires the Colorado School of Public Health to "…do a systematic review of the scientific research related to the physical and mental health effects of high-potency THC marijuana and concentrates." This review will include "…all available scientific evidence-based research regarding the possible physical and mental health effects of high-potency THC marijuana and marijuana concentrates regardless of the location of the research." "The research must study the effect of high-potency THC marijuana on the developing brain and the effect of marijuana concentrates on physical and mental health."

"The research must systematically curate and synthesize existing research, identify evidence gaps, and identify new research that is needed to better understand the health implications of high-potency THC marijuana products and the specific THC potency levels and amounts at which various health concerns arise."

This research will inform a public health campaign "…regarding the effect of high-potency marijuana on the developing brain and mental health." The research will also inform rules for prescriptions to indicate "…maximum THC potency level of medical marijuana being recommended" and a level for THC toxicity screening.

1.2 Rationale for conducting a scoping review

Systematic reviews aim to answer a well-defined research question by critically appraising literature that is subject to relevant inclusion and exclusion criteria, and synthesizing the findings. In contrast, scoping reviews have a broader purview, aiming to 'map' the range, extent, and nature of research relevant to a broad question.[6] There are six possible indications for conducting scoping reviews: 1) to identify the types of evidence available in a given field; 2) to clarify key concepts; 3) to examine how research is conducted on a certain topic; 4) to identify key factors or characteristics related to a concept; 5) as preparation for a systematic review; and 6) to identify and analyze knowledge gaps.[6]

Given the heterogeneity in how "potency" of marijuana is defined, the broad range of outcomes that are of interest, and the variety of study designs that may have addressed health effects of high-potency products, this scoping review will be useful to clarify the key concepts related studying health benefits and harms of high-potency cannabis products, examine how research is conducted on this topic, and identify the key characteristics and factors associated with these studies. Because scoping reviews use systematic review methods, if subsets of homogeneous studies are identified, their results can be synthesized. As the term "cannabis" is frequently used in the scientific literature, this scoping review will refer to "cannabis" rather than marijuana.

2. Objectives

Identify and describe studies that explore the relationship of high-potency cannabis products with beneficial health outcomes.

Identify and describe studies that explore the relationship of high-potency cannabis products with adverse health outcomes.

Identify and describe studies that report adverse effects of exposure to high-potency products (with no comparison group).

3. Methods

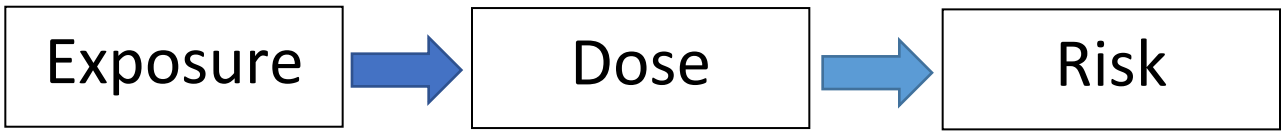
We will employ Joanna Briggs Institute [7] and Cochrane [8] methodologies for conducting scoping reviews in the conduct of the review and synthesis.

3. Criteria for considering studies for this review

3.1 Concept

The focus of this review is high-potency THC cannabis products and concentrates. The relationship between THC concentration in a product and health effects is complex and influenced by several modifying factors. In conceptualizing how environmental exposures (consider cannabis and high-potency THC products as such) increase risk for various health outcomes, a simple linear paradigm involving exposure, dose, and risk is often applied (Figure 1a). Exposure constitutes the contact of the agent with people; dose is the amount of the agent that enters the body; and risk is the probability that an event will occur. In a relevant example, we are all exposed to ambient or outdoor air pollution (the exposure) and we inhale the air pollutants, such as small particles, into our lungs (the dose), leading to increased risk for various adverse health outcomes, including increased risk for dying.

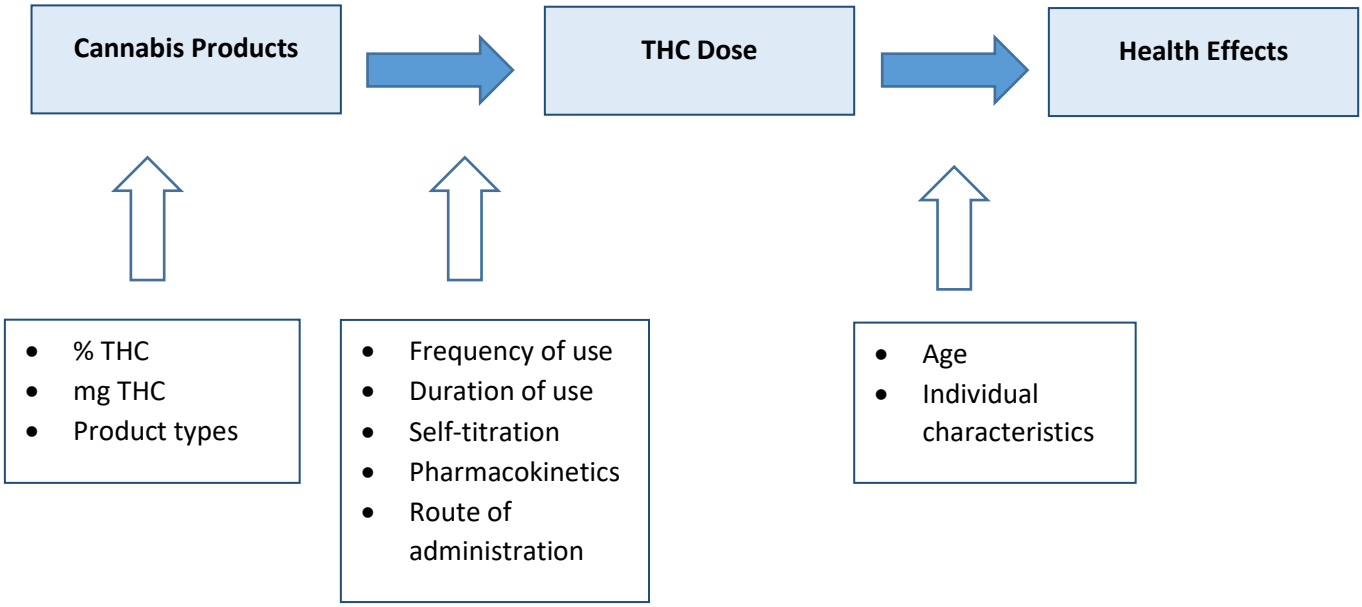
Figure 1a.



In Figure 1b, we generalize this paradigm to high potency cannabis products. The product now represents exposure while dose refers to the amount of THC entering the body, whether through ingestion or inhalation. Risk refers to the range of potential outcomes related to exposure and the attendant doses. The characteristics of the product are critical to determining THC dose, as is how it is used—frequency, pattern of use over time, and the route of administration (i.e., ingestion or inhalation). The dose of THC that reaches the brain will also vary with the way that each individual handles the product and particularly how the THC is distributed and metabolized, i.e., the pharmacokinetics. As implied by Figure 1b, the health outcomes will vary with the characteristics of the user and they need to

be considered in the context of the purpose for which the product is used, particularly recreational or therapeutic.

Figure 1b.



For this review, we will focus on studies that report the potency of the product being studied and have a potency level considered as "high-potency" as defined in the below Exposure section. Potency is also referred to as "concentration" and is typically measured as percentage THC. We will also include studies that assess a dose-response relationship, or allow some conclusions about dose, associated with beneficial or harmful health effects.

3.2 Context

We will include research conducted in any country, research on recreational/non-prescription cannabis use and/or medicinal cannabis use.

3.3 Study design

We will include systematic reviews of studies of any design, including case reports; studies of any epidemiological design, including randomized controlled trials (RCTs), cohort studies, case-control studies. We will include non-systematic reviews of case reports/series that may be useful for identifying toxic levels, such as reviews of toxicology reports.

We will exclude individual case reports, case series (e.g., from Poison Control Centers). We will not conduct our own analyses of case reports.

3.4 Population

We will include all human studies; any age; predefined subgroups of children/youth, pregnant women.

We will exclude animal studies. We will exclude lab or simulation-based mechanistic studies.

3.5 Exposure

3.5.1 Potency

Potency, or concentration, is not the same as dose or level of exposure. The effect experienced is influenced by dose, specific type of cannabis product, route of administration, duration, frequency of intake, experience/tolerance of user, self-titration, etc. (see Figure 1b).

For this scoping review, we will include studies that report THC concentration for a cannabis product taken by any route of administration; or, where THC concentration must be extrapolated from product description (e.g., "high-potency concentrate").

We will characterize potency by stratifying by THC amount/strength:

- Edibles: <5 mg, 5-10 mg, > 10 mg.
- Inhalation products: < 5%, 5-15%, 15-20%, and > 20%.

We will collect reports that measure potency in different ways. If possible, we will convert to a common metric for analysis (e.g., percentage THC typically for inhaled products, THC mg amount for ingested products). Most reports refer to content of THC in the cannabis product as either a percentage THC or mg per serving for edible products [2,3], although some may calculate THC mg for smoked products as well.

Some analyses of cannabis health effects use a THC/cannabidiol (CBD) ratio for medicinal use.[9] Some states regulate access to low THC/high CBD products; hence the use of this ratio for assessing potency. However, using the THC/CBD ratio can be misleading because there can be a high THC/CBD ratio, and still have a relatively low concentration of THC.

3.5.2 Types of products

We will include exposures to the following types of cannabis products [3]: marijuana plant (dried or undried), marijuana edible preparation, marijuana oral capsule or pill preparation, marijuana concentrated extract (e.g., dabs, wax, shatter), oils, tinctures, marijuana e-cigarettes, and other or unknown preparations.

We will exclude CBD, cannabinol only products. We will exclude studies of dronabinol, nabilone, and other orally administered synthetic cannabinoid products for medicinal use only (see Supplemental Tables in Appendix A).

3.6 Comparison

We will include comparisons of different THC amounts/levels; comparison to no/low exposure or placebo. We will include reviews of toxicology reports and case studies that may have no comparison but meet a "high-potency" threshold as defined above.

3.7 Outcomes

We will include any beneficial and adverse health outcomes of high-potency THC cannabis products and concentrates. Tables 1 and 2 summarize some examples from other reports.[2-4]

Table 1: Examples of therapeutic effects of high-potency THC cannabis products and concentrates

Category	Disease/condition
Cancer	Glioma tumor
Pain	Chronic pain in adults, palliative care
Psychosocial	Social anxiety, quality of life
Mental health	Anxiety, depressive symptoms, posttraumatic stress disorder (PTSD), schizophrenia
Substance use/substance dependence	Addictive substance use treatment such as opioids
Death	Decreased mortality associated with traumatic brain injury, intracranial hemorrhage
Gastrointestinal	Chemotherapy-associated nausea and vomiting, HIV/AIDS associated anorexia and weight loss, cancer-associated anorexia-cachexia, anorexia nervosa, symptoms of irritable bowel syndrome
Neurological	Dyskinesia, dementia, epilepsy, spasticity associated with multiple sclerosis or spinal cord injury, symptoms associated with Tourette syndrome, motor and cognitive symptoms of Huntington's disease, Amyotrophic Lateral Sclerosis, and Parkinson's disease, levodopa-induced dyskinesia, dementia, mortality and disability associated with traumatic brain injury or intracranial hemorrhage
Ocular	Glaucoma intraocular pressure
Sleep	Sleep disturbances

Table 2: Examples of adverse effects of high-potency THC cannabis products and concentrates

Category	Disease/condition
Cancer	Testicular germ cell tumors
Cardiometabolic risk	Acute myocardial infarction, stroke, metabolic dysregulation, diabetes, and hypertension
Respiratory disease	Pulmonary function, COPD, respiratory symptoms including chronic bronchitis, and asthma
Immunity	Immune competence, susceptibility and progression of infectious disease
Pre-, peri-, and neonatal risks	Pregnancy complications, fetal growth and development, neonatal conditions, and later developmental outcomes
Psychosocial	Quality of life, cognition, academic achievement, employment and income, social relationships and other social roles
Mental health	Schizophrenia and other psychoses, bipolar disorder, depression, suicide, anxiety, PTSD, psychological distress, sleep quality, and sleep disturbance
Substance dependence/substance use disorder	Alcohol, tobacco, opioids, and cannabis use disorder
Injury and Death	All-cause mortality, occupational injury, and motor vehicle crashes
Adverse effects	Acute effects of dizziness, nausea, and sedation
Gastrointestinal	Hyperemesis

4. Search methods for identification of studies

4.1 Electronic database search

An experienced medical information specialist (CP) will design a comprehensive search strategy for the concepts of marijuana or tetrahydrocannabinol. Relevant publications will be identified by searching the following databases with a combination of controlled vocabulary and keywords: Ovid MEDLINE All (1946 to present), Embase (via Elsevier, Embase.com, 1947 to present), AMED (Allied and Complementary Medicine via Ovid, 1985 to present), Cochrane Library (via Wiley, including Cochrane Database of Systematic Reviews and Cochrane Central Register of Controlled Trials), Database of Abstracts of Reviews of Effects (DARE, 1995 – March 2015, via crd.york.ac.uk), CINAHL (Cumulative Index to Nursing and Allied Health Literature via EBSCOhost, 1981 to present), and ToxLine (via Pubmed.gov using the ToxLine subset).

We will limit the searches to English language and Human studies when possible. We will exclude comments, editorials, interviews, news articles, and letters as publication types when possible. We will not apply any date limitation. We will develop the search initially for Ovid MEDLINE and will translate the search to the other databases. The search strategy will be peer reviewed by another experienced medical information specialist prior to execution using the PRESS checklist.[10] All search strategies can be found in Appendix B. We will update the search before the submission of the report. We will export all results to DistillerSR [11] where duplicates will be identified and removed automatically by the software.

4.2 Supplemental searches

We will search for grey literature (e.g., governmental reports, unpublished studies) for relevant studies.[12] An example search of US state reports can be found in Appendix C. Additionally, we will search for articles citing or cited by included studies using the program citationchaser.[13]

5. Data collection and charting

5.1 Screening process

To capture the full range of research on health effects of high-potency cannabis products, we intend for our search to be sensitive, but not specific. Therefore, it will be necessary to screen a potentially large number of records to identify studies that meet the inclusion criteria. We will train all screeners before they begin screening activities.

5.1.1 Title and abstract screening

We will use artificial intelligence (AI) text-mining features available in DistillerSR to assist in screening.[11] We will train the AI classification algorithm in DistillerSR with 1000 randomly selected records. These records will be screened and labeled by two senior screeners, coding independently, with discrepancies decided by discussion. The training set will provide the baseline ratio of included and excluded titles and abstracts, as well as the baseline accuracy of DistillerSR's AI classification prediction.

We will then use the 'trained' DistillerSR's AI algorithm to rank the remaining unreviewed titles and abstracts. Unreviewed titles and abstracts with a high likelihood of inclusion (score: 0.70 to 1) and

exclusion (score: 0.30 to 0.000) will be screened by a single reviewer. The titles and abstracts ranked in between (score: 0.30 to 0.70) will be screened by two screeners independently with discrepancies adjudicated by a senior screener. This set of references will use continuous AI prioritization; every 200 records screened, the AI algorithm ranks and reorders records so those scored highly for inclusion are screened sooner.[11] Note that depending on the accuracy of AI classification described above, we may choose different thresholds for independent dual screening.

5.1.2 Full text screening

We will retrieve full text reports of potentially relevant citations. Two screeners will review the full text against the eligibility criteria independently with disagreements decided by a senior screener. Reasons for excluding full text reports will be recorded and reported in the scoping review.

5.1.3 Screening quality control and quality assurance

Senior reviewers will check 2% of all screening decisions at both titles and abstracts and full text screening stages, discuss problems at routine group meetings, and retrain screeners as needed. We also will run DistillerSRs 'Check for Screening Errors' tool to check the human screening decisions against the AI rankings.[11] Flagged references will be reevaluated for inclusion by a senior reviewer.

We will report the search and conduct according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses extension for scoping reviews (PRISMA-ScR).[14] None of the reviewers involved in screening have published research on cannabis that could be eligible for inclusion and, therefore, will not have an a priori basis to introduce bias in the selection of studies.

5.2 Data extraction

We will develop and pilot test a data extraction form in DistillerSR to manually extract study details from full text reports. One reviewer will extract data into the data extraction form, which will be verified by another reviewer.[15,16] We will extract data on the following characteristics:

- Publication information, including authors, type of report, journal, year, type of publication, funding source, country.
- Study topic and objectives.
- Study design, including trial design, location, setting, and inclusion/exclusion criteria.
- Characteristic of population, including age, gender, developmental stage, race/ethnicity, pregnancy, and comorbidities.
- Details of exposure, including specific type of cannabis product, route of administration, duration, frequency of intake, experience/tolerance of user, self-titration on measured, and concentration (e.g., percentage THC, THC to CBD ratio, and other measures of concentration).
- Details of comparison exposure, if applicable.
- Outcomes, including outcome descriptor, measurement method, metric, method of aggregation, and time-point. The outcomes of interest are described under the "outcome" section.

We will contact the study authors for incomplete or unclear information. If the authors do not respond for two weeks, we will pursue analyses using available data.

6. Evaluation of included studies

Two senior researchers will work independently to assess risk of bias in included systematic reviews using the ROBIS tool.[17] We will assess each of the following domains:

- Concerns regarding specification of study eligibility criteria.
- Concerns regarding methods used to identify and/or select studies.
- Concerns regarding methods used to collect data and appraise studies.
- Concerns regarding the synthesis and findings.

As per scoping review methods, we will not assess risk of bias for primary studies due to heterogeneity of study designs included.[7] We will extract study designs and key characteristics that will enable selection of the appropriate risk of bias tool if studies are grouped for further analysis as described in the above 5.2 Data Extraction section.

7. Analysis / synthesis of included studies

Due to the breadth of outcomes addressed by the review and the heterogeneity of evidence we expect to identify for each question, we do not anticipate that a quantitative summary of the evidence (using meta-analysis, for example) will be feasible. Therefore, we will present the results of the scoping review according to the Synthesis Without Meta-Analysis (SWIM) reporting guideline developed by Cochrane.[18]

We expect to describe studies addressing the following questions:

- An overview of the literature on high-potency cannabis products - What journals are publishing this research? Who are the major funders? Where is the research conducted? How has potency been defined? How is exposure measured? What types of populations, exposures and outcomes have been studied? What are timelines and trends in research?
- Identification of clusters of studies that allow formulation of specific research questions that warrant further analysis - Is there a commonly used definition of “high-potency”? Are there clusters of exposures that have been studied? In the case of clusters of outcomes – are they harmful or beneficial?
- Identification of gaps in the evidence base - Are there relevant exposures, outcomes, interventions that have not been or been rarely studied?
- What identification study designs have been used to address different questions? What are their strengths, limitations, and suitability for the question?
- At what potency levels has toxicity been observed? We will produce visual displays of potency levels associated with various outcomes (for example, using bubble plots).

We will describe: 1) the rationale for grouping studies for synthesis, 2) standardized metrics and transformation methods used (if any), 3) methods used for synthesis other than meta-analysis, 4) criteria used to prioritize results for summary and analysis, 5) how heterogeneity will be investigated, 6) how certainty of evidence will be rated, and 7) what data presentation methods will be used (e.g., forest plots, harvest plots, albatross plots). We will provide a description (using text and visual displays) of the synthesized evidence and certainty of the findings for each question. We will provide a tabular description of study characteristics and findings for each included study. In addition, if data are available, we will conduct subgroup analyses by age and pregnancy status at exposure. We will use the following age

groupings: child (less than 9 years), adolescent (9-17), young adult (18-24), adult (25-64), older adult (65 and over).[19]

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