The Use of Cannabis Derived Medical Products in the Treatment of Children's Cancer: A Systematic Review

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Abstract

Legislative change to cannabis use has generated significant interest into the therapeutic utility of cannabis-derived medical products, particularly in the field of oncology. However, much of this research has focused on adults, leaving physicians and caregivers uncertain as to the safety and efficacy of cannabinoids amongst the pediatric demographic. To this end, the aim of this review is to examine the scope of pharmaceutical cannabis in treatment of pediatric cancer, evaluating its utility as an anti-cancer therapeutic as well as symptom relief agent. This systematic review was conducted following the PRISMA guidelines. 30 included articles comprised of 16 clinical and 14 preclinical studies. There is reasonable evidence to support the use of cannabis in CINV, with plausible utility for other facets of symptomatic relief. Preclinical pediatric cancer models, investigating anti-cancer cannabinoid effect, have provided evidence that may warrant first phase clinical trials.

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Abbreviations

Abbreviation	Full Term
ALL	Acute Lymphoblastic leukaemia
BCL2	B Cell Lymphoma 2
BMJ	British Medical Journal
BTZ	Bortezomib
CBD	Cannabidiol
CBN	Cannabinol
CBR	Cannabinoid Receptor
CBX	Chrombox
CINV	Chemotherapy Induced Nausea and Vomiting
CNS	Central Nervous System
D9THC	Delta-9 Tetrahydrocannabinol
ECS	Endocannabinoid system
GPCR	G-protein coupled receptor
MCU	Mitochondrial Calcium Uniporter
MOMP	Mitochondria Outer Membrane Permeability
NBL	Neuroblastoma
OS	Osteosarcoma
PRISMA	Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement
P/O	Per Oral
RCT	Randomised Control Trial
RMS	Rhabdomyosarcoma
ROS	Reactive Oxygen Species
RTX	Resiniferatoxin
THC	Delta-8 Tetrahydrocannabinol
TRPV1	Transient receptor potential cation channel subfamily V member 1
VDAC	Voltage-dependent Anion Channel

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This systematic review was conducted following the PRISMA guidelines. 30 included articles comprised of 16 clinical and 14 preclinical studies.

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1.0 Introduction

Childhood cancer is one of the leading causes of death among children.[1] Approximately 429,000 children receive an oncological diagnosis each year. [2] Recent therapeutic advances have significantly enhanced treat-

ment outcomes. However, among economically developing nations less than 30% of children with cancer survive. [3] [4]

The endocannabinoid system (ECS) is a neuromodulatory system essential for synaptic plasticity, normal central nervous system (CNS) development and integration of various stimuli in response to environmental and endogenous stress. [5] The fundamental rudiments of the ECS are cannabinoid receptors (CBR's). CBR1 and CBR2 are G-protein coupled receptors (GPCR) that can be activated through binding of endogenous cannabinoids, plant-derived (phytocannabinoids) cannabinoids and synthetic cannabinoids, all of which generate comparable receptor binding sequelae. [5] CBR1's are most abundantly expressed in the CNS, lungs, liver and kidneys, while CBR2's in the immune and vascular systems. Over 400 non-identical chemical compounds have been identified from within the cannabis plant, 60 of which have been classed as phytocannabinoids. [6]The primary psychoactive phytocannabinoid is Delta-9 tetrahydrocannabinol (D9THC). Other significant phytocannabinoids include cannabidiol (CBD), cannabinol (CBN) and delta-8 tetrahydrocannabinol (THC). [6] CBN and D8THC are psychoactive, while CBD is non-psychoactive. The lack of psycho-active appurtenance has made CBD particularly compelling to researchers.[7]

Before attaining its status as an illegal substance, cannabis had been used as a therapeutic for centuries. [8] The early 2000's saw a resurgence in investigative interest into cannabis derived medical products with recent legislative change across many states in the US and in Great Britain further igniting fervour among research teams. [9] [10] An assortment of clinical literature has supported the use of cannabis derived medical products among oncological patients for various anti-symptomatic indication. [11] [1213] [14] Furthermore, several pre-clinical adult cancer models have found cannabinoids to have both anti-tumour and anti-sickness effects. [1516] [17] [18]

McLennan et al., sought to gain insight into clinical perspectives concerning medicinal cannabis use. The study found that 85% of oncologists surveyed felt they required more knowledge about cannabinoids before they would feel comfortable administering them, and, of these, only 30% were believed that they could make a qualified decision. [19] This reflects the lack of secondary, pre-appraised literature pertaining to the use of cannabis in oncological practise. This is especially true when we apply this to pediatric populations as there are even fewer studies that have collated the literature surmising both the anti-cancer and anti-symptomatic effects of cannabinoids. To this end, the aim of this review is to examine the scope of cannabinoids / pharmaceutical cannabis in treatment of pediatric cancer, evaluating its utility as an anti-cancer therapeutic as well as symptom relief agent.

2.0 Methods

This study utilised the Preferred Reporting Items for Systematic Reviews and Meta-Analyses statement (PRISMA). [20] As this was a review of published literature, no requirement of ethical approval needed to be addressed.

2.1 Search Strategy

Searches were conducted between 21st – 23rd March 2022 across 4 databases: *PubMed, EMBASE, CINAHL and Web of science* . The central conceptual tenets of the research objective were identified as 'cannabis', 'cancer' and 'pediatric'. These words were deployed, along with all synonyms and all alternative MeSH terms, into each of the 4 databases. Searches were homogenized using the Boolean operators 'AND' and 'OR'. (Table 1) Reference lists of papers were cross-checked.

TABLE 1 Identification of key concepts and derivation of key words.

#1	Cannabis [MeSH] OR "Cannabinoids" [MeSH] OR "Cannabidiol" [All Fields] OR "Marijuana" [All Fields] OR "delta-8-
#2	Neoplasms [MeSH] OR "Cancer" [All Fields] OR "Malignancy" [All Fields] OR "Oncology" [All Fields] OR "Neoplasia"
#3	Child [MeSH] OR Adolescent [MeSH] OR "Pediatric" [All Fields] OR "Children" [All Fields] OR "Infant" [All Fields] C
#4	#1 AND #2 AND #3

2.2 Study selection

Inclusion and exclusion criteria were outlined in accordance with the research objective. Clinical trials (Phases 1, 2 and 3), case series, prospective and retrospective cohort studies and cross-sectional studies were all considered for review. Preclinical research that assessed the use of cannabinoids as an intervention among pediatric cancer models were included. All types of pediatric cancer and medicinal cannabinoids were included. The outcome measure was symptomatic relief and/or antitumour effects. Papers were excluded if they were not in the English language, in abstract form only, not published in a peer reviewed journal, ongoing trials and trials assessing both adults and children. The explicit inclusion and exclusion criteria are presented in *Table 2* . Two reviewers independently reviewed references and screened all retrieved literature. (NG, SR) Final inclusion was determined by consensus from all authors.

TABLE 2 Inclusion and Exclusion Criteria outlined prior to procurement of relevant literature.

Inclusion Criteria
All types of pediatric cancer
Only presenting primary source data
If human study, over half the population must have been aged 0-21 years or paediatric data presented separately in the rese
All types of medicinal cannabis as an anti-cancer agent and/or symptomatic relief
Published in a Peer reviewed Journal

2.3 Data extraction

Preclinical and clinical study characteristics and results were extracted by reviewer (NG) and proofread by reviewer (SR). Two separate data extraction tables were produced for clinical and preclinical papers. The coding sequence facilitated ubiquitous data synthesis across the articles, this was collated into a synthesis matrix on a Microsoft Excel spreadsheet.

3.0 Results

3.1 Search Results

Initial search yielded 2213 articles across the four databases. The reference management software EndNote X9 was used to catalogue the research studies. Endnote facilitated de-duplication of citations, yielding 1511 non-identical articles. Phase 1 retrieval involved screening the titles and abstracts, seeking to eliminate any articles that were immediately irrelevant to the study. The reason for omission was documented for each article, many papers met more than one criterion for exclusion and as such the reason judged to be the most egregious were recorded. Phase 1 retrieval yielded 107 articles suitable for full text screening. Phase 2 retrieval involved full text article review to identify primary research evaluating the potential utility of cannabinoid-based therapy in the field of pediatric oncology. This generated 30 articles suitable for review. 16 articles documented primary clinical data and 14 articles provided data pertaining to the use of cannabinoids in pediatric cancer preclinical models. This is summarised in Figure 1.

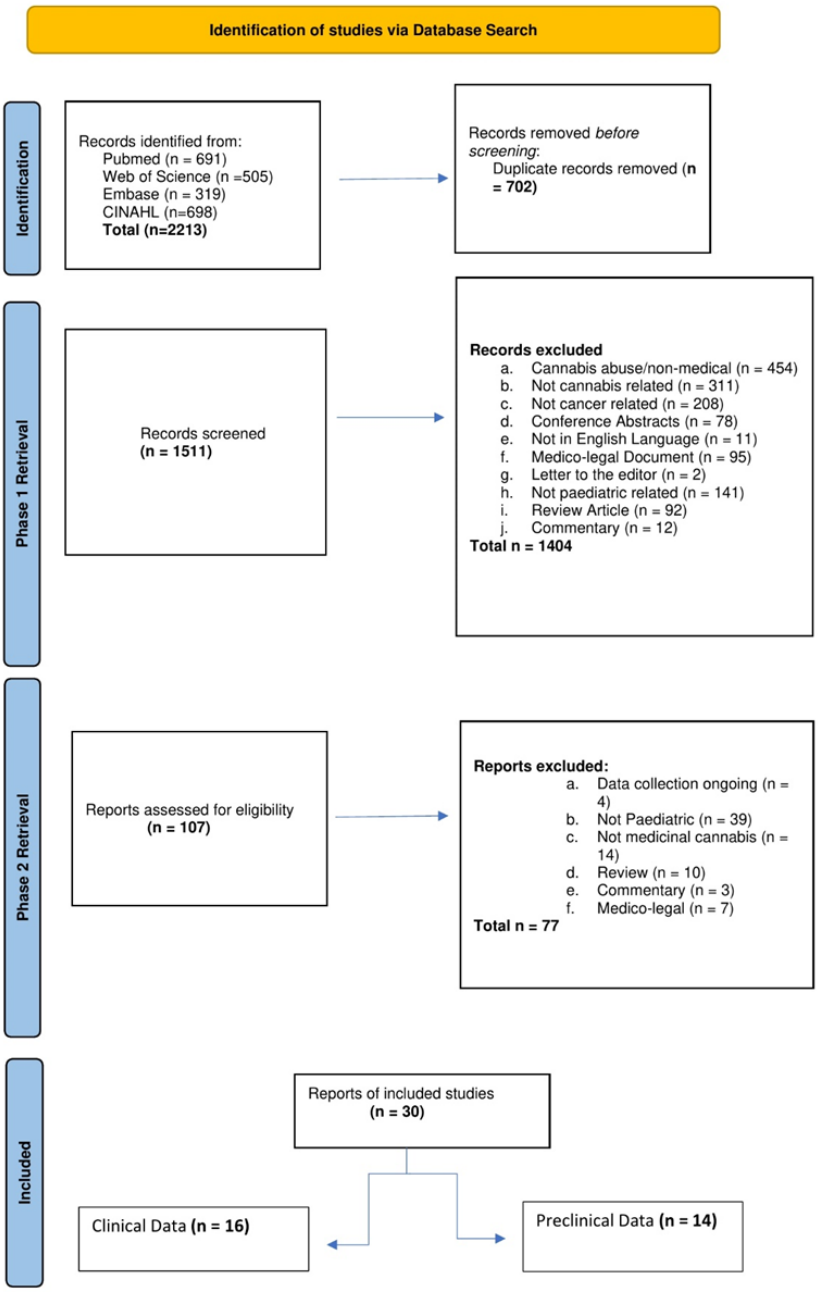
3.2 Clinical Data

There was no limit on the age of papers, and they ranged from 1979-2021. Four were retrospective reviews [21 22 23 24], four case series [25 26 27 28], three randomised control trials (RCT) [29 30 31], two institutional reviews [32 33], one open label trial [34], one pilot study [35] , one patient survey[36]. The sample sizes in each study varied, the smallest had just 1 patient and the largest was 110. Cannabinoids used included CBD (n = 5), THC (n = 5), Dronabinol (n = 3) and Nabilone (n = 3), in four studies THC and CBD were seen to be used in combination. The most common pediatric cancer observed across the articles was leukaemia. The mean age of patients ranged from 6.6 years to 19 years.

3.3 Preclinical Data

Fourteen articles presented pre-clinical research investigating the use of cannabis derived medical products in paediatric cancer cell models. Seven studies examined leukaemia [3738] [39] [4041] [42] [43], two osteosarcoma (OS) [44] [45], two neuroblastoma (NBL) [46] [47], two CNS tumours [48] [49] and one rhabdomyosarcoma (RMS) [50].

FIGURE 1 PRISMA 2 phase screening process, generating 16 clinical articles and 14 pre-clinical articles that met inclusion criteria and encompass any exclusion criteria.



3.3.1 Chemotherapy Induced Nausea and Vomiting (CINV)

Seven studies looked at the effectiveness of cannabis derived medical products to mitigate CINV. (Table 3) [34] [30] [29] [31] [22] [12] [24]

Three double blind controlled trials found that cannabinoids were more effective at relieving CINV than standard of care controls. Ekert et al., conducted two double blind crossover trials investigating the propensity of THC isolate to ameliorate CINV. In both trials, THC was found to be significantly more effective at reducing CINV than control, with no difference in side effects. Similarly, Dalzell et al., assessed the effectiveness of Nabilone (Cesamet®) to ameliorate CINV compared to the commonly used anti-emetic, Domperidone. [29] When taking Nabilone, patients experienced a significantly reduced number of vomits alongside reduction in nausea symptoms. 66% of patients preferred Nabilone. The most common side effects observed were drowsiness and dizziness. Chan et al., employed a randomized, double-blind cross over study design to investigate the efficacy of Nabilone for CINV among a cohort of 40 patients. It was found that Nabilone was significantly more effective than Prochlorperazine at reducing CINV in the pediatric oncologic population.[30]

Elder et al., Polito et al., and Rower et al., all found when retrospectively reviewing patient that cannabis-based medical products could be effective at ameliorating CINV during chemotherapy cycles.[22] [12] [24] Elder et al. found that amongst their cohort of 58 patients who had received Dronabinol for CINV during multiple cycles of chemotherapy (mean = 3.5 cycles) that a 'good' threshold was reached on 60% of occasions. In congruence with this finding, Polito et al., observed, in their review of 110 patients, 52.7% were said to have obtained 'complete CINV control' through use of Nabilone, regardless of chemotherapy emetogenicity.

TABLE 3 Seven Studies Investigating the Effectiveness of Cannabis Derived Medical Products to Ameliorate Chemotherapy Induced Nausea and Vomiting Among Pediatric Patients

Author	**No. of Patients**	**Mean age (years)**	**Cannabinoid**	**Dosage**	**Route of Administration**	**Study Design**	**Reference**
Abrahamov et al.	8	6.6	Dronabinol	18mg/ml 2 hr before start of anticancer treatment, 6mg/ml every 6 hrs for 24hrs.	P.O w/ oil drops on tongue or on bread.	Open Label Trial	[34]
Chan et al.	40	11.8	Nabilone	0.5-2mg, based on weight. First dose 8-12 hours preceding chemotherapy and the same dose repeated 2x or 3x daily thereafter.	Oral Capsule	Double Blind Crossover	[30]

Author	No. of Patients	Mean age (years)	Cannabinoid	Dosage	Route of Administration	Study Design	Reference
Dalzell et al.	18	7.9	Nabilone	Below 18kg - 0.5mg twice daily, 18-36kg 1mg twice daily, above 36kg 1mg three times daily. First dose was taken night before starting chemotherapy cycle and last dose 24 hours after stopping.	Oral Capsule	Double Blind Crossover	[29]
Ekert et al.	19, 14	12.5	THC	10mg/m^2 up to maximum dose of 15mg/m^2	Oral Capsule	2 Double blinded cross-over studies	[31]
Elder et al.	58	13.9	Dronabinol	Most common dosage 2.5mg/m^2 6hrly 55% had scheduled dosage 95% did not receive weight-based dose of 5mg/m^2.	Oral Capsule	Retrospective chart review	[22]

Author	No. of Patients	Mean age (years)	Cannabinoid	Dosage	Route of Administration	Study Design	Reference
Polito et al.	110	14	Nabilone	Nabilone frequency received: Once daily n = 5 Twice daily n = 91 Three times daily n = 14 Mean Initial nabilone dose (?g/kg/dose; range) Once daily 19 (3.20–3.09) Twice daily 17 (5.00–38.80) Three daily 14 (9.10–19.40)	P/O	A multicenter, retrospective chart review	[12]
Rower et al.	National cohort n = 7510 Regional cohort n = 41	National cohort - median age 15 years Regional cohort - median age 12 years	Dronabinol	Dose amount (mg) 2.5 NC - 68.2%, RC - 65.4% 5 NC - 39.3%, RC - 34.0% 10 NC - 0.8%, RC - 7.4% Unknown - NC - 0.03%, RC - 0% Median dose amount (mg/m) = 2.5 IQR = 1.8-3.6	P/O	A multicentre, retrospective chart review	[24]

3.3.2 Other symptomatic Relief

Five studies investigated the use of cannabinoids for other symptomatic indications, namely for appetite and anorexia, pain, mood, and sleep. (Table 4) [21] [32] [3335] [36]

Doherty et al., found that all children who had received cannabinoids for pain reported an improvement in their symptoms. Pain was also the second most common indication, following CINV, for administration Carver et al.'s retrospective institutional review wherein 38% of children had received cannabis based

therapeutic as means of pain relief. However, it was identified by Carver that 97% of oncologists in their institute were reluctant to administer cannabinoids in trepidation of unknown drug interactions. Ofir et al., offered insight into short term efficacy and safety of cannabis use, concluding that when administered at low infrequent doses and intermittently increasing the dose, cannabinoids could reduce improve physical and psychological suffering of the patient. Side effects were observed in a minority of cases, reported side effects included burning throat (10%), increased anxiety (10%) and stomach pain (4%). Podda et al., surveyed patients within their institution who had received cannabis-based therapy as part of their cancer treatment. 48% reported improved appetite, 29% improved pain control and 19% reduced anxiety.

TABLE 4 Five Studies Investigating the Effectiveness of Cannabis Derived Medical Products to Ameliorate Symptoms other than Chemotherapy Induced Nausea and Vomiting Among Pediatric Cancer Patients

Author	**No. of Patients**	**Mean Age (years)**	**Cannabinoid**	**Dosage**	**Route of Administration**	**Study Design**	**Reference**
Carver et al.	90	11	THC, CBD or combination	N/A	N/A	Retrospective Institutional Review	[32]
Chapman et al.	64	N/A	N/A	N/A	P/O Oil (85.7%) Edibles (35.7%) Inhaled (50%) Capsules (7.1%)	Patient Survey	[35]
Doherty et al.	21	8.3	CBD, THC or Combination	Variable, most patients with cancer were on dosing schedules of 2,3 or 4 times per day.	P/O	Retrospective Institutional Review	[21]

Author	No. of Patients	Mean Age (years)	Cannabinoid	Dosage	Route of Administration	Study Design	Reference
Ofir et al.	50	13	THC, CBD	Products were introduced gradually, starting with 1 oil drop PO for several days at beginning of treatment and gradually increasing until desired effect achieved. Patients who preferred smoking were instructed once daily before nights sleep with a possible increase according to efficacy of symptom control.	Oil drops (n = 30) Smoking (n = 11) Combination oil drops and smoking (n = 6) Smoking and Vaporization (n = 2) Capsules (n = 2)	Retrospective Institutional Review	[33]
Podda et al.	66	19	N/A	N/A	N/A	Patient Survey	[36]

3.3.3 Adverse Events

Doherty et al. outlined 2 children who had experienced a cannabis overdose following caregiver administration. [21] The cannabis-derived medical products administered in these instances were THC (10–22mg/mL) and CBD (<0.5mg/mL). One child experienced extreme drowsiness and required extensive medical investigation to rule out other causes, while the second child required hospitalization due to extreme tiredness, headache, and vomiting.

2 case series' documented the adverse experience of miscellaneous caregiver administration of cannabis derived medicinal products during cancer therapy cycles. (Table 5) [2726]

Madden et al., described a 13-year-old female who had been experiencing nociceptive pain controlled on 7.5mg of methadone p/o twice daily. However, following caregiver CBD administration the patient presented with marked somnolence, much worse than baseline. Serum methadone was 271ng/mL. An interaction between the CBD and methadone was hypothesised and the child CBD intake was immediately halted.

7 days after stopping the CBD, methadone levels dropped to 149ng/mL and after 14 to 125ng/mL with marked symptomatic improvement. [27] Li et al., described 2 cases of miscellaneous reaction following parental administration of cannabis-derived medical products. The first case presented a 2-year-old male being treated for an ependymoma. After the patient's final dose of chemotherapy, they presented with marked somnolence worsening throughout the day with blood pressure readings emulating the downward trajectory, during the night pressure dropped to 50/30mmHg. A rapid 20-mL/kg bolus of saline was administered, which corrected the hypotension. It was later revealed that in the days preceding the patient's hypotensive episode they had increased the dose from 1 drop 3 times daily to 3 drops 3 times daily. The second case documented a 4-year-old female, her mother autonomously administered a few drops of THC-CBD of unknown concentration. During the night, the patients pressure dropped from 99/47 mmHg to 80/33 mmHg, she presented fatigued but alert. The patient was infused with a rapid 20-mL/kg bolus and THC-CBD was halted. The patient experienced no further hypotensive episodes. [26]

TABLE 5 Two Case Studies Documenting Adverse Events Following Administration of Cannabis Derived Medical Products Among Pediatric Oncological Patients

Author	**Age of Patient (s)**	**Cannabinoid**	**Dosage**	**Route of Administration**	**Concomitant Therapy**	**Nature of Adverse Events**	**Reference**
Madden et al.	13	CBD	5mL (25mg/mL) 3x daily, increasing the frequency to 6x daily.	Oil P.O	7.5mg methadone p/o twice daily	Marked somnolence	[27]
Li et al.	Case 1: 2 Case 2: 4	THC, CBD	Case 1 - 1 drop 3x daily to 3 drops 3x daily over the course of chemotherapy cycle Case 2 - N/A	Oil P.O	Case 1: cyclophosphamide, methotrexate, etoposide and cisplatin Case 2: Bone marrow transplant + Immunosuppression	Marked hypotension	[26]

3.3.4 Anti-Neoplasia

Articles documenting the anti-cancer effects of cannabis-derived medical products were limited to just two case studies documenting the experiences of three patients. [25] [28]

Foroughi et al., described two pediatric cases of spontaneous pilocytic astrocytoma regression and their apparent association with autonomous cannabis use. The first case documented an 11-year-old female who had undergone subtotal resection of her tumour leaving residual fragments at the forniceal region. After 6 years, the tumour was found to have diminished in volume to 0.27 cm^3, falling from 1.28 cm^3 at 9 months post-op. From the ages of 14 to 17 years the patient had been taking cannabis via inhalation reportedly 3 times per week. The second case described a 13-year-old female who had undergone subtotal resection for

a pilocytic astrocytoma, with post-operative MRI scans again revealing tumour remnants. Scans taken 6 years post-operatively revealed almost complete clearance of residual tumour. Tumour volume was 6 years post-op was 0.28 cm^3regressing from 3.3 cm^3 at 18 months post-op. The patient had reportedly started taking cannabis via inhalation at the age of 14 years and from the ages of 16-19 was taking it on a nearly daily basis. [25]

Singh and Bali described the experience of a 14-year-old patient diagnosed with Philadelphia positive acute lymphoblastic leukaemia (Ph +ve, ALL). The patient had reached the limits of her treatment and was placed in a palliative care home. The patient's parents sought alternative therapy in the form of hemp oil. Over 78 days, the patient received increasing doses of hemp oil starting at 0.02ml once daily to 1ml 3 times daily by d78. During this period, blast cell count was monitored, and the authors were able to generate a dose response curve. 78 days following the onset of treatment the patient passed away following bowel perforation secondary to neutropenic colitis.[28]

3.4.1 Leukaemia

Seven preclinical studies documented effects and mechanisms of cannabinoids on leukemic cell lines. (Table 6) [3738 39 4041 43]

Concerning the impact of cannabinoid treatment on leukemic cell lines, the articles unequivocally conclude that cannabinoid-intrinsic apoptotic pathway interaction induces cancer cell death. Two studies provided evidence to support subsidiary extrinsic pathway involvement.[37] [39] Moreover, Scott et al., demonstrated that this effect could be enhanced through combination with more than one cannabinoid and alongside chemotherapeutic agents.[42]

Herrera et al., demonstrated that when treating leukaemia cells with THC alongside a selective CBR2 antagonist (SR144528) the pro-apoptotic effect of THC observed when treated in isolation was lost, demonstrating the importance of CBR binding. [37] In contrary, Soto-Mercado et al., demonstrated that the cannabinoid, CP55940 can induce apoptosis among Jurkat's independent of CBR binding. Despite the inaccessibility of CBR's, when treated with CP55940, apoptosis was successfully induced. Soto-Mercado et al., observed that CP55940's 3 hydroxyl groups were involved in generating the oxygen species H_2O_2. H_2O_2 was demonstrated to have been critical in inciting oxidative stress through activation of cell death related redox sensors. [43]

Alternatively, Olivas-Aguirre et al., demonstrated direct CBD-mitochondrial interaction causing alterations to calcium handling. The group deciphered, through in silico analysis of VDAC-CBD interactions, the specific residues upon which CBD-VDAC interactions were based. The interaction between the VDAC channel and CBD fixed the channel in a calcium ion permanent state, activating MCU alongside generation of a large negative potential across the inner mitochondrial matrix culminating in calcium overload. [41]

TABLE 6 Seven Preclinical Studies Investigating the Anti-Cancer Properties of Cannabis Derived Medical Products among Models of Leukaemia

Author	**Experimental Model**	**Cannabinoid**	**Proposed Treatment Effect**	**Conclusion**	**Reference**
Blanca Herrera et al.	Jurkat cells	THC	Induction of Apoptosis via CB2 Receptors.	THC induces de novo ceramide synthesis, causing MOMP and subsequent cell death.	[37]

Author	Experimental Model	Cannabinoid	Proposed Treatment Effect	Conclusion	Reference
Jia et al.	Jurkat cells	THC	Induction of apoptosis, implicating the importance of downstream Raf/MEK/ERK signalling and Bad location.	THC binding to CBR2's causes Bad translocation from the cytoplasm to the mitochondria through interruption of the Raf-1/MEK/ERK/RSK pathway.	[38]
Lombard et al.	Jurkat cells	THC	Induction of apoptosis, implicating intrinsic and extrinsic pathway cross talk.	THC causes activation of both the extrinsic and intrinsic cell death pathways, however activation of intrinsic is the main mechanistic action of cell death.	[39]
McKallip et al.	EL-4, Jurkat, MOLT-4	CBD	Induction of apoptosis, through CBD binding to CBR2 on leukaemia cells.	CBD elicits its anti-tumour effect via CBR2, where the results show cause increased expression of NAD (P) H oxidases, causing an increase in ROS species precipitating cell death.	[40]

Author	Experimental Model	Cannabinoid	Proposed Treatment Effect	Conclusion	Reference
Olivas-Aguirre et al.	Jurkat, MOLT-3, CCFR-CEM, K562, Reh, RS4;11	CBD	Induction of apoptosis via mitochondrial Ca2+ overload, stable mitochondrial transition pore formation and cell death.	CBD directly targets mitochondria in T-ALL and changes their capacity to handle Ca2+, which in turn affects multiple cellular functions, including ROS production and Ca2+ signalling, metabolic switch and the induction of autophagy and cell death.	[41]
Scott et al.	CEM (acute lymphocytic leukaemia), HL60 (promyelocytic leukaemia)	CBD, CBG, THC	Induction of apoptosis, synergistically with multiple cannabinoids alongside anti-cancer therapy.	When anti-leukaemia agents treated the leukaemia cell lines and cannabinoids were added subsequently, there was a significant improvement in the reduction of cell viability.	[42]
Soto-Mercado et al.	Human peripheral blood lymphocytes (PBL) Jurkat cells, Cells from T-ALL patients	CP55940	Induction of apoptosis in Jurkat cells implicating H2O2-mediated signalling pathway, independent of CBR's.	CP55940 can selectively induce apoptosis in leukaemia cell lines, independent of CBR's, through inducing the generation of ROS and intrinsic mitochondrial pathways.	[43]

3.4.2 Neuroblastoma (NBL)

Two studies investigated cannabinoid anti-cancer efficacy in NBL preclinical models. (Table 7) [46] [47]

Fisher et al., found that THC and CBD reduced NBL cell viability in a dose and time dependant manor through induction of apoptosis and cell cycle arrest. [47]

Alharris et al. expanded on this work, investigating precise CBD induced cell death mechanisms. Pre-treatment of cells with caspase 2 and 3 inhibitors caused a significant reduction in apoptosis compared to CBD positive vehicle controls. There was also a significant reduction in apoptosis when cells were pre-treated with GPR55 antagonist (ML-193), TRPV1 antagonist (A784168), or 5-HT2A receptor antagonist (MDL100907) implicating potential CBD interaction with 5-HT2A and TRPV1 receptors. CBD was demonstrated to insight miRNA expression alterations crucial to cell death induction. The has-let-7a sequence (resulting in increased expression of caspase 3 and GAS-7) was found to be downregulated following CBD treatment and has-mir-1972 (decreased expression of BCL2L1 and SIRT2 genes) upregulated. Taken together, CBD insights apoptosis in NBL cells with evidence supporting the involvement of serotonin and vanniloid receptors and consequential miRNA sequence alterations.[46]

TABLE 7 Two Preclinical Studies Investigating the Anti-Cancer Properties of Cannabis Derived Medical Products among Models of Neuroblastoma (NBL)

Author	Experimental Model	Cannabinoid	Proposed Treatment Effect	Conclusion	Reference
Fisher et al.	NBL SK-N-SH cells	THC and CBD	Induction of Apoptosis Cell cycle arrest.	CBD was observed to inhibit tumour cell viability through induction of apoptosis and cell cycle arrest.	[47]
Alharris et al.	human NBL cell lines, SH SY5Y and IMR-32	CBD	Induction of apoptosis Inhibition of cell migration and invasion Alteration to mitochondrial metabolism.	CBD alters the expression of several miRNA that target critical signalling pathways implicated in apoptosis, migration and invasion, and metabolic functions in NBL cells.	[46]

3.4.3 Osteosarcoma (OS)

Two studies investigated cannabinoid anti-cancer efficacy in OS preclinical models. (Table 8)[44] [45]

Punzo et al., demonstrated a synergistic relationship between Bortezomib (BTZ), an approved anticancer agent used in the treatment of OS, and selective agonism of ECS receptors through Resiniferatoxin (RTX). When treated with BTZ alongside RTZ there was a significant increase in levels of apoptosis and reduction in cell cycle progression. Because both CBR2 and TRPV1 receptors are susceptible to proteasomal degradation,

BTZ proteasomal inhibition make receptors more accessible for agonist binding and thus ameliorates their potential to inflict cell death on human OS cells. [45]

Xu et al., found that both in vivo and in vitro, CBD treatment caused significant downregulation of CBX expression. Further analysis identified SP1 as an upstream regulator of CBX2 and bound directly to the gene sequence to upregulate its expression. Concordantly, Xu showed that among CBD treated OS cells there was a significant decrease in SP1 promotor binding to CBX2 sequences. Taken together CBD was observed to induce apoptosis through inhibiting SP1 transcription factor function, consequently causing downregulation of the apoptotic inhibitor CBX2, culminating in reduced expression of BCL2 and increased expression of BAX and caspase 3. [44]

TABLE 8 Two Preclinical Studies Investigating the Anti-Cancer Properties of Cannabis Derived Medical Products among Models of Osteosarcoma

Author	Experimental Model	Cannabinoid	Proposed Treatment Effect	Conclusion	Reference
Punzo et al.	HOS (Osteosarcoma) cell lines	Selective agonists at CB2 (JWH-133) and TRPV1 (RTX) receptors	Synergistic induction of apoptosis via stimulation of CB2 and TRPV1 receptors and inhibition of ubiquitin proteasomal system in osteosarcoma cell lines.	Where BTZ and Cannabinoid agonists were utilized there was a significant increase in rate of apoptosis, reduction in progression through cell cycle, reduction in OS progression and reduction in migration.	[45]
Xu et al.	MG63 cells, Human OS cells, Female BALB/c nude mice	CBD	Induction of apoptosis through alteration of the SP1-CBX2 axis Inhibition of cell migration.	CBD can induce apoptosis in OS cells in vitro and in vivo through alteration of the SP1-CBX2 pathway.	[44]

3.4.4 Rhabdomyosarcoma (RMS)

One study investigated cannabinoid anti-cancer efficacy in an RMS preclinical model. (Table 9) [50]

Oesch et al., found that there was significantly higher expression of CBR1 mRNA in all tposRMS cells compared to control cell lines. It was observed that CB1 receptor agonism via HU210 reduced cell viability through the induction of apoptosis. HU210 treated animals demonstrated significantly more tumour free areas of connective tissue as well as increased apoptotic areas after 13 days. The mechanism of apoptosis induction is thought to involve a reduction in the cytoprotective Akt pathway. [50]

TABLE 9 Summary of Oesch et al.'s study investigating the Anti-Cancer Properties of Cannabis Derived Medical Products in preclinical models of Rhabdomyosarcoma

Author	Experimental Model	Cannabinoid	Proposed Treatment Effect	Conclusion	Reference
Oesch et al	RMS13, RD, MRC-S lung fibroblast cells, Rh4, Rh28 tposRMS cells	THC, Met-F-AEA, AM251, HU210	Induction of apoptosis, via inhibition of Akt signalling and induction of stress-associated transcription factor p8.	CBR1's were upregulated in Rh positive cells. When activated with exogenous cannabinoids cell viability was significantly reduced. The mechanism of apoptosis induction involves a reduction in the Akt pathway and upregulation of p8 - the pro-apoptotic transcription factor.	[50]

3.4.5 CNS tumours

Two studies investigated CBR expression in pediatric CNS tumours.[48] [49]

Ellert-Miklaszewska et al., found that expression of CBR in CNS tumours is linked to the tumour stage and subtype. CBR2 expression was consistently higher in less differentiated regions of tumour samples. CBR2 expression was observed to correlate proportionally with the invasiveness of astrocytic tumours and other glial neoplasms. Embryonal tumours showed no trace of CBR2 expression. CBR2 expression was higher in astrocytomas/glioblastomas than in oligodendrogliomas, ependymomas or meningiomas of the same grade. [48]

Sredni et al. applied integrated molecular analysis to decipher molecular markers among low grade pediatric gliomas. Compared to stable tumours, 7 mRNA and associated miRNA sections differed significantly among involuted tumours. The biggest difference was in CBR1 expression. It was posited that binding of endogenous cannabinoids to tumours with greater CBR expression was responsible for their involution, therefore exhibiting a therapeutic target. [49]

Both articles propose that overexpression of CBR's among CNS tumours make them susceptible to apoptotic induction by cannabinoids treatment.

TABLE 10 Two Preclinical Studies Investigating the CBR Expression in Pediatric CNS Tumours

Author	Experimental Model	Cannabinoid	Proposed Treatment Effect	Conclusion	Reference
Ellert-Miklaszewskaa et al.	Adult and paediatric brain tumour cell samples	CBR Expression	Implication of CBR2 expression in certain types of paediatric brain tumour.	CBR2 expression in pediatric brain tumours depends on the histopathological origin of the tumour as well as the stage of differentiation. High CBR2 expression in pediatric glial tumours may imply a potential therapeutic target.	[48]
Sredni et al.	Tumour samples of primary, untreated tumors from patients with P-LGG who underwent STR	CBR Expression	Binding of circulating cannabinoids (anandamide) to CBR1 expressed on tumour cells, precipitates involution through cell cycle arrest and apoptosis.	High expression of CBR1 correlated with involution, therefore it may be speculated that binding to CBR1 on tumour cells through anandamide may have induced these observations.	[49]

4.0 Discussion

16 clinical and 14 preclinical studies investigating the use of cannabis derived medical products in paediatric oncology were included and systematically reviewed. The current assortment of published clinical literature is by enlarge in support of medicinal cannabis use as a symptomatic and side effect relief agent; however, the quality of this literature was poor, incorporating only 3 blind controlled trials. There was significant heterogeneity among the preclinical articles concerning outcome measures and pediatric cancer type, however findings consistently demonstrated cannabinoid anti-tumour action.

The findings of the present study reciprocate derivations concerning the literary consensus of medicinal cannabis use. A Cochrane review evaluated 23 adult RCT's assessing the use of cannabinoids in CINV.[51] They concluded that cannabinoid antiemetic efficacy is probable. However, the quality of evidence currently available is insufficient to generate definite guidelines and further gold standard RCT data is essential to adequately assess their efficacy. Wong et al., through means of systematic review, assessed the role cannabinoids across pediatric medicine. [52] They identified that the antiemetic properties may have clinical utility however concluded that further high-quality research is required. A review published in the British Medical Journal (BMJ) accrued 2805 records of cannabinoids in adult cancer treatment and concluded they provided

no additional benefit to pain when administered alongside opioids. [53] Taken together, the lack of quality clinical evidence is preventative when drawing definite conclusions regarding the efficacy of cannabinoids in oncology, this is the same across both adult and pediatrics.

As with any systematic review, there are limitations to the scope of this review. An important weakness of the reviewed articles is the quality of the data. Only three of the studies were double blinded controlled trials. Furthermore, no study evidenced power calculation and thus it is conceivable that they were underpowered. Among non-blinded studies, there may have been a degree of the Hawthorne Effect.[54] Given that these studies are in pediatrics, and it has been recognised that children often desire to please adults, if children are aware they are being given trialled agent for symptomatic benefit, they may report positively to staff/ parents as they believe this is the 'correct' thing to do. [54] Similarly, among retrospective review papers, if children believe it will please adults to answer survey questions positively, they may be more inclined to select 'yes' to questions regarding Cannabinoid effects. A limitation of the adverse effects case reports is the unknown quantity of cannabinoid administered. In each of the papers it was reported caregivers had provided the cannabinoid, thus accurate dosing cannot be confirmed. These papers highlight the need for proper legislation and guidance surrounding medicinal cannabinoid use.

The present study presents several potential uses of cannabinoids in pediatric oncology. Clinically, the most researched area at present is its use in CINV, however, there has not been a RCT performed since 1987. Therefore, there is definite scope to support further clinical research, particularly among cases of intractable CINV, as this side effect has been shown to play a significant role in adherence to treatment.[55] [56]

Preclinical data and 3 clinical papers implied a cannabinoid exerted anti-tumour effect. However, this conclusion cannot be fully accepted. The clinical papers are case reports, and the preclinical data is explores treatment in cancer models. However, given the positive findings of these papers, there is conceivably sufficient preclinical evidence to warrant a clinical trial assessing cannabinoids as anti-cancer agents. Furthermore, research conducted by Scott et al. reported an interesting finding that cannabinoids have a symbiotic effect with current chemotherapy, this finding may be considered, and potentially implemented in a clinical trial.

5.0 Conclusions

The true efficacy of cannabinoids for symptom relief and as anti-cancer agents cannot be concluded from the current assortment of published literature. The research suggests cannabinoids are likely effective in CINV and other symptoms. It is unknown whether they are efficacious as anti-cancer agents. Preclinical data should be considered, and phase I clinical trials may be warranted. There is a necessity for further clinical research to address these limitations and gain greater insight into the utility of cannabinoids in pediatric oncology.

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Figures and Legends

FIGURE 1 PRISMA 2 phase screening process, generating 16 clinical articles and 14 pre-clinical articles that met inclusion criteria and encompass any exclusion criteria.