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REVIEW ARTICLE

Pharmacological evidence of medicinal cannabis in oncology: a systematic review

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Abstract

Purpose This systematic literature review examines research into the use of medicinal cannabis in cancer management. The aim was to identify the gaps in knowledge on the dose, dosing schedule and absorption of the administration routes of medicinal cannabis use in oncology.

Methods A comprehensive search of the literature was conducted across six databases to identify original data reporting the pharmacology of medicinal cannabis in oncology.

Results Eighteen articles were selected for review. Of the selected articles, ten were identified as randomised control trials, two experimental studies, two retrospective cohort studies and four case studies. Four articles reported absorption data and one drug interaction study was identified.

Conclusions There is little evidence reported in the literature on the absorption of medicinal cannabis in cancer populations. Various reasons are explored for the lack of pharmacokinetic studies for medicinal cannabis in cancer populations, including the availability of assays to accurately assess cannabinoid levels, lack of clinical biomarkers and patient enrolment for pharmacokinetic studies.

Keywords Medicinal cannabis · Cannabinoids · Pharmacology · Cancer · Oncology · Integrative medicine

Introduction

Increased legal access to medicinal cannabis has continued the debate surrounding cannabis application in disease management [1]. Cannabis is by no means a new medicine [2]. In modern history it was part of the United States Pharmacopoeia and British Pharmacopoeia, until being restricted, criminalised and removed in the twentieth century [3]. In 2013, *Cannabis* spp. were reintroduced in the American Herbal Pharmacopoeia [4].

Clinical trials on medicinal cannabis have focused on the management of the side effects associated with first-line cancer therapy that can compromise patient quality of life and compliance to potential curative treatments. These include the investigation of medicinal cannabis for chemotherapy-induced nausea and vomiting, cachexia and pain management [5]. Clinical trials investigating anticancer actions have been limited, with the focus on the tolerability of medicinal cannabis [5, 6]. Preclinical studies on the anticancer actions of medicinal cannabis exhibit promising anticancer properties through the modulation of key cellular pathways involved in cell survival and immunomodulatory factors [7]. Additionally, cannabinoids have demonstrated the ability to sensitise some cancer cells to first-line therapy [8–11]. However, there is no consensus on the effectiveness of medicinal cannabis as an anticancer agent in oncology [5, 7].

With the global cancer burden predicted to increase to 20 million new cases by the year 2025, an understanding the pharmacology of cannabis cannabinoids and metabolites in oncology can assist with the therapeutic application of medicinal cannabis in cancer populations [12].

Medicinal cannabis is defined for purpose of this review as pharmaceutical cannabis–based medicine (standardised cannabinoid extracts) from *Cannabis* sp.; non-pharmaceutical cannabis–based medicine (undefined cannabinoid extracts) from *Cannabis* sp., and single-molecule cannabinoids.

Pharmaceutical cannabis–based medicines and single-molecule cannabinoids are approved for use in several

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countries despite a common conclusion within the broader medical community that medicinal cannabis lacks adequate evidence [13]. In cancer populations, nabilone (Cesamet®), a single-molecule cannabinoid is prescribed to manage chemotherapy-induced nausea and vomiting. The cannabis-based medicine nabiximol (Sativex®) is prescribed in the management of refractory cancer pain.

Knowledge of the complexity of cannabis pharmacology has expanded since the identification of the endocannabinoid system in the mid 1990s, followed by the discovery of G protein-coupled cannabinoid receptors 1 and 2, and the endogenous ligands (endocannabinoids) anandamide (AEA) and 2-arachydonylglycerol (2-AG) [14–17]. The most recent count of phytocannabinoids identified from the *Cannabis* sp. numbers over 100 [18]. Of principle medical interest are the decarboxylated phytocannabinoids, delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD) derived from *Cannabis* sp.

Phytocannabinoids interact with the human endocannabinoid system which is known to mediate key cellular pathways that exert both palliative and modulatory effects in cancer management [19]. When this knowledge is combined with the identification of further pharmacological constituents from cannabis, including terpenoids, the therapeutic potential of this plant is continuously espoused [2].

Despite the continued understanding of cannabinoid receptors and their distribution and the role of endocannabinoids, there is a paucity of evidence on how best to modulate the individual's endocannabinoid system for therapeutic outcomes. Cannabis pharmacology remains the same irrespective of use [2, 20–23]. However, an understanding of the pharmacology of medicinal cannabis in respect to administration, dose, absorption and potential drug interactions in cancer populations is fundamental in the assessment of efficacy, therapeutic index and safety profile of this medicine [24].

This systematic literature review examines the literature surrounding the administration, dosing and absorption of medicinal cannabis reported in oncology across human studies. Eighteen articles have been systematically identified from the years 2000 to 2017. These dates were chosen to reflect the relevant pharmacological understanding of the endocannabinoid system.

Methodology

A comprehensive search of the literature was conducted to identify original data reporting on the pharmacological study of medicinal cannabis, with the primary endpoint to capture administration, dosage and absorption data of medicinal cannabis in cancer management. Standard systematic review protocol was followed in accordance with the PRISMA statement [25].

Article eligibility criteria

Inclusion criteria captured all types of cancer and medicinal cannabis, including both pharmaceutical and non-pharmaceutical cannabis–based medicines, and synthetic singular molecule drugs. Original data included in the review required articles to report a minimum of two of the following pharmacokinetic considerations: administration, dosage and absorption. Where medicinal cannabis dosage was described, a minimum of two dosage ranges must have been provided. Articles were excluded on the basis of not reporting original data, full-text availability, not available in English, not cancer specific, not medicinal cannabis as described above, reporting on the synthetic cannabinoid analogue levonantradol and reporting in vivo and in vitro data. Date restrictions on publications were applied to all searches. Full-text screened articles previous to 2000 were excluded in order to reflect a consistent pharmacological understanding of the endocannabinoid system.

Identification and selection of studies

The following six databases, including grey literature sources, were searched within the date range of 2000 to 2017: PubMed (US National Library of Medicine), Scopus (ELSEVIER), CINAHL (EBSCOhost), EMBASE (ELSEVIER), Cochrane Library (Wiley Online Library), AMED (Allied and Complementary Medicine Database). The search terms used were ((cancer OR oncology OR neoplas* OR malignan*)), ((medicinal cannabis OR cannabis OR medicinal marijuana OR marijuana OR cannabinoids OR phytocannabinoids)) and ((clinical trial OR case study OR trial OR study and human)).

Data extraction and appraisal

All relevant sources were used for data extraction including full-text journal articles, conference proceedings and abstracts. All identified articles were imported into EndNote Bibliography referencing software management program. Duplicates were removed and articles analysed first by title, secondly by abstract and finally in full text, and once again in full text, culminating in a final selection of articles that met inclusion criteria. Discussion between authors was undertaken throughout to reach consensus in the case of uncertainty or disagreement. Articles were characterised by study type and thematically grouped by common characteristics involving multiple readings to identify themes to allow for contrast and comparison of the reported findings within the identified articles [26].

Critical appraisal

Standard critical appraisal tools from the Joanna Briggs Institute (JBI) were used to evaluate the methodological quality of articles selected for inclusion [27, 28]. These included 3 variations: JBI Critical Appraisal Checklist for Randomized Controlled Trials, JBI Critical Appraisal Checklist for Case Reports and JBI Critical Appraisal Checklist for Cohort Studies [27, 28]. This approach was chosen to assess the identified research types for internal validity.

Results

A total of 18 articles were selected for review between 2000 and 2017 (See Fig. 1). All studies reported dose schedules and administration data. Four of the 18 articles reported absorption data [6, 29–31]. Safety assessments were reported in ten articles through the identification of adverse events (AEs). AEs were commonly characterised by somnolence, fatigue, hallucinations and toxicity measured by common toxicity criteria with no report of serious adverse events relating to the intervention [6, 29–37].

The primary outcomes of the included articles focused on the characterisation of medicinal cannabis as an antiemetic ($n = 5$) appetite stimulant ($n = 3$), analgesic ($n = 4$), anticancer ($n = 3$) and anticholinergic ($n = 1$). Other outcomes were related to its effect as an adjuvant treatment in radiotherapy treatment ($n = 1$). One study investigated clinical pharmacokinetic interactions of medicinal cannabis with chemotherapeutics in cancer management ($n = 1$) (See Table 1).

Of the selected articles, ten were identified as randomised control trials (five of the ten were further defined as a pilot trial ($n = 3$), phase II trial ($n = 1$) and phase III trial ($n = 1$)), three experimental studies (non-randomised), two retrospective cohort studies and four case studies (See Table 2). The participants across all studies included adult, adolescence and young adults (AYA) and paediatric population with multiple cancer presentations.

Intervention

The medicinal cannabis interventions include single-molecule analogues of THC, namely dronabinol (Marinol®) or nabilone (Cesamet®); pharmaceutical cannabis–based medicine including nabiximols (Sativex® 2.7 mg THC, 2.5 mg CBD), Bedrocan® tea (18%THC, 0.8% CBD); and non-pharmaceutical cannabis-based medicines reported as 'hemp oil' and inhaled cannabis sourced from *Cannabis* sp. plant.

Cannabis-based medicine (CBM) interventions were used to investigate anticancer, antiemetic, analgesic and appetite stimulant actions. The single-molecule cannabinoid dronabinol was investigated as an antiemetic and appetite stimulant; nabilone for quality of life (QOL) outcomes and

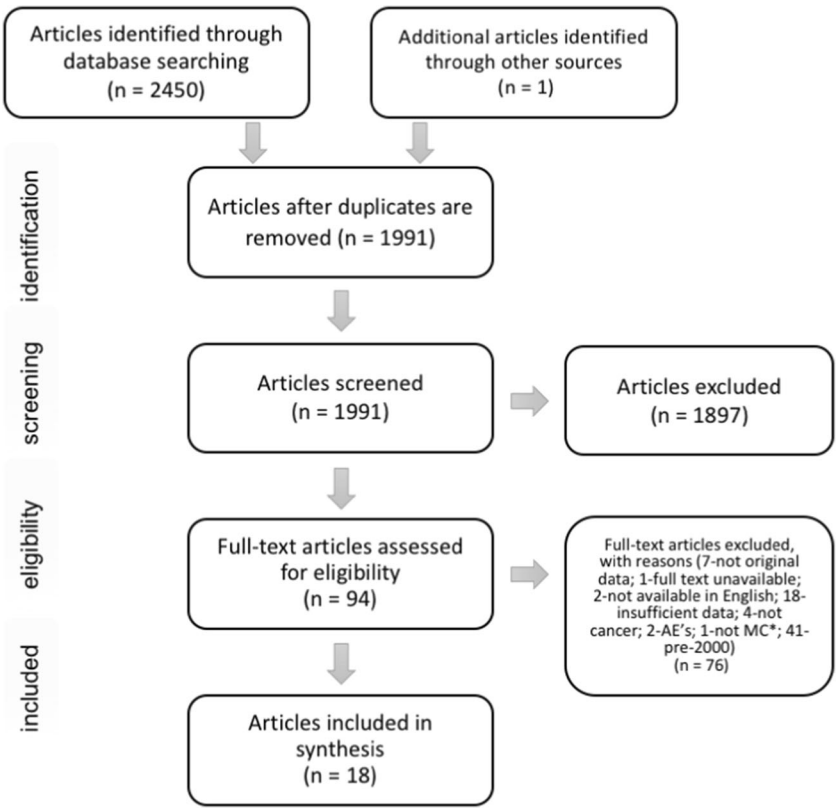

Fig. 1 PRISMA flow diagram outlining the process of articles selected to be included in the review

Table 1 Therapeutic action and intervention of medicinal cannabis and number of studies reported in this review. (*Clinical drug interaction study. *QOL* quality of life)

Action	Single-molecule cannabinoids			Cannabis-based medicine (CBM)			
	Dronabinol (Marinol®)	Nabilone (Cesamet®)	THC isolate	Pharmaceutical CBM	Nabiximols (Sativex®)	Bedrocan®	Hemp oil, leaf, flower
Anticancer			1				2
Antiemetic	4				1		
Analgesic					4		
Appetite stimulant	2			1			
Anti-cholinergic		1					
QOL adjuvant		1					
*Drug interactions						1	

anticholinergic action. A standardised THC isolate investigated anticancer actions, and similarly non-standardised CBM as inhaled or oil-based product reported anticancer actions.

Dosing

Dose titration was reported in 11 studies reporting variable dosages between participants to achieve an individual dose–effect relationship [6, 30, 34–42]. All variable dosages were characterised by a maximum allowable dose over 24 h. Under-dosing of medicinal cannabis was reported in two studies [36, 40].

The range in dosing for each intervention was variable dependent on the type of medicinal cannabis and route of administration (See Fig. 2). Oral administration included dronabinol (Marinol®) at 2–5 mg once (QD) or twice (BID) a day to maximum titration of 15 mg for antiemesis [39–41, 43]. As an appetite stimulant in cancer-associated anorexia and chemosensory alterations, dronabinol (Marinol®) was initially given 2.5 mg BID titrated to a maximum of 20 mg per day [32, 44]. CBM was prescribed BID either THC:CBD (2.4 mg:1 mg) or THC (2.5 mg) for cancer-related anorexia [31]. Nabilone (Cesamet®) was dosed between 2 and 4 mg QD for quality of life measures [33, 45]. Bedrocan® was dosed at 1 g, infused as a tea in 200 ml of water QD to investigate potential interaction with anticancer drugs [29]. Hemp oil was extracted from *Cannabis indica* 'chronic'; afghan/thai strain was dosed as drops up to 1 ml BID [42]. The oromucosal administration of nabiximols (2.7 mg THC:2.5 mg CBD) was dosed no more than 8 actuations, over a 3 h, at maximum dose of 48 actuations over 24 h for antiemetic and analgesic effect [30, 35–37]. Intratumourally administered THC was dosed to a maximum of 180 μg a day [6].

As an antiemetic, dronabinol (Marinol®) was administered 1–3 h before chemotherapy [39–41]; for postoperative nausea and vomiting following breast surgery, dronabinol was scheduled preoperatively [43]; finally, the cannabis-based medicine Sativex® was administered 2 h after chemotherapeutic treatment [30]. For analgesic effect cannabis–based medicines, nabiximols were first titrated to optimal individual dose, and not exceeding more than 4 doses over 3–4 h, or 1 dose before bed and increasing by 2 doses until optimal effective dose was reached [34–37]. As an appetite stimulant, dronabinol (Marinol®) was scheduled at meal time and/or before bed [32, 44]. CBM THC:CBD or CBD only was scheduled before lunch and dinner, with milk for cancer-related anorexia [31]. For quality of life including management of nocturnal hyperhidrosis, nabilone (Cesamet®) was scheduled before bed for the hypothesised management of hyperhidrosis associated with cancer or scheduled once a day before the first radiotherapy treatment [33, 45]. The CBM Bedrocan® was prescribed once daily, in the evening for drug interactions study [29]. Potential anticancer actions were reported for cannabis-based medicine (hemp oil) or the single constituent THC [6, 42].

Administration route

The route of administration for pharmaceutical and non-pharmaceutical cannabis–based medicines was orally via capsule or as 'hemp oil' ($n = 10$) [31–33, 39, 41–45]. oromucosal spray ($n = 5$) [30, 34–37], a herbal tea ($n = 1$) [29] and inhalation ($n = 1$) [38]. Single-molecule THC isolate was intratumourally administrated via subcutaneous reservoir ($n = 1$) [].

Oral administration of pharmaceutical medicinal cannabis via capsule containing single-molecule THC concentrations was used predominantly for antiemesis ($n = 5$), or as an appetite stimulant for chemosensory alterations ($n = 1$) and cancer-associated anorexia ($n = 1$). Oral capsules containing THC (2.5 mg) or THC:CBD (2.5 mg:1 mg) investigated appetite in cancer-related anorexia ($n = 1$). Oral capsules containing THC (1 mg) investigated anticholinergic action ($n = 1$) and quality of life (QOL) ($n = 1$). Oromucosal administration of nabiximols investigated pain management ($n = 4$) and antiemesis ($n = 1$). Inhalation of non-pharmaceutical CBM

Table 2 Data extraction table in order of medicinal cannabis intervention type and date, highlighting author, study type, number of participants, intervention, administration, daily dose, dosing schedule, pharmacokinetic data, outcome measures and primary outcomes for articles included in the review

Author	Study type	*N*	Intervention (action) *type*	Admin	Daily dose	Dosing schedule	Pharmacokinetic data	Outcome measures	Primary outcomes
Engels et al. 2007	Cohort	24	Bedrocan® (clinical interaction study) *dried flower*	Herbal tea	200 ml (1 g/l) once daily (15 days) (18% THC and 0.8% CBD)	Controlled	Samples were screened semi-quantitatively for presence of the primary urinary metabolite of orally ingested THC (11-nor-THC-9-carboxylic acid) using a validated cannabinoids assay	TDx/FLx® cannabinoids assay; Abbott Laboratories, Abbott Park, IL	Co-administration of the evaluated medicinal cannabis, as herbal tea, in cancer patients treated with irinotecan or docetaxel does not significantly influence the plasma pharmacokinetics of these drugs.
Foroughi et al.,2011	Case study	2	*Cannabis* sp., (anticancer) *unknown*	Inhalation	Patient (1) smoked 3/week (3 years) (2) smoked almost daily (approximately 3) (no details were available on the type, strength, and amount of Cannabis consumed.)	Variable	No absorption data reported	Magnetic resonance imaging (MRI)	Over 3 years, one case was dormant and the other showed slight increase in size, followed by clear regression of both residual tumours over the following 3-year period.
Strasser et al. 2006	Phase III randomised double-blind placebo-controlled clinical trial	243	Cannabis-based medicine (appetite) *Cannabis sativa L.,*	PO	2.5 mg THC and 1 mg CBD; or THC only at 2.5 mg. BID (once before lunch; once before dinner or bedtime with milk)	Controlled	Cannabinoid urinary test at weeks 0–2–4–6	Vital signs and ECOG PS, urinary cannabinoids VAS; Appetite; European Organisation for Research and Treatment of Cancer Quality of Life Questionnaire C30 (EORTC QLQ-C30)	No differences between the three groups over 6 weeks of treatment for the primary end points of appetite and QOL, for cannabinoid-related toxicity, or for secondary end points such as mood or nausea. CE at the oral dose administered was well tolerated
Jatoi et al. 2002	Double-blind randomised trial	19	Dronabinol (appetite)	PO	2.5 mg THC, BID (5 mg daily)	Controlled	No absorption data reported	North Central Cancer Treatment Group questionnaires for appetite and weight were used at baseline, weekly for 4 weeks, and then monthly. QOL assessment; FAACT	In the doses and schedules studied, megestrol acetate provided superior anorexia palliation among advanced cancer patients compared with dronabinol alone. Combination therapy did not appear to confer additional benefit
Layeeque et al. 2006	Retrospective cohort review	242	Dronabinol (anaesthesia antiemetic)	PO	5 mg THC preoperatively	Controlled	No absorption data reported	Episodes of postoperative nausea and vomiting, and number of postoperative antiemetic used (AE count)	Preoperative treatment with dronabinol and prochlorperazine significantly reduced the number and severity of episodes of PONV
Meiri et al. 2007	Randomised double-blind placebo-controlled parallel study (5 days)	64	Dronabinol (antiemesis)	PO	THC = 10 mg or 20 mg orally daily 2.5 mg and 5 mg PO QID used in the fixed (day 2) and flexible (days 3–5) dosing phases.	Variable	No absorption data reported	Self-reporting the number of vomiting and/or retching episodes in the previous day. Patients also recorded the daily presence or absence of nausea and its duration.	No statistically significant differences between active treatment groups were observed. 71% patients receiving dronabinol responded to treatment
Elder et al. 2015	Retrospective analysis	66	Dronabinol (antiemesis)	PO	5 mg/m^2 THC (body surface area–BSA)	Variable	No absorption data reported	Number of emetic events from dronabinol administration until discharge, repeated courses of dronabinol,	60% of patients had a defined positive response to dronabinol. 95% patients did not receive the recommended dose of dronabinol. Median

Table 2 (continued)

Author	Study type	*N*	Intervention (action) *type*	Admin	Daily dose	Dosing schedule	Pharmacokinetic data	Outcome measures	Primary outcomes
								and outpatient prescriptions written for dronabinol. Tolerability was indirectly measured using repeat courses and outpatient prescriptions as surrogate markers.	dronabinol doses received per hospitalisation were 3.5, with a wide range (1–129 doses) received per patient
Hernandez et al. 2015	Case study	1	Dronabinol (antiemesis)	PO	THC = 1–10 mg daily PO: titrated to a maximal dose of 5 mg BID. (co-administered w/ondansetron 8 mg IV every 8 h (q8h) and dexamethasone 4 mg IV q8h.	Variable	No absorption data reported	Self-rated nausea scale (10-point scale)	Dronabinol was well tolerated and was dramatically effective, with prompt resolution of the vomiting after the 15 mg/day dosage was reached; patient rated nausea at 0 or 1/10
Singh et al. 2013	Case study	1	'hemp oil' (anticancer) *Cannabis indica 'chronic'; afghan/thai strain, from 5 different sources*	PO	PO 1–3 doses daily. Hemp oil (undefined cannabinoid extracts) (1) 0.02–0.133 ml; (2) 0.166–1.0 ml; (3) 0.5 ml; (4) 0.5–0.8 ml; (5) 0.8–1.0 ml.	Variable	No absorption data reported	Blast cell counts	Cannabinoid resin extracts demonstrate a possible relationship in reduction of blast cell count for ALL with a positive Philadelphia chromosome mutation. The clinical observation in this study revealed a rapid dose–dependent correlation.
Brisbois et al. 2011	Two centre, randomised, double-blind placebo-controlled pilot study (NCT00316563)	46	Dronabinol (chemosensory)	PO	2.5 mg THC (one daily for first 3 days, max dose 20 mg/day)	Controlled	No absorption data reported	Taste and Smell Survey; 100 ml Satiety-Labelled Intensity Magnitude (SLIM) scale; Macronutrient Preference List (MPC); FAACT questionnaire	THC, compared with placebo, improved and enhanced chemosensory perception, altered macronutrient preference, appeal of savoury foods, appetite, relaxation and quality of sleep for advanced cancer patients with chemosensory alterations.
Maida et al. 2008	Case report	4	Nabilone (anti-cholinergic)	PO	patients 1 and 2: 1 mg/day; (synthetic single-molecule THC = 1 mg) patients 3 and 4: 1 mg BID (total 2 mg) (synthetic single-molecule THC)	Controlled	No absorption data reported	ESAS questionnaire on initial consultation and at 48-h intervals thereafter.	All patients reported improvement of night sweats within 48 h of initiating therapy with nabilone. None of the patients experienced any significant burden of side effects from the addition of nabilone.
Cote et al. 2016	Randomised double-blind placebo-controlled trial	46	Nabilone (QOL)	PO HS	Week 1: 0.5 mg HS; (synthetic single-molecule THC = 0.5 mg) Week 2: 0.5 mg BID; (synthetic single-molecule THC = 1 mg) Week 3: cont. max 4 mg/day (synthetic single-molecule THC = 4 mg)	Controlled	No absorption data reported	EORTC-QLQ-C30, VAS; weight; count of days on feeding tube or gastrostomy; independent questionnaire to evaluate appetite, nausea, count of antiemetic medication, AEs	Nabilone alone demonstrated no significant QOL improvement. Nabilone's toxicity is limited and that this medication is well tolerated by patients receiving radiotherapy treatments.
Lynch et al. 2014	Double-blind placebo-controlled pilot trial	16	Nabiximol (analgesic) *unknown*	Oromucosal spray	One spray. Titration by 1 to 2 sprays per day until they reached a dose that helped their pain; max 12 sprays	Variable	No absorption data reported	NRS-PI; Short Form-36 Health Survey (SF-36®); QST; collection of adverse	There was no statistically significant difference between the treatment and the placebo groups on the NRS-PI.

Table 2 (continued)

Author	Study type	*N*	Intervention (action) *type*	Admin	Daily dose	Dosing schedule	Pharmacokinetic data	Outcome measures	Primary outcomes
					per day dose continued over 4 weeks. Min dose: 2.7 mg THC: 2.5 mg CBD Max dose: 32.4 mg THC: 30 mg CBD			events; concurrent medications and changes during study	Demonstrated that nabiximols are a safe medication. There were no SAEs and the AEs experienced were mild and transient and did not lead to withdrawal from the study or discontinuation of the medication.
Duran et al. 2010	Double-blind pilot, parallel, placebo-controlled phase II clinical trial	16	Nabiximol (antiemesis) *Cannabis sativa L., leaf and flower*	Oromucosal spray	Titrate to 3 sprays over 2-h period; Over 4 days titration up to 8 sprays within any 4-h period every 24 h Min dose: 2.7 mg THC: 2.5 CBD Max dose: 29.6 mg THC: 120 mg CBD	Variable	Five blood samples were collected from each patient in heparinized tubes, centrifuged, with plasma was stored at − 20 °C until analysis. Three samples were collected at time 0 (basal), 60 and 240 min on day 0.	Plasma concentrations of THC, CBD and the two metabolites of THC (11-OH-THC and THC-COOH) using a modified previously described method known as the trimethylsilyl derivatives by GC/MS. The lower limit of sensitivity for all compounds was 0.5 ng ml^{-1}. VAS; MANE survey	Sativex® added to standard antiemetic therapy was well tolerated and provided better protection against delayed CINV. A higher proportion of patients in the BDS group experienced a complete response during the overall observation period with no major AEs reported.
Portenoy et al. 2012	Multi-centre randomised placebo–controlled graded dose trial	263	Nabiximol (analgesic) *Cannabis sativa L., leaf and flower*	Oromucosal spray	1-week blinded dose titration period followed by 4 weeks of stable dosing; Group 1 (low dose) titrated intervention to between 1 and 4 sprays/day. Group 2 (medium dose) titrated intervention between 6 and 10 sprays/day. Group 3 (high dose) titrated to between 11 and 16 sprays/day Min dose: 2.7 mg THC:2.5 mg CBD Max dose: 43.2 mg THC:40 mg CBD	Variable within treatment arms	No absorption data reported	Daily NRS-PI via call from an interactive voice recording system (IVRS). BPI-SF, EORTC LQ-C30 Version 3,1 PAC-QOL, MADRS.15 Patients also completed a PGIC at the study termination visit.	Notable pattern of under-dosing particularly in the nabiximols treatment groups, where the proportion of patients who were not taking the targeted dose increased markedly as the target increased.
Johnson et al. 2010	Two-week randomised double-blind placebo-controlled parallel-group trial	177	Nabiximol (analgesic) *Cannabis sativa L., leaf and flower*	Oromucosal spray	Each 100 mL (2.7 mg/ml THC and 2.5 mg/ml CBD. The maximum permitted dose of all study medication was 8 actuations in any 3-h period and 48 actuations in any 24-h period. Min dose: 2.7 mg THC; 2.5 mg CBD Max dose: 129.6 mg THC: 120 mg CBD	Variable	No absorption data reported	The NRS question 'indicate your level of pain' asked 3/day. BPI-SF, and EORTC (QLQ-C30 Version 3 were completed by patients at Visit 1 and at the end of the study.	THC:CBD combination showed a more promising efficacy profile than the THC extract alone as an adjunctive for cancer-related pain.
Johnson et al. 2013	Open-label multi-centre follow-up study	43	Nabiximol (analgesic) *Cannabis sativa L., leaf and flower*	Oromucosal spray	Each 100 mL (2.7 mg/ml THC and 2.5 mg/ml CBD)	Variable	No absorption data reported	Patient diaries, BPI-SF, EORTC QLQ-C30 scores	Some patients will continue to obtain relief of cancer-related pain with long-term use of THC/CBD spray, without

Table 2 (continued)

Author	Study type	*N*	Intervention (action) *type*	Admin	Daily dose	Dosing schedule	Pharmacokinetic data	Outcome measures	Primary outcomes
					The maximum permitted dose of all study medication was 8 actuations in any 3-h period and 48 actuations in any 24-h period. Min dose: 2.7 mg THC: 2.5 mg CBD. Max dose: 129.6 mg THC: 120 mg CBD				increasing their dose of this or other pain-relieving medications over time, suggesting that the adjuvant use of THC/CBD spray in cancer-related pain could provide benefit to cancer patients
Guzman et al. 2006	Pilot phase I trial (cohort)	9	THC (anticancer) *unknown*	Intra-tum-ouraly	THC solution (> 96.5% THC, < 1.5% of its isomer D8-THC, < 0.5% butyl-THC and < 0.5% propyl-THC) was administered to the patients for different times starting at days 3–6 after surgery at a rate of 0.3 ml min with a syringe pump connected to the subcutaneous reservoir. Average 10-day cycle (repeated)	Variable	Plasma and urine concentration of THC determined daily in patients 1 and 2 during the first 7 days of administration. The concentrations of THC and two metabolites were below detection limits in all analyses performed in plasma and urine.	Fluorescence polarisation immunoassay kit (AxSYM Cannabinoid Assay, Abbott, Abbott Park, IL, USA; detection limit, 50 ng ml^{-1}), a cloned enzyme donor immunoassay kit (Microgenics CEDIA DAU Multi-Level THC, Microgenics, Pleasanton, CA, USA; detection limit, 50 ng ml^{-1}) and gas chromatography/mass spectrometry (detection limit, 10 ng ml^{-1}). Tumour cells cultures-collagenase DMEM. Western blot, confocal microscopy.	THC does not facilitate tumour growth nor decreases patient survival in this cohort of brain tumour patients expressing cannabinoid receptors.

PO peri-oral, *HS* before bed, *BID* twice daily, *QID* four times daily, *IV* intravenous, *THC* tetrahydrocannabinol, *VAS* Visual Analogue Scale, *ECOG PS* Eastern Cooperative Oncology Group Performance Scale, *AE* adverse events, *EORTC-QLQ-C30* European Organization for Research and Treatment of Cancer Quality of Life Questionnaire, *C30 NRS-PI* Pain Intensity Numerical Rating Scale, *GC/MS* gas chromatography mass spectrometry, *FAACT* Functional Assessment of Anorexia/Cachexia Therapy, *PONV* postoperative nausea and vomiting, *ESAS* Edmonton Symptom Assessment System, *MANE survey* Morrow assessment of nausea and emesis, *BPI-SF* Brief Pain Inventory-Short Form, *PAC-QOL* Patient Assessment of Constipation Quality of Life, *MADRS* Montgomery-Asberg Depression Rating Scale, *PGIC* Patient Global Impression of Change

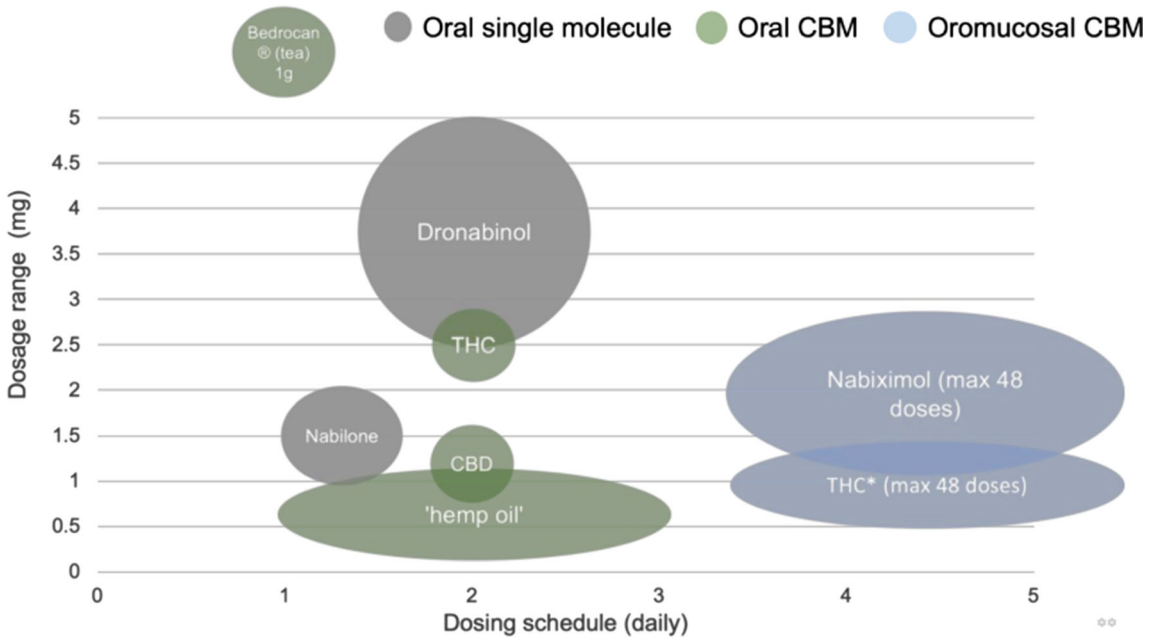

Fig. 2 Illustrative example of dosing and scheduling of medicinal cannabis in oral single–molecule medicinal cannabis, oral cannabis–based medicine (CBM) and oromucosal CBM *Tetrahydrocannabinol **Cannabidiol

($n = 1$), hemp oil extract ($n = 1$) and intratumoural injection of THC (> 96.5% THC, < 1.5% of its isomer D8-THC) ($n = 1$) investigated anticancer actions. Cannabis tea (18% THC and 0.8% CBD) was given orally in a clinical interaction study ($n = 1$).

Absorption

Of the 18 studies identified, four measured the absorption of medicinal cannabis in oncology through validated cannabinoid assays [6, 29–31]. A 2007 clinical drug interaction study measuring the interaction of medicinal cannabis tea (Bedrocan®) with the chemotherapeutic agents, irinotecan and docetaxel, concluded that at the stated dose of medicinal cannabis, no interactions were observed [29]. Urine cannabinoid levels were measured semi-quantitatively, having a threshold for detection of below 50 ng/ml (undetected) and above 50 ng/ml (detectable) to assess patient compliance to the intervention. Pharmacokinetic studies were centred on the chemotherapeutic agents to assess potential interactions [29].

A pilot phase I clinical trial investigating anticancer actions of inter-cranial delivery of THC investigated plasma and urine concentration of THC daily during the first 7 days of administration for two patients and resulted in undetectable levels of cannabinoids and metabolites [6]. A phase II clinical trial investigating chemotherapy-induced nausea and vomiting screened for plasma concentrations of THC, CBD and the two metabolites of THC (11-OH-THC and THC-COOH) [30]. CBD and THC were detected at pre-dose on day 1 for two of seven patients in the cannabis-based medicine group, and the inactive metabolite 11-nor-9-carboxy-delta-9-tetrahydrocannabinol (THC-COOH) was detected in five patients. A phase III random, double blind placebo controlled clinical trial investigating cancer cachexia that measured, although did not report the findings of urinary cannabinoid tests taken at week 0, 2, 4 and 6 [31].

Cannabinoid testing included preliminary urinary samples employing a fluorescence polarisation immunoassay kit to assess the presence of THC, CBD and THC metabolites 11-OH-THC and THC-COOH (AxSYM Cannabinoid Assay, Abbott Laboratory, Abbott Park, IL, USA; detection limit, 50 ng ml 1; TDx/FLx® cannabinoids assay; Abbott Laboratories, Abbott Park, IL). Oral fluid sample testing for the presence of metabolites 1-11-nor-Δ9-THC, THC-COOH, 11-OH-9THC, Δ8THC, cannabinol and cannabidiol (Microgenics CEDIA DAU Multi-Level THC, Microgenics, Pleasanton, CA, USA) as well as conformational gas chromatography/mass spectrometry (GS/MS).

Critical analysis

Standard critical appraisal tools from the Joanna Briggs Institute (JBI) were used to evaluate the methodological quality of articles selected for inclusion. All articles beyond one sample number were subject to differences within participant groups, and subject to confounding variables during the intervention period, including concomitant medications. Randomised control trials (RCTs) met most of the critical analysis criteria. Limitations were commonly noted due to sample size. Five of the ten in total RCTs reported sample size calculations. Three of the five RCTs that reported sample size calculations achieved the necessary sample size required to

conduct the proposed data analysis with confidence [34, 37, 44]. The remaining two RCTs either finished short due to insufficient differences between intervention and placebo [31] or did not meet sample size calculations, and as such statistical analysis was not performed for some outcomes [39]. Experimental and cohort studies measured exposure only with no control group, or own control. Case studies met all criteria of the JBI tool, reporting intervention criteria where available. All articles meet the overall criteria for the respective JBI critical appraisal tools.

Discussion

The collection and analysis of pharmacokinetic data streamlines the development of new medicines [46]. Much of what is known on the pharmacokinetics of medicinal cannabis has been determined via the examination of healthy subjects will also apply to cancer populations. For example, it is understood that differing routes of administration demonstrate varying rates of absorption, and therefore determine the dose and scheduling of a therapeutic outcome [21].

Individual tolerability to cannabinoid therapy is dependent on a number of biological parameters. These include first pass metabolism and secondary enterohepatic pathways metabolised via cytochrome P450 (CYP450) isoforms which are common metabolic pathways [47].

The lipophilic nature of cannabinoids can affect individual tolerability and therapeutic outcomes of medicinal cannabis, and when administered with fats or polar solvents, the absorption of cannabinoids is improved [21, 48]. Furthermore, the pharmacodynamics involved with previous exposure to cannabinoids can affect individual tolerability to medicinal cannabis, while individual body composition can influence the level of cannabinoids detected in plasma over an extended timeline [21]. Pharmacogenetic considerations of the endocannabinoid system also provide an insight into polymorphisms involved in cannabinoid metabolism offering a novel insight into cannabinoid therapy and individualised approach to medicine [49].

Almost all medicinal cannabis interventions reported in this review use oral-administered single-molecule cannabinoids or pharmaceutical cannabis–based medicine, the exception being two articles that reported results on inhaled and oil-based extract of non-pharmaceutical cannabis–based medicines [38, 42]. Pharmacokinetic biomarkers of cannabis use have focused on the acute administration of inhaled cannabis which may not be applicable to other routes of administration [50]. Moreover, limits of quantification (LOQ) for both invasive and non-invasive methods of detection of cannabinoids result in only the indication of the presence of limited cannabis analytes above a specified level of sensitivity [51, 52].

Pharmacokinetic data collection often involves invasive multiple sampling procedures that can raise issues concerning patient perception of non-therapeutic pharmacokinetic interventions [46, 53]. This can result in low rates of participation for these type of trials that theoretically may impact research translation in to clinical practice [53].

Clinical guidelines for the pharmaceutical medicinal cannabis interventions Marinol® (dronabinol) and Sativex® (nabiximol) recommend a low starting dose and slow titration [13, 54–56]. Dose titration is used to identify an individual dose effect and to navigate the therapeutic window of a cannabinoids to avoid adverse events [13]. However, dose titration is not without challenges and can result in prescriptive and patient under-dosing, potentially impacting on reported efficacy of the cannabis intervention and patient quality of life [13].

For example, a retrospective chart study ($n = 58$) on medicinal cannabis (dronabinol) in paediatric chemotherapy–induced nausea and vomiting reported that dose scheduling was followed in just 19% of cases, with 55 of 58 patients receiving a lower than recommended dose [40]. Furthermore, dronabinol was prescribed incorrectly as a rescue medication in 45% of cases [40]. In this instance, outcomes of a lower dose of medicinal cannabis were reported as favourable for the majority of patients (60%).

Although the role of the endocannabinoid system in cancer remains unclear, various cancer cell lines have demonstrated irregular cannabinoid receptor expression and endocannabinoid levels that vary dependent on the cancer presentation [57]. Increased expression of cannabinoid receptors has been associated with cancer aggressiveness; however, cannabinoid receptors are not reliable marker of cancer progression or predictability [7, 57, 58]. Endocannabinoids and enzymes involved in cannabinoid synthesis and metabolism similarly do not provide consistent data for use as tumour markers, or as an indication of tumour progression [57].

Cannabis-based medicines derived from whole plant extracts have an expanded phytochemical profile beyond the commonly standardised cannabinoids that has been coined the entourage effect. The synergy of constituents, including terpenoid-derived cannabis-based medicines may influence the pharmacokinetics through multi-target effects, improving bioavailability and modulating potential adverse events associated with medicinal cannabis [17, 59, 60]. Moreover, cannabis-based medicines have broadly demonstrated increased efficacy and patient compliance when compared to single-molecule cannabinoids [59, 61, 62]. The generalised outcome associated with the entourage effect does not specify what indication the CBM was prescribed for; however, in moving forward, it is an element to consider in cannabis pharmacology and patient-centred outcomes.

Determining guidelines for cannabis-based medicine, given the complexity of the phytochemical profile, and the

confounding variables of both the plant and the patient can be difficult. For example, different batches of 'hemp oil' (non-pharmaceutical cannabis–based medicine) extracted from *Cannabis indica* 'chronic'; afghan/thai strain used to treat acute lymphoblastic leukaemia (ALL) demonstrated dose- and batch-dependent positive response in the reduction blast cells count—a biomarker of ALL [42]. Nuances within the confirmation of cannabis species have lead experts to argue that without biochemical analysis of individual plants within the species, claims, for example that *Cannabis indica* has a higher CBD to THC ratio when compared to *C. sativa* have no scientific validity [63].

Potential complementary effects of medicinal cannabis with first-line treatments in oncology have been reported in preclinical studies. Reduced therapeutic resistance and enhanced chemosensitivity to antineoplastic agents in glioblastoma multiforme cell lines has been observed with CBD treatment, while a THC and CBD combination induced glioma cell death and anti-proliferation of tumour xenografts in combination with the antineoplastic agent, temozolomide [64, 65]. Similarly, CBD has been shown to enhance the anticancer effects of radiation [66, 67]. To date, only one clinical study has investigated the pharmacological interactions of antineoplastic agents with a medicinal cannabis tea, Bedrocan® [29].

Limitations

A number of conference papers were identified that met the required inclusion criteria; however, these were not included without further peer reviewed publication being available. Date restriction due to the exclusion of articles previous to 2000 in order to reflect a consistent pharmacological understanding of the endocannabinoid system may have limited the identification of absorption studies. Guidelines on pharmacokinetic studies, including subject participation, particularly among paediatric population, may have limited potential absorption studies. Heterogeneity of participants and small study numbers may have limited the statistical significance of primary outcomes.

Conclusion

A lack of clear biomarkers and an ability to accurately assess what the body does to the drug on administration of medicinal cannabis makes it difficult to establish clarity for precise individual dosing and scheduling. Similarly, biomarkers are lacking in terms of disease state and the modulatory effect of medicinal cannabis on the endocannabinoid system. As access to medicinal cannabis increases, the continued understanding of the complex pharmacology of this plant and the ability to modulate the endocannabinoid system can best inform prescriptive practices and support patient centred outcomes in cancer populations.

This review highlights gaps in the literature reporting medicinal cannabis dosage and prescriptive practices in oncology that may impact efficacy investigations and patient quality of life. Evidence from this review suggests future studies should emphasise investigations into the administration, dosing schedules and absorption of medicinal cannabis to further explore its application in cancer management. The context of this knowledge will allow a better assessment of the efficacy of medicinal cannabis in oncology.

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Compliance with ethical standards

Ethical statement This article does not contain any studies with human participants or animals performed by any of the authors.

Conflict of interest The first author is a recipient of tuition scholarship for Honours candidature (Endeavour College of Natural Health, Australia) from FIT-BioCeuticals Ltd. The authors have full control of all primary data and agree to allow the journal to review the data if requested.

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