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Cannabinoids for Medical Purposes in Children: A Living Systematic Review

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ABSTRACT

Aim: We developed a living systematic review (LSR) that will continuously map the safety and reported benefit data related to cannabinoid use for medical purposes in children.

Methods: MEDLINE, Embase, PsycInfo, and the Cochrane Library were searched from inception to April 2023. Studies involving at least one child < 18 years who was administered plant-derived or pharmaceutical cannabinoids as an intervention or treatment for medical conditions were included.

Results: Of 37 189 identified citations, 276 studies were included: 84 interventional, 131 observational, 54 surveys, and 7 qualitative studies. Among interventional and observational studies, common indications for cannabinoids in children were refractory epilepsy ($n = 146$ studies, 188 726 participants), cancer and cancer symptoms ($n = 30$ studies, 208 753 participants), and autism spectrum disorder ($n = 18$ studies, 1285 participants). Common cannabinoids identified in interventional studies were purified cannabidiol (CBD) (78.6%, $n = 66$ studies, 5235 participants) with dose range of 2–50 mg/kg/day, tetrahydrocannabinol (6%, $n = 5$ studies, 148 participants) with dose range of 2.5–10 mg/day (max dose of tetrahydrocannabinol in nabiximols 32.4 mg) and nabilone (6%, $n = 5$ studies, 267 participants) with dose range of 0.5–2 mg/day. In randomised controlled trials, purified cannabidiol was reported to reduce seizure frequency ranging between 30% and 50%. Common adverse events (> 20% studies) in studies enrolling children were somnolence, diarrhoea, vomiting, and decreased appetite.

Conclusion: These findings will continue to be updated to inform practice and reveal knowledge gaps for future research.

Abbreviations: ADHD, attention deficit hyperactivity disorder; CBD, cannabidiol; CNS, central nervous system; DRE, drug-resistant epilepsy; ICD, international classification of disease; ICTRP, international clinical trials registry platform; IQR, interquartile range; LSR, living systematic review; PRISMA, preferred reporting items for systematic review and meta-analysis; PRESS, peer-review of electronic search strategies; RCTs, randomised controlled trials; SWiM, synthesis without meta-analysis; THC, tetrahydrocannabinol.

Summary

- Cannabinoids are used for medical purposes in children with an expanding array of products and conditions studied, including drug-resistant epilepsy, autism spectrum disorder, symptoms experienced by patients with cancer, and various other health conditions.
- Purified cannabidiol (CBD) is the most studied cannabinoid in children with drug-resistant epilepsies.
- Knowledge gaps on long-term cannabinoid-related adverse events, drug interactions, benefits, and tolerability of cannabinoids in children with medical complexities exist.

1 | Introduction

The cannabis plant has been used for medical purposes since ancient times [1]. In recent years, there has been a considerable increase in research on potential therapeutic applications of cannabis to address health illnesses in both adults and children [2]. In some countries, including Australia and Canada, authorisations permit the purchase of cannabis products for medical purposes in children [3, 4]. Families of children with complex health challenges are increasingly accessing cannabis-based products for epilepsy, autism spectrum disorder, cancer symptom management, and headaches [4]. For example, 92% of Canadian paediatric oncologists and palliative care providers reported caring for a child with cancer taking cannabinoids for symptom management in the past 6 months, despite limited studies in this population [4].

In 2017, a systematic review reported a paucity of evidence supporting the use of medical cannabis in children [5]. Since then, research on cannabinoids use for medical purposes in children has markedly expanded, and many countries like Canada [6], Italy [7] United Kingdom [8] and Australia [3] have initiated medical cannabis programs that include children to facilitate regulated access to medical cannabis. The landscape of cannabis-based products and populations using cannabis is evolving globally as more jurisdictions move towards legalisation [9]. Purified cannabidiol with > 98% has been approved by the United States Food and Drug Administration, Australian Therapeutic Goods Administration, European Medical Agencies, and various other regulatory bodies for use in children with drug-resistant epilepsies (DREs) [10].

While previous reviews have focused primarily on DREs [5, 11] and included interventional studies only [11, 12], there remains a lack of comprehensive, up-to-date evidence covering a broader range of indications, formulations, safety, and reported benefits in paediatric populations. Recently, we published a systematic review and meta-analysis summarising the safety profile of cannabinoids used as an intervention in randomised controlled trials for medical purposes in children [13]. A holistic perspective is required to ensure healthcare providers, public health mavens, patients, parents, and decision-makers have access to a comprehensive summary of the available evidence. Our objective was to conduct a living systematic review on the use of cannabis-based products in children that will continue to comprehensively map the evolving evidence related to the use of cannabinoids (doses, types, formulations, route of administration, indications, safety, and reported benefits) for medical purposes in children.

2 | Methods

The systematic review was registered with PROSPERO (CRD42020187433). We followed the preferred reporting items for systematic review and meta-analysis (PRISMA) [14], PRISMA-S guidelines [15], Cochrane Guidance for Living Reviews [16], and Cochrane Collaboration [17] reporting items to ensure accurate and complete reporting. This review followed a living systematic review methodology [16, 18] and will run literature searches every 2 years to update the evidence base. Future iterations will be published on our website (medcannkids.ca), held in an open-access repository (MedRxiv), and submitted for publication in a peer-reviewed journal.

2.1 | Eligibility Criteria

The review included original research studies involving at least one child under 18 years of age who was administered either plant-derived cannabinoids or synthetic pharmaceutical cannabinoids by any route and dose, as an intervention or treatment for any self-reported or diagnosed medical condition. Studies of all designs were considered, including randomised controlled trials (RCTs), such as parallel, factorial, crossover, cluster, pooled, adaptive, stratified, split-body, single-subject trials, quasi-experimental studies (non-randomised controlled trials, pre-post studies), and observational studies, including case–control, prospective or retrospective cohort series, uncontrolled cohort studies, case reports, case series, and cross-sectional studies. We excluded editorials, expert opinions, review articles, and articles lacking data from primary sources. We included studies published in English or French only. We did not apply any publication time restriction for including studies related to cannabinoid use for medical purposes in children.

2.2 | Outcomes

The primary outcomes for this living systematic review were indications, types, doses, and formulations of cannabinoids used for medical purposes in children. The secondary outcomes were the safety and reported benefits of cannabinoids use for medical purposes in children. Further, secondary outcomes were operationalised based on available data across different identified study designs.

2.3 | Search Strategy

The search strategy was designed with the assistance of an experienced health sciences librarian (ML) using a combination of subject terms and keywords related to cannabis (hemp, marijuana, cannabidiol, nabilone, tetrahydrocannabinol, epidiolex, sativex, nabiximols, and dexanabinol) and children or adolescents (preschool,

infant, kindergarten, teenagers, and adolescent). Subsequently, the search strategy was peer-reviewed by another health sciences librarian using the Peer-Review of Electronic Search Strategies (PRESS) checklist to create an extensive, robust, and comprehensive search strategy [19]. The search was conducted from inception to April 24, 2023, in four databases—MEDLINE (Ovid), Embase (Ovid), PsycInfo (Ovid), and the Cochrane Library (Wiley). Search results were restricted to human studies only, without any restriction to study type, year of publication, and language. A manual search and grey literature search, including trial registries (WHO International Clinical Trials Registry Platform and ClinicalTrials.gov) were conducted to identify additional relevant studies. Finally, the search results were de-duplicated in EndNote and uploaded to Covidence for screening [20]. The complete database search strategies are available in Appendix S1 and via https://doi.org/10.34990/FK2/MV6CMP.

2.4 | Study Selection and Data Extraction

Two reviewers (MC, AP, or OA) performed first-pass screening (title and abstracts), second-pass screening (full-text screening), and data extraction. Any disagreements among reviewers that could not be resolved through discussion between the reviewers were adjudicated by the senior author (LEK).

2.5 | Data Synthesis and Analysis

A narrative synthesis of the extracted data was conducted using Microsoft Excel. The synthesis without meta-analysis (SWiM) guidelines for systematic reviews and Cochrane guidance for living reviews [16, 21] were followed. Given the diversity of included studies, no test for heterogeneity between studies or meta-analysis on reported benefit or safety was performed in this analysis. We did not account for qualitative data analysis from qualitative studies for synthesising findings. For safety outcomes, we considered the number of studies reporting the safety outcomes rather than the number of patients experiencing these outcomes.

3 | Results

3.1 | Search Results and Study Selection

Of 37 189 identified citations, 276 unique studies were included: 84 interventional, 131 observational, and 61 survey and qualitative studies. Figure 1 describes the selection process using the PRISMA flow diagram. The cumulative number of studies on medical cannabis, including children, substantially increased over the years, jumping from 13 studies in 2002 to 19 studies in 2010, followed by 170 studies in 2020 and reaching 276 studies in 2023. Nine interventional trials on cannabinoids to prevent Chemotherapy-Induced Nausea and Vomiting (CINV) that include children were published between 1979 and 1995.

3.2 | Characteristics of Included Studies

The characteristics of the included studies varied broadly. Tables 1 and S1 present detailed characteristics of interventional and observational studies related to cannabinoids used for medical purposes in children that were included in this review.

Interventional studies ($n=84$) on cannabinoids used for medical purposes enrolled 7767 participants with children Trials were mostly single-arm trials (71.4%, $n=60$) and randomised controlled trials (RCTs) (28.6%, $n=24$). Nearly half of the interventional studies (44%, $n=37$) were registered with clinical trial registries, of which most (36.9%, $n=31$) were registered with ClinicalTrials.gov. The median(IQR) number of participants in the included interventional studies was 73 (31–111) in RCTs and 38 (18–93) in non-randomised trials. The median(IQR) duration of treatment in interventional studies was 12 (8–15.5) weeks, and in RCTs was 12 (6.25–14) weeks, which was similar to non-randomised trials that treated children for a median duration of 12 (11.7–22) weeks. Almost a third of interventional studies (30.9%, $n=26$) were blinded.

Observational studies ($n=131$) on cannabinoids for medical purposes that included children enrolled 267 028 participants. Surveys (88.5%, $n=54$) and qualitative interviews (11.4%, $n=7$) related to cannabinoid use for medical purposes in children were conducted in North America (55.7%, $n=34$). In observational studies, the most common design was described as chart review (26.7%, $n=35$), followed by cohort studies (16%, $n=21$) and cross-sectional studies (9.2%, $n=12$). The median (IQR) number of participants in chart reviews, cohort studies, and cross-sectional studies were 50 (21–108), 69 (27–91), and 918 (44–13 931) participants, respectively.

3.3 | Age Group

Most interventional studies related to cannabinoids used for medical purposes included children from the following age groups: 12–18 years (90.5%, $n=76$), 6–11 years (84.5%, $n=71$), and 2–5 years (75%, $n=63$). Similar patterns in age distribution were observed in observational studies: 12–18 years (70.2%, $n=92$), followed by 6–11 years (54.2%, $n=71$), and 2–5 years (42.7%, $n=56$). Table 1 compares different age groups across the included studies.

3.4 | Conditions for Which Cannabinoids Were Administered in Children

The common diagnostic categories for which cannabinoids were administered to children for all the study designs included nervous system disorders, mental and behavioural disorders, and cancer. The most common indications for cannabinoids in children were DRE, followed by cancer and cancer symptom management, autism spectrum disorder, traumatic brain injury, cerebral palsy, and depression. Other indications included cannabis use disorder, headache, migraine, and low back pain. Table S2 details the identified indications of cannabinoids used for medical purposes in children.

3.5 | Description of Cannabinoids Studied for Medical Purposes in Children

Purified CBD was used in 78.6% ($n=66$) of interventional studies and 64.9% ($n=85$) of observational studies, followed by

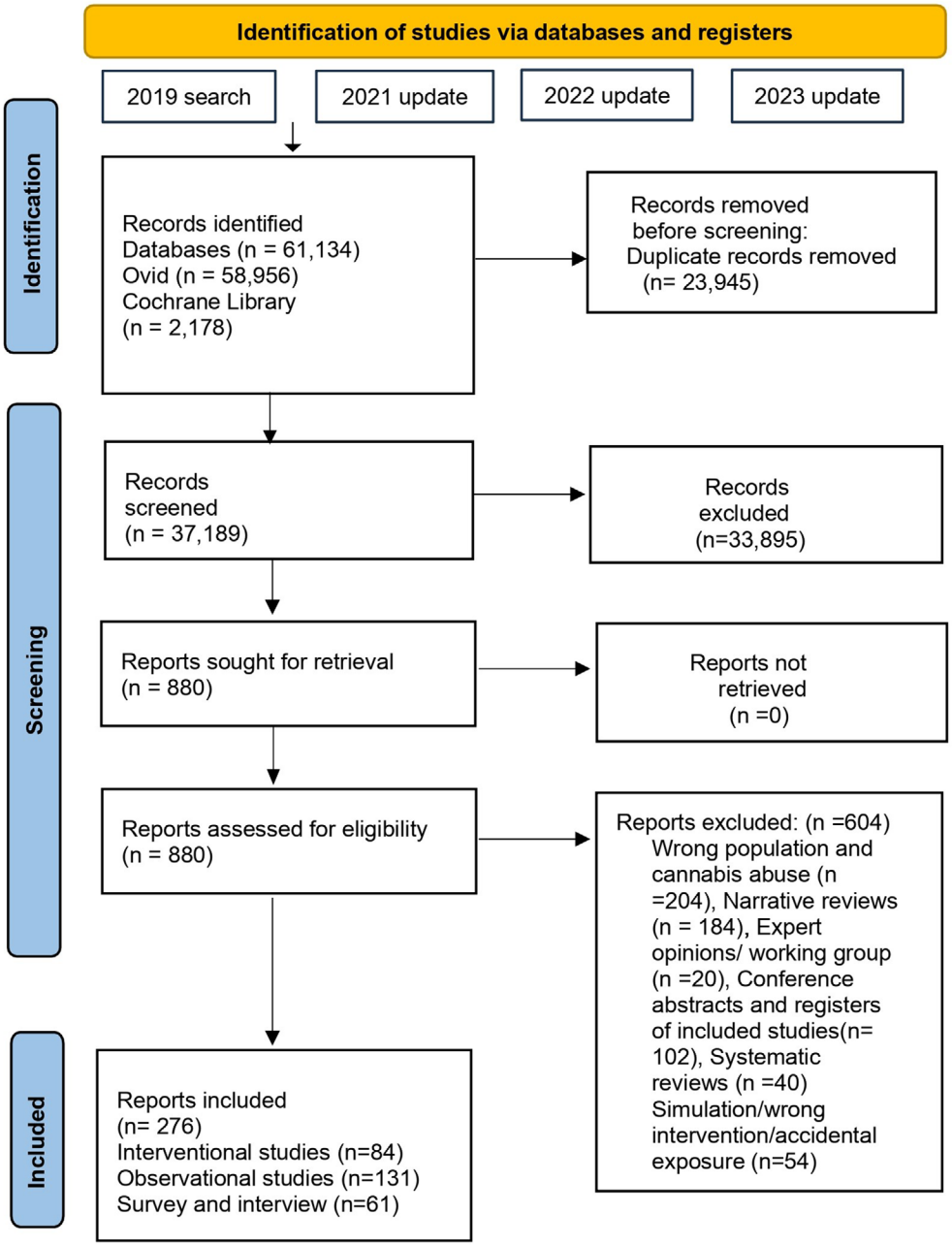

FIGURE 1 | The PRISMA flow diagram of the studies included in the living systematic review.

synthetic THC in 6% ($n = 5$) of interventional and 3.1% ($n = 4$) of observational studies. Other cannabinoids included dronabinol, nabilone, cannabis extract, dexanabinol, cannabidivarin, and nabiximols. While all observational studies described the cannabinoid contents, 12.9% ($n = 17$) of observational studies did not clarify the composition of cannabis components. Table 2 compares the different patterns of cannabinoids across the included studies.

The most common routes of cannabinoid administration in children were oral, inhalational, followed by sublingual, topical, and transdermal. The most frequently used cannabinoids were oral solutions, capsules, and topical formulations (lotions, creams, salves, liniments, and gels). The formulation was not specified in 26.4% ($n = 52$) of observational studies, surveys, and qualitative studies. A ratio of THC: CBD of 1:20 was most commonly reported among the included studies. Based on the category of cannabinoid products, purified CBD (CBD ≥ 98%) was the most studied cannabinoid [22]. Cannabinoids in the included studies were given at a dose range of 2–50 mg CBD/kg/day [23–30], and 2.5–10 mg or 18 mg/m^2 of THC [31–33] based on body surface area. In an interventional study, cannabidivarin, a minor phytocannabinoid, was given at a dose range of 2.5–10 mg/kg/day [34]. Nabiximols, which contain a near-equal ratio of THC and CBD, included a maximum dose of 32.4 and 30 mg/day, respectively [35]. Undefined cannabis herbal extracts (CHEs) were used in 12.9% ($n = 17$) observational studies with doses ranging from 0.6 to 20 mg/kg/day [36]. Dronabinol, a synthetic formulation of THC, was administered at a dose range of 2.2–9.1 mg/day in interventional studies and 0.7–25 mg/day in observational studies [37–44]. The dose range of nabilone, a different synthetic cannabinoid

TABLE 1 | Characteristics of included studies.

Variables	Interventional studies ($n=84$)	Observational studies ($n=131$)	Surveys and interviews ($n=61$)
Number of included participants			
Median (IQR) number of participants	45.3 (20–100)	18 (2–79.5)	103 (25.75–554.75)
Total number of participants enrolled	7767	267 028	72 972
Number of studies that included paediatric age groups[a]			
Preterm neonatal births (prior to gestation)	2 (2.4%)	4 (3.1%)	2 (3.3%)
Neonates (0–27 days)	3 (3.6%)	6 (4.6%)	5 (8.2%)
Infants (28 days-1 year)	22 (26.2%)	21 (16%)	9 (14.8%)
Toddlers (13–23 months)	27 (32.1%)	29 (22.1%)	12 (19.7%)
Early childhood (2–5 years)	63 (75%)	56 (42.7%)	18 (29.5%)
Middle childhood (6–11 years)	71 (84.5%)	71 (54.2%)	21 (34.4%)
Early adolescence (12–18 years)	76 (90.5%)	92 (70.2%)	33 (54.1%)
Late adolescence (19–21 years)	48 (57.1%)	41 (31.3%)	20 (32.8%)
Adults (over 21 years)	39 (46.4%)	34 (26%)	18 (29.5%)
Not reported	1 (1.2%)	14 (10.7%)	27 (44.3%)
Continents where participants were enrolled[a]			
North America	41 (48.8%)	61 (46.6%)	34 (55.7%)
Europe	18 (21.4%)	43 (32.8%)	15 (24.6%)
Australia/New Zealand	13 (15.5%)	6 (4.6%)	8 (13.1%)
South America	11 (13.1%)	10 (7.6%)	1 (2.7%)
Asia	2 (2.4%)	16 (12.2%)	3 (4.9%)
Number of study centers			
Single centric	40 (47.6%)	96 (73.2%)	27 (44.3%)
Multi-centric	29 (34.5%)	11 (8.4%)	8 (13.1%)
Not reported	15 (17.9%)	24 (18.3%)	26 (42.6%)
Funding agency[a]			
Government	25 (29.8%)	12 (9.2%)	8 (13.1%)
Academic or research institutions	11 (13.1%)	9 (6.9%)	7 (11.5%)
Private	23 (27.4%)	16 (12.2%)	9 (14.8%)
Industry	53 (63.1%)	12 (9.2%)	2 (3.3%)
Unclear	1 (1.2%)	1 (0.8%)	NA

[a]Total will not add up to 100% because more studies met more than one category.

that acts as a THC analog, in interventional studies was 0.5–2 mg [45–48], and its mean range in observational studies was 3.20–3.09 mg [49, 50]. Dexanabinol, a synthetic cannabinoid enantiomer which does not directly mimic THC, was administered as a single-shot injection at a dose of 150 mg [51, 52]. The dose range of levonantradol, a synthetic derivative of THC, was 0.5–1.5 mg in interventional studies [53]. Table 3 provides comprehensive information on dosing and frequency of cannabinoids in children.

3.6 | Reported Benefit of Cannabinoid in Children

In RCTs, purified CBD was reported to be beneficial in reducing median seizure frequency by 30%–50% compared to baseline in children with DREs(Dravet syndrome, Lennox–Gastaut syndrome) [24–28, 30]. In single-arm trials, purified CBD [54–57] and CHE [58–61] decreased seizure frequency (> 50% reduction in seizures from baseline in 20%–100%), duration, and severity [51]. Purified CBD was also reported to

TABLE 2 | Description of cannabinoids used for medical purposes in included studies.

Variables	Interventional studies ($n = 84$)	Observational studies ($n = 131$)	Surveys and interviews ($n = 61$)
Types of cannabinoids in included studies			
Cannabidiol	66 (78.6%)	85 (64.9%)	20 (15.26%)
Cannabidivarin	1 (1.2%)	0 (0%)	0
Cannabis extract	2 (2.4%)	14 (10.7%)	1 (1.6%)
Delta-9 THC/THC	5 (6%)	4 (3.1%)	1 (1.6%)
Dexanabinol	2 (2.4%)	0 (0%)	0
Levonantradol	1 (1.2%)	0 (0%)	0
Nabilone	5 (6%)	2 (1.5%)	0
Nabiximol	1 (1.2%)	0 (0%)	0
Dronabinol	1 (1.2%)	9 (6.9%)	0
CBD and THC	0	0	6 (9.8%)
Unspecified	0	17 (13%)	33 (54.1%)
Formulations of cannabinoids in included studies[a]			
Capsules	12 (14.3%)	6 (4.6%)	3 (4.9%)
Lotions, Creams, Salves, Liniments, Gels	4 (4.8%)	5 (3.8%)	4 (6.6%)
Oil/solutions	72 (73.9%)	69 (52.6%)	19 (31.14%)
Edibles	0	4 (3%)	3 (4.9%)
Tinctures/Sprays	2 (2.4%)	7 (5.3%)	5 (8.2%)
Tablet	0	1 (0.8%)	2 (3.3%)
Cigarettes	1 (1.2%)	2 (1.5%)	2 (3.3%)
Vaporizers	0	3 (2.2%)	1 (1.6%
Unspecified	4 (4.8%)	62 (47.3%)	46 (75.4%)
Powder	0	1 (0.8%)	0
Paste	0	2 (1.5%)	0
Decoction/decoction in milk	2 (2.4%)	0	2 (2.4%)
Route of administration[a]			
Oral	72 (85.7%)	89 (67.9%)	17 (27.8%)
Inhalational/Smoked	1 (1.2%)	6 (4.6%)	11 (18.03%)
Topical	0	2 (1.5%)	7 (11.5%)
Transdermal	4 (4.8%)	0	0
Sublingual	2 (2.4%)	6 (4.6%)	1 (1.6%)
Intramuscular	2 (2.4%)	0	2 (2.4%)
Unspecified	3 (3.6%)	40 (30.5)	48 (78.6%)
Intravenous	2 (2.4%)	0	2 (2.4%)
Category of cannabinoids products[a,b]			
CBD medicinal product (CBD ≥ 98%)	49 (58.3%)	67 (51.1%)	15 (24.5%)
CBD dominant product (CBD ≥ 60% and < 98%)	29 (34.5%)	24 (18.3%)	2 (3.2%)

(Continues)

TABLE 2 | (Continued)

Variables	Interventional studies ($n=84$)	Observational studies ($n=131$)	Surveys and interviews ($n=61$)
THC medicinal product (THC > 98%)	5 (6%)	10 (7.6%%)	1 (1.6%)
Balanced CBD and THC	2 (2.3%)	3 (2.3%)	2 (3.2%)
THC dominant (THC 60%–98%)	0	3 (2.3%)	0

Abbreviations: CBD, Cannabidiol; THC, Tetrahydrocannabinol.
[a]Total will not add up to 100% because more studies met more than one category.
[b]Based on reported CBD:THC ratios using Therapeutic Goods Administration categories.

reduce anxiety and depressive symptoms and improve social and functioning scales in children with refractory epilepsy [62]. CHEs in children with autism were used for psychomotor agitation, concentration, appetite, sleep, stereotype nature, and speech impairment [63]. In the RCTs [63]; however, there was no difference in aggressivity in children with ASD compared to the placebo [63]. Interventional studies reported the superiority of THC, nabilone, and dronabinol over commonly used antiemetics such as domperidone, prochlorperazine, and metoclopramide in controlling nausea and vomiting in children undergoing chemotherapy, respectively [31–33, 39, 40, 45–49, 53, 64–71]. Compared to the placebo, dexanabinol had non-significant improvement in the Glasgow outcome scale in children with TBI [51]; however, there was a significant reduction in intracranial pressure (< 25 mmHg), cerebral perfusion pressure (< 50 mmHg), and systolic blood pressure (< 90 mmHg) [52]. The Table S3 reports complete reported benefit of cannabinoid use in children by included studies.

3.7 | Safety of Cannabinoids in Children

The most common cannabinoid-related adverse events (> 20% of studies) in studies enrolling children were somnolence, diarrhoea, vomiting, and decrease in appetite. The Table S4 provides further comparisons of safety event reporting. Other commonly reported cannabinoid-related adverse events reported by 10%–20% of interventional and observational studies in children include pyrexia, fatigue, elevated transaminases, dizziness, nausea, pneumonia, sedation, irritability, and status epilepticus.

4 | Discussion

In this review, we found that there is mounting literature on the use of cannabinoids for medical purposes in children with an expanding array of products and conditions studied, including DRE, autism spectrum disorder, cancer symptoms, traumatic brain injury, spasticity due to traumatic brain injury, cerebral palsy, and various other health conditions. Purified CBD, nabilone, THC, dronabinol, dexanabinol, nabiximol, levonantradol, and CHEs were the most common cannabinoids used for medical purposes in children. This LSR will be updated frequently to help healthcare providers, patients, caregivers, research teams, and policymakers access evidence on the current use of cannabinoids for medical purposes in children. Indication-specific meta-analyses should supplement these findings to inform benefits, safety measures, and clinical care guidelines.

This LSR providing comprehensive data on cannabinoid use for medical purposes in children is entirely different from our meta-analysis published elsewhere [13], in terms of the number of studies (10 times more) and study designs of included studies. The analysis in the LSR is descriptive (only number, percentage, mean with SD/median with IQR), mapping the expanding literature on cannabinoid use in children and comparing across observational, interventional, survey, and qualitative interview studies. In our included interventional studies, cannabinoids have been used outside of these approved indications to manage seizures in developmental and epileptic encephalopathy, febrile infection-related epilepsy syndrome, fragile X syndrome, epileptic spasms (West syndrome), Lennox–gastaut syndrome, Sturge–Weber syndrome, refractory epileptic encephalopathy, and infantile neuronal ceroid lipofuscinosis [72, 73]. We also found observational studies on cannabinoids in children with doose syndrome, epileptic Spasms (west syndrome), KCNT1-related epilepsy, and Rett syndrome. However, no clinical trials supported their use in children with these indications. This may be related to the rareness of these conditions or the lack of incentives for clinical trials to evaluate efficacy in a randomised controlled trial. CBD was also reported to be beneficial in managing seizures and other symptoms associated with tuberous sclerosis complex [56]. Indications of cannabinoid use for medical purposes identified in this review align with those reported in a systematic review of randomised controlled trials by Whiting and colleagues in 2015 [74]. They found evidence for use of cannabinoids in conditions such as spasticity, pain, epilepsy, sleep disorder, and anxiety [74].

Nabilone and dronabinol were used more commonly to prevent CINV in children with cancer, but children receiving THC were reported to experience adverse events such as drowsiness and dizziness [75]. It is important to note that the use of these products in children is off-label. Studies reported the use of nabiximol and dronabinol in children with spasticity related to multiple sclerosis and cerebral palsy [35, 76], but there were no RCTs related to spasticity due to multiple sclerosis in children. These findings align with systematic reviews on cannabinoids in adults with spasticity [77]. CBD and THC may help manage symptoms related to autism, such as aggression, anxiety, irritability, and hyperactivity [78] and have also shown promise in improving communication and sleep in this population [36]. There is a lack of supporting evidence on the beneficial effects of THC in reducing symptoms in children with Tourette syndrome and ADHD [79].

Cannabinoid doses in identified studies including children varied based on type, formulation, and indication. CBD was

TABLE 3 | Dosing and frequency of cannabinoids in children.

Cannabinoids	Starting dose range	Maximum dose range	Frequency of cannabinoid administration			
			BID	TID	Other	Not reported
Interventional studies (n = 84)						
Cannabidiol	2 mg/kg/day, 200 mg/day	50 mg/kg/day, 800 mg/day	47 (56%)	2 (1.2%)	0	17 (20.2%)
Cannabidivarin	2.5 mg/kg/day	10 mg/kg/day	1 (1.2%)	0	0	0
Cannabis extract	2 mg/kg/day	12 mg/kg/day	1 (1.2%)	0	0	1 (1.2%)
Delta-9 THC	2.5 mg/day, 10 mg/m^2	10 mg/day, 18 mg/m^2	0	0	3[a]	0
Dexanabinol	48 mg/day	150 mg/day	0	0	2 (2.4%)[b]	0
Levonantradol	0.5 mg/day	1.5 mg/day	0	0	1 (1.2%)[c]	0
Nabilone	0.5 mg/day	2 mg/day	0	2 (1.2%)	2 (1.2%)[d]	0
Nabiximol	NA	THC: 32.4 mg/day, CBD: 30 mg/day	0	0	1 (1.2%)[e]	
Dronabinol	2.2 mg/day	9.1 mg/day	0	1 (1.2%)	0	0
Observational studies (n = 131)						
Cannabidiol	0.1 mg/kg/day, 50 mg/day	50 mg/kg/day, 600 mg/day	23 (17.5%)	3 (2.2%)	9 (6.8%)[f]	50 (38.1%)
Cannabis extract	0.6 mg/kg/day	20 mg/kg/day	2 (1.2%)	0	0	12 (9.1%)
Delta-9 THC	0.2 mg/day	12 mg/day	1 (0.8%)	0	3 (2.2%)[h]	3 (2.2%)
Nabilone	Mean (range)19 (3.20–3.09) mg/day	NA	1 (0.8%)	2 (1.2%)	2 (1.2%)[g]	1 (0.8%)
Dronabinol	2.5 mg/day, 2 mg/m^2	0.7 mg/kg, 25 mg/day	2 (1.2%)	0	0	7 (5.3%)

[a]Study 1: every 3 h in one study, study 2: 2 h before the chemotherapy followed by 0, 4, 8, 16, 24 h after the chemotherapy and study 3 every 6 h.
[b]Study 1 and study 2: single dose injection.
[c]Every 4 h.
[d]30 min before chemotherapy followed by every 6 h.
[e]12 sprays per day.
[f]Study 1: BID or TID, study 2: Two to three times a day, Study 3: 1st case: TID; 2nd case: BID, study 4: QD, BID and TID, study 5: CBD oil (NR), CBD supplements (HS); sublingual spray (PRN), Study 6: Once daily, study 7: Q4D, study 8 and 9: QID.
[g]Study 1 once daily, twice daily.
[h]Study 2: three times daily; study 1: once a day, study 2: QD, BD, TID, study 3: QD, BID: two times a day; Q4H/QD: every 4 h, TID: three times a day.

administered at 2–50 mg/kg/day, while THC doses ranged from 2.5 to 10 mg or 18 mg/m^2. Nabiximols (THC:CBD ~1:1) had a maximum dose of 32.4 mg/day (THC) and 30 mg/day (CBD). Synthetic cannabinoids like dronabinol (THC) ranged from 0.7 to 25 mg/day, and nabilone from 0.5 to 3.2 mg/day. Dexanabinol was given as a single 150 mg injection. With all cannabinoids, trial duration remains a significant barrier to understanding the potential impacts on the developing brain. In single-arm trials of purified CBD, the maximum length of follow-up was up to 1 year [81], while in the observational studies, the maximum follow-up duration for purified CBD was up to 2 years. None of the CBD-related CHE studies had a follow-up duration beyond 20 weeks [58–61]. Therefore, there is an urgent need for priority funding mechanisms to evaluate the long-term efficacy and safety of cannabinoids used for medical purposes in children. Consistent with other systematic reviews, interventional studies reported more cannabinoid-related adverse events than observational studies [5, 11] likely implicating an underreporting of events in observational literature. Parents and clinicians must conduct a risk–benefit analysis before considering cannabinoids for children, which is challenging to do if treatment-emergent adverse events are not well characterised.

4.1 | Gaps in Literature

Observational studies lacked information related to specific cannabinoids used, dosage form, frequency, and route of administration. Interventional studies investigating cannabinoids for medical purposes in children were limited to oral or sublingual routes of administration, and formulations were limited only to oil or solutions. Included studies pose a challenge in calculating the number of participants for specific indications because of overlapping reporting of indications of cannabinoids. Real-world studies and pharmacovigilance efforts should provide complete information related to the route of administration, dosage forms, and specific cannabinoid contents to understand the safety and effectiveness of cannabinoids better. Most of the identified studies originated from North America and Europe, with limited representation from developing countries. This geographic concentration highlights a significant knowledge

gap regarding the use of cannabinoids in paediatric populations operating under different regulatory frameworks and clinical practices. To improve the completeness of safety reporting, a guideline for research on cannabinoid interventions is warranted. Additionally, purified CBD was the most common cannabinoid used in clinical trials due to industry investment and marketing authorisation. Given the complexity of the cannabis plant (such as the number of active compounds that are present, including terpenes and flavonoids), purified CBD is unlikely to be directly comparable to CBD-enriched cannabinoid products available in different jurisdictions, even when used at the same dose.

4.2 | Strengths and Limitations

The rigorous methods used in this living systematic review are a strength, including a registered protocol, comprehensive search strategy, independent screening, and data extraction to ensure the reliability and validity of the summarised evidence. The LSR is comprehensive and includes all study designs and cannabinoid product types. This allows for greater flexibility to include studies on cannabinoid use in children and helps to generate reliable findings on the use of cannabinoids applicable over different indications in this initial report.

Several limitations must also be considered when interpreting our findings. A quality assessment of included studies was not performed since this qualitative synthesis focused only on types of cannabinoids, indications, and a listing of cannabinoid-related adverse events. In this systematic review, we did not evaluate the potential risk of publication bias in our identified studies related to cannabinoid use for medical purposes in children.

Given the heterogeneity of cannabinoids and populations studied, we did not pool adverse events or efficacy outcomes in this report. Population and indication-specific meta-analyses are warranted to synthesise the data on adverse events and efficacy across multiple cannabinoid product types.

5 | Future Directions

Although there is widespread use of cannabinoids in children, there is no uniformity in the dose, CBD-THC ratio, type of cannabinoids, or how cannabinoid-related adverse events are reported. There are only a few studies on the long-term safety and efficacy of cannabinoids in children across the various indications for which medical use has been reported [11]. To fill this evidence gap, rigorous studies investigating the long-term safety and efficacy of cannabinoids in children are needed across a wide range of therapeutic indications and populations. A pragmatic approach should be adopted to generate new knowledge on the safety and effectiveness of cannabinoids in the real world with a longer duration of follow-up. Questions related to rare adverse events, long-term safety, cannabinoids' ability to interact with other prescription drugs, and effects on children with comorbidities require further exploration. Increasing parental inquiry coupled with our findings that observational studies reported lower rates of adverse events compared to interventional studies signals an urgent need for unbiased, rigorous, patient- and family-informed prospective clinical trials.

6 | Conclusion

Cannabinoids have been used in children for various health indications using various study methodologies. Knowledge gaps on the long-term cannabinoid-related adverse events, drug interactions, efficacy, and tolerability of cannabinoids in children with medical complexities have been identified. Multicenter, multidisciplinary collaborations are needed to bridge evidence gaps by conducting innovative RCTs and real-world evidence studies that can be combined and contrasted across indications and jurisdictions.

Author Contributions

Manik Chhabra: methodology, writing – review and editing, formal analysis, validation, visualization, writing – original draft, data curation, investigation. **Arun Paul:** writing – review and editing, methodology. **Omaymah Abulannaz:** writing – review and editing, methodology. **Mê-Linh Lê:** writing – review and editing, data curation, software. **Holly Mansell:** writing – review and editing. **Yaron Finkelstein:** writing – review and editing. **Richard J. Huntsman:** writing – review and editing. **Lauren E. Kelly:** conceptualization, funding acquisition, project administration, supervision, resources, writing – review and editing, methodology.

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Disclosure

This systematic review has been registered with the International Prospective Register of Systematic Reviews (CRD42020187433).

Conflicts of Interest

L.E.K. is the Scientific Director for The Canadian Collaborative for Childhood Cannabinoid Therapeutics (C4T) academic research team. She holds funding from the Canadian Institutes of Health Research, Canadian Cancer Society, Research Manitoba, the Sick Kids Foundation, the Children's Hospital Research Institute of Manitoba, the University of Manitoba and a Mitacs Accelerate award in partnership with Canopy Growth. Dr. Kelly is also a member of the Scientific Advisory Board for Health Products Containing Cannabis at Health Canada. L.E.K. is a member and President-Elect of the Board of Directors for the Canadian Consortium for the Investigation of Cannabinoids (CCIC). R.J.H. is a clinical lead for both the Cannabinoid Research Initiative of Saskatchewan and C4T. He is developing a research protocol in which cannabis products will be purchased from MediPharm Labs. He previously acted as co-chair of the Scientific Advisory Committee for Health Products Containing Cannabis at Health Canada. M.C. was granted the 2022 Research Manitoba–George & Fay Yee Centre for Healthcare Innovation in Health Research PhD Studentship Award. Y.F. Holds a Canada Research Chair in Paediatric Drug Safety and Efficacy (Tier I). M.-L.L., H.M., A.P., and O.A. have no conflicts of interest to declare.

Data Availability Statement

All search strategies used and RIS files with articles located and screened can be found at: https://doi.org/10.34990/FK2/MV6CMP.

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Supporting Information

Additional supporting information can be found online in the Supporting Information section.