Expert Opinion on Investigational Drugs

ISSN: 1354-3784 (Print) 1744-7658 (Online) Journal homepage: https://www.tandfonline.com/loi/ieid20

Cannabis for cancer – illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology

Ilit Turgeman & Gil Bar-Sela

To cite this article: Ilit Turgeman & Gil Bar-Sela (2019) Cannabis for cancer – illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology, Expert Opinion on Investigational Drugs, 28:3, 285-296, DOI: 10.1080/13543784.2019.1561859

To link to this article: https://doi.org/10.1080/13543784.2019.1561859

EXPERT OPINION ON INVESTIGATIONAL DRUGS
2019, VOL. 28, NO. 3, 285–296
https://doi.org/10.1080/13543784.2019.1561859

Taylor & Francis
Taylor & Francis Group

REVIEW

Cannabis for cancer – illusion or the tip of an iceberg: a review of the evidence for the use of Cannabis and synthetic cannabinoids in oncology

Ilit Turgeman[a] and Gil Bar-Sela[b,c]

[a]Division of Oncology, Rambam Health Care Campus, Haifa, Israel; [b]Center for Malignant Diseases, Emek Medical Center, Afula, Israel; [c]Faculty of Medicine, Technion-Israel Institute of Technology, Haifa, Israel

ABSTRACT

Introduction: A flowering plant of variegated ingredients and psychoactive qualities, Cannabis has long been used for medicinal and recreational purposes. Regulatory approvals have been gained across a broad range of palliative and therapeutic indications, and in some cases, included in standard treatment guidelines.

Areas covered: The use of Cannabis and cannabinoid-based-medicines in oncology is summarized in this article. Cannabinoids are classified according to natural and synthetic subtypes and their mechanisms of action expounded. The variability of available products is discussed in the clinical context and data regarding chemotherapy-induced nausea and vomiting, cancer-related pain, anorexia, insomnia, and anxiety are presented. Moreover, immunological and antineoplastic effects in preclinical and clinical trials are addressed. Concepts such as synergism or opposition with conventional treatment modalities, the sequence of administration and dosage, molecular cross-talk and malignancy-cannabinoid congruence, are explored. Finally, side-effects, limitations in trial design and legislation barriers are related.

Expert opinion: Sufficient evidence supports the use of Cannabis for palliative indications in oncology; however, patients should be carefully selected, guided and followed. Promising research suggests the potent antineoplastic activity, but more data must be accrued before conclusions can be drawn.

ARTICLE HISTORY
Received 5 June 2018
Accepted 17 December 2018

KEYWORDS
Cannabis; medical marijuana; cancer; nausea and vomiting; pain; palliative oncology; anti-neoplastic; immunology; drug interactions

1. Introduction

1.1. History of Cannabis use for medicinal and recreational purposes

Cannabis has been used as a healing herb and mild-altering drug since ancient times. In the 28th century B.C., Chinese Emperor Shen Nung prescribed Cannabis for ailments involving the loss of *yin*, such as malaria, constipation, rheumatism and absentmindedness, to heal the body by restoring harmony between opposing forces *yin* and *yang*. Centuries later the Greek historian Herodotus chronicled Cannabis-based burial customs, while Indian folklore called it the 'drink of warriors.' [1] With the advent of Cannabis cultivation in the New World, the burgeoning plant became a prosperous cash crop, used in clothing, rope, and paper. Moreover, it registered in the American Pharmacopeia in the late 19th century for a broad range of indications, but with cautions regarding 'alarming effects' associated with overdose [1]. Thereafter, rising tensions among physicians and law-makers led to restrictions on Cannabis use in the form of tariffs and strict registration requirements, until ultimately the Controlled Substances Act in 1970 assigned Cannabis Schedule I status, alongside heroin and lysergic acid diethylamide [2].

1.2. Modern approvals of Cannabis and cannabinoid-based medicines (CBMS)

The political landscape has since undergone many changes. In the United States, medical marijuana has been legalized in 28 states and Washington, DC, and recreational marijuana made legal in eight states and Washington, DC [2]. Approval has also been gained in Canada, Israel, Austria, Belgium, Bulgaria, Croatia, Cyprus, Czech Republic, Denmark, Estonia, Finland, France, Germany, Greece, Hungary, Iceland, Ireland, Italy, Latvia, Lithuania, Luxembourg, Malta, Netherlands, Norway, Poland, Portugal, Romania, Slovakia, Slovenia, Spain, Sweden, Switzerland, and the United Kingdom Estonia [3]. Countries have facilitated patient access while conducting clinical trials and studies in parallel. Substantial literary evidence has led to regulatory approvals of Cannabis and CBMs in chronic pain, chemotherapy-induced nausea and vomiting (CINV), multiple sclerosis, spasticity, and more recently, intractable seizures [4]. Studies demonstrate benefit in a wide range of conditions such as prevention of graft versus host disease after stem cell transplantation [5] inflammatory bowel disease, [6] fibromyalgia, arthritis, sleep problems, appetite, and weight loss, anxiety, Tourette syndrome, cancer and others [2].

This Review aims to provide a thorough investigation of the therapeutic use of Cannabis in oncology. Much information is yet to be elucidated concerning the benefits and risks of the controversial drug, as high-quality clinical trials are too few and hardly standardized. We first summarize its mechanisms of action and discuss current CBM formulations and routes of administration. We then explore its utility in five palliative indications, namely CINV, cancer-related pain, anorexia, insomnia, and depression. We move on to the anti-neoplastic and immunological properties of Cannabis as single agent therapy

CONTACT Gil Bar-Sela gil_ba@clalit.org.il Center for Malignant Diseases, Emek Medical Center, Yitzhak Rabin Blvd. 21, Afula 1834111, Israel

Article highlights

- Cannabis has historically been used as a healing herb and mild-altering plant and is currently approved in many countries for recreational and medicinal use.
- Favorable outcomes are shown in chemotherapy-induced nausea and vomiting and cancer pain, with evidence of advantageous neurological interactions.
- Cannabinoids have shown antineoplastic effects in preclinical studies in a wide range of cancer cells and some animal models, and distinct signaling pathways are implicated in these results.
- Conflicting reports show that Cannabis contains immunosuppressive properties and oncogenic potential.
- Combining Cannabis with conventional cancer treatment modalities may cause enhancing or diminishing effects.
- Research is hampered by high variability and lack of standardization in trial construction and drug formulation and pharmacodynamics.
- Clinical trials and in-depth drug and patient analyses are needed to find the right constellation of drug composition, dose, and means of administration, to tailor specific Cannabis-based medicine per indication and per patient.

or adjunct, from basic research to formal clinical trials. We conclude with a description of adverse effects as well as the barriers and limitations of Cannabis research today.

2. How it works

2.1. Description of cannabinoids and mechanism of action on the body

Cannabinoids are classified according to their source of production: synthetic cannabinoids are manufactured for use in research and development of therapeutic agents; phytocannabinoids occur naturally in the Cannabis plant; and endocannabinoids (eCBs) such as N-arachidonoyl ethanolamide (AEA, anandamide) and 2-arachidonoyl glycerol (2-AG) are produced endogenously by humans and other mammals. Cannabinoid types are delineated in Figure 1.

Synthetic analogs include both classical and non-classical agents or those structurally similar to eCBs and others with chemically different properties. In addition to mimicking the effects of eCBs, alternative approaches to influence the endocannabinoid system include receptor agonist/antagonism and inhibition of degradation [7].

Cannabis is a genus of flowering plant that includes species *sativa, indica*, and *ruderalis*. Indigenous to central Asia and India and cultivated in tropical and equatorial regions, Cannabis comes in the form of marijuana, or dried flower buds, and hashish, blocks of resin. Unique qualities of each Cannabis variety, or chemovar, derive from three bioactive molecules: flavonoids, terpenoids, and cannabinoids. Relative proportions of the nearly 100 different cannabinoids determine the psychoactive potency of a Cannabis plant, the two most well-known of these being delta-9tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), others including cannabinol, tetrahydrocannabivarin, and cannabigerol [8,9].

Individual cannabinoids exert their pharmacological effects by stimulating the endogenous cannabinoid system and altering levels of eCBs or neurotransmitters that derive from arachidonic acid and contribute to physiological and cognitive processes such as reward, motivation, memory, learning, and pain processing [9]. Δ^9-THC and CBD display a range of opposing biological effects, as the former acutely impairs learning, contains psychoactive qualities and increases anxiety, whereas the latter can enhance learning and lessen psychosis and anxiety [9].

The endocannabinoid system is comprised of G-protein-coupled cannabinoid receptors 1 and 2 (CB_1 and CB_2) that exhibit 44% overall homology and modulate a variety of signaling pathways. Depending on their interaction with cannabinoids, they generally inhibit adenylate cyclase, stimulate

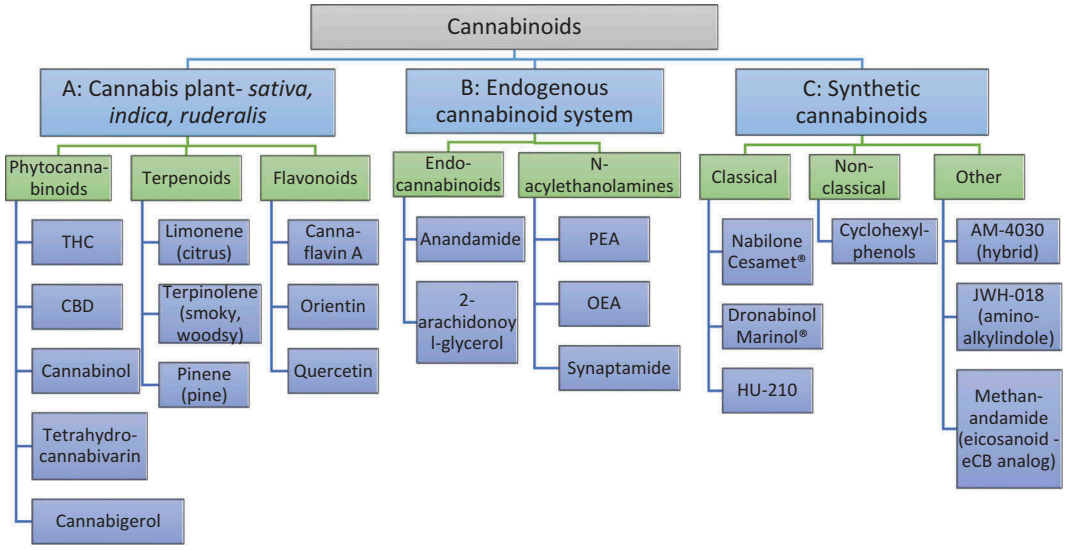

Figure 1. Classification of cannabinoids by system and select bioactive molecules.

A: A cannabis plant contains varying compositions of bioactive phytocannabinoids alongside the aromatic terpenoids and flavonoids.B: Endogenous endocannabinoids are a part of a complex signaling system of distinct receptors and enzymes, located in the mammalian nervous system.C: Cannabinoids formulated to stimulate endocannabinoid receptors in the body are divided into five main categories: classical cannabinoids are THC analogs, non-classical cannabinoids are used recreationally or for potential medication, hybrid forms contain structural similarities to both classical and non-classical preparations, aminoalkylindoles are easier to synthesize and dissimilar to THC, and eicosanoids are endocannabinoid analogs.THC: delta-9tetrahydrocannabinol; CBD: cannabidiol; PEA: Palmitoylethanolamide; OEA: oleoyl-ethanolamide; eCB: endocannabinoid

mitogen-activated protein kinases, and CB_1 receptors are also known to modulate calcium and potassium channels [10]. These receptors are widely distributed throughout the body. CB_1 receptors are the most abundant and extensively found in the central nervous system, affecting circulation and psyche; CB_2 receptors mostly occur on immune cells, including leukocytes, spleen, and tonsils, causing enzymatic hydrolysis by the fatty acid hydrolase and monoacylglycerol lipase [8]. As lipid-based retrograde neurotransmitters, eCBs are synthesized 'on demand' and generally released from a post-synaptic cell to act on a pre-synaptic cell, where dense target receptors are temporarily prevented from releasing conventional neurotransmitters. Therefore, the ultimate net effect depends on the specific neurotransmitter that is blocked, for instance, increased excitability by blockage of GABA or decreased excitability by blocking glutamate [8]. Recent data suggests newer members of the endocannabinoid system to be non-eCB orphan receptors GPR55 and GPR18 [11]. In addition, non-endocannabinoid N-acylethanolamines, namely palmitoylethanolamide (PEA) and oleoyl-ethanolamide (OEA), exhibiting anti-inflammatory and anorexic activity, respectively, are also known to bind into the eCB system [12].

2.2. Formulation and administration

Cannabinoids may be extracted naturally from the plant and taken in herbal form or else they can be manufactured synthetically. They can be mixed with food or tea, inhaled, smoked or injected. Absorption, distribution, metabolism, and excretion of Cannabis varies according to drug formulation and route of administration.

2.2.1. Oral route

Oral Cannabis formulations – including oils, capsules, edibles or spray – are convenient, generally easy to dose and have a long duration of action of up to 8 h. However, onset is slow (one to 3 h) and absorption may be erratic and dependent on multiple variables. For instance, absorption may be reduced with food or enhanced with lipid or oil solvents [13]. To date, three synthetic CBMs are available for marketing: dronabinol and nabilone are analogs of Δ9-THC and used in treating CINV [3,14]. The third approved CBM, nabiximols oromucosal spray, contains a 1:1 mixture of Δ^9-THC and CBD isolated directly from Cannabis sativa, which bypasses gastrointestinal metabolism and thereby is more rapidly absorbed sublingually. Extensively researched, it is approved for treatment of neuropathic pain and symptoms of multiple sclerosis. Additional CBMs include a form of dronabinol containing pure Δ9-THC in a formulation that uses emulsifying drug delivery technology. Cannabidiol is an oral extract formulation of CBD with anticonvulsant properties [15].

2.2.2. Inhaled route

Smoking remains the most common and most rapid route of Cannabis administration, with an onset of action of up to 10-min and a duration of two to 4 h, especially helpful for the treatment of acute symptoms. However, combustion at extremely high temperatures produces toxic byproducts, and chronic use is associated with respiratory symptoms [13]. Patients are also more likely to develop side effects due to the dexterity required in self-titration, with variability in depth, duration, and intervals of inhalation and breath holding; they are thereby instructed to wait 15 min after the first inhalation and add subsequent inhalations in 15–30-minute intervals until the required symptom control is achieved [13]. Vaporizers are safe and efficient devices that are temperature controlled and electronically driven to decarboxylate inactive cannabinoids are release active potent cannabinoid compounds [16]. A novel thermal-metered-dose device for Cannabis showed positive results in a phase Ia study of patients with neuropathic pain, proposing a smokeless and more precise means of Cannabis delivery [17].

3. What it does – palliative indications in oncology

3.1. Chemotherapy-induced nausea and vomiting

Emesis results from stimulation of complex reflex pathways controlled by the brain. Neurotransmitters such as dopamine, histamine, acetylcholine, serotonin, and substance P are common targets for anti-emetic medicines, each affecting a distinct aspect of the emetic pathways [18]. Endocannabinoid receptors richly populate these very neuronal tracts, thereby signifying an additional target for treating CINV. The dorsal vagal complex is a region in the brain associated with gastrointestinal function and pathophysiology, and at the root of emesis regulation. This region includes the area postrema, the nucleus of the solitary tract (nTS) and the dorsal motor nucleus of the vagus, and contains vagal outputs in the gastrointestinal tract – all of which contain CB-1 receptors that have demonstrated anti-emetic effects when activated by Δ^9-THC [18]. In contrast, serotonin agonists that induce nausea have shown opposite effects on the nTS compared to Δ^9-THC [19]. Located just outside the blood-brain barrier in the fourth ventricle of the brain, the area postrema provides direct communication between blood-borne signals such as chemotherapy and the autonomic neurons that elicit emesis [18].

CBMs are increasingly incorporated in the drug arsenal for management of CINV. Dronabinol and nabilone were approved by the FDA for refractory nausea and vomiting and are included in the most recent NCCN guidelines for antiemesis [20]. In a meta-analysis of 30 randomized controlled trials (RCTs) by Machado et al. investigating synthetic Δ^9-THC in cancer patients receiving chemotherapy, dronabinol demonstrated superior anti-emetic activity to neuroleptics, while other CBMs had a clinical but not statistical advantage [21]. Two other systematic reviews comparing Δ9-THC-derived drugs to older anti-emetics in first-line therapy demonstrated greater effectiveness of cannabinoids, especially in medium-emetogenic chemotherapy regimens [22,23], however, a more recent comprehensive meta-analysis found the high risk for bias and taken together, low-quality evidence for improvements in CINV [24]. A synergistic effect for dronabinol and prochlorperazine was shown in an RCT by Lane et al., with a reduction in occurrence, duration, and severity of CINV among patients receiving chemotherapy [25]. Meiri et al. undertook a blinded, placebo-controlled comparison between

CBMs and 5-HT_3 antagonists, and determined non-inferiority for dronabinol, though synergism with ondansetron was not achieved [26]. A phase II study investigated nabiximols in 16 patients and found that 4.8 sprays daily was more effective than placebo in conjunction with standards antiemetics [27]. CBMs have anecdotally shown greater activity in suppressing anticipatory nausea than 5-HT_3 antagonists in animal studies [28]. Data comparing CBMs to newer antiemetics is lacking and an important area of investigation, as is the potential advantage of smoked marijuana in treating CINV.

3.2. Cancer-associated pain

Cannabis has long been used for its analgesic purposes. CB-1Rs in the hippocampus and associational cortical regions, the cerebellum, and the basal ganglia consist of remarkably similar neuroanatomical, neurochemical and pharmacological characteristics to receptors of the opioid system. They are thought to modulate nociceptive processing in the brain, independently and in synergism with exogenous opioids [29]. CB-2Rs located in areas of intense nociceptive integration such as dorsal root ganglion sensory neurons and the spinal cord may also have a role in analgesia; in neuropathic pain models, they have been shown to stimulate the release of beta-endorphins and reduce C-fiber activity. Moreover, peripheral cannabinoid receptors have been implicated in anti-nociception by activation of noradrenergic pathways [29].

Accumulating research suggests potency of CBMs in pain relief, particularly neuropathic pain and as a therapeutic adjunct to other analgesics. Large studies have enrolled diverse patient populations and often found positive results [30] especially in neuropathic pain [31], but only a handful included those with cancer-related pain, making it difficult to assess their specific efficacy. One review of 28 RCTs did incorporate three trials with cancer patients and concluded moderate-quality evidence to support the use of CBMs in chronic pain without clear distinction according to type of pain (cancer or otherwise) [24]. Data, therefore, is mostly taken from individual trials. Already in 1975, Noyes et al. demonstrated, with a small sample size, that high doses of Δ^9-THC were significantly superior to placebo in pain reduction and comparable to codeine, however, were associated with considerable sedation [32]. Since then numerous trials have examined the analgesic effects of Δ^9-THC/CBD preparations on subjects with opioid-refractory cancer pain. Portenoy et al. found a higher proportion of patients reporting analgesia with low and medium dose nabiximols than placebo, while poor drug tolerability was noted in the high dose group [33]. Johnson et al. found superior pain relief in patients treated with Δ^9-THC/CBD as opposed to Δ^9-THC alone or placebo, which was sustained for as long as two years without need for elevations in opioid dosages [34]. Similarly, Bar-Sela et al. performed an observational study evaluating patient-reported cancer-related symptoms while on CBMs and found not only pain lessening but also reduction in opioid dose in close to half of the subjects [35].

3.3. Anorexia and cachexia syndrome

Early reports of increased appetite and weight stability in HIV/AIDs patients using dronabinol [36] sparked a wave of research in oncology. Anorexia and cachexia in cancer patients refer to a spectrum of metabolic changes that begins with reduced caloric intake and variable degrees of inflammation and progresses to a refractory, pro-catabolic state linked to low performance and short survival. Jatoi et al. randomized nearly 500 patients to receive dronabinol or megestrol acetate for cancer-associated anorexia and had significant findings in favor of megestrol [37]. A subsequent large, multicenter phase III trial by the Cannabis-In-Cachexia-Study-Group comparing Δ^9-THC to Δ^9-THC+CBD to placebo found no significant improvements in survival, weight, or other nutritional variables [38]. Cannabis has, however, been associated with improved taste, smell and food enjoyment [39].

3.4. Insomnia

A large meta-analysis by Whiting et al. reviewed 19 studies that evaluated sleep as an outcome as well as two trials specifically investigating sleep problems and found a positive association between cannabinoids and improved sleep quality. The study cohort included patients with chronic pain and multiple sclerosis; thus, implications for cancer patients are not certain [24].

3.5. Depression and anxiety

In the aforementioned meta-analysis, no trials evaluating depression fulfilled inclusion criteria. In the five trials of non-cancer patients where depression was reported as an outcome measure, no difference was found compared to placebo, with the exception of a negative effect for high dose nabiximols in one. Positive results were found, however, in individuals with the social anxiety disorder, as well as in anxiety outcomes in patients with chronic pain [24]. Figure 2 outlines the four aforementioned major palliative indications of cannabinoids in oncology as well as therapeutic uses that will be discussed in the next section.

4. What we know – basic research in oncology

4.1. Anti-cancer effects

Stimulation of the eCB system leads to a cascade of cellular activity affecting sodium and potassium ion channels, production of cyclic adenosine monophosphate (cAMP) and modulation of members of mitogen-activated protein kinase families (MAPKs), like extracellular signal-regulated kinase-1 and 2, p38,

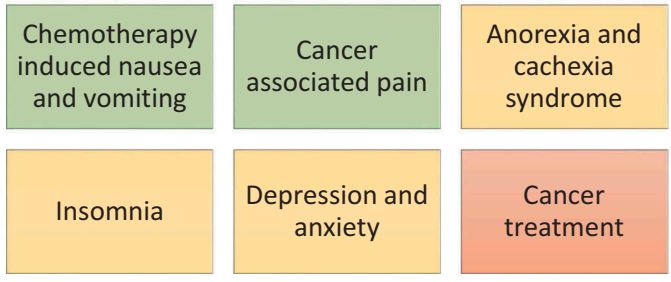

Figure 2. Indications in oncology: strong evidence for treatment of CINV and cancer-related pain (green); weak evidence for weight gain, sleep and mood disorders (yellow); no significant clinical evidence for cancer treatment (red).

MAPK, and c-Jun N terminal kinase [40]. Robust evidence has shown the heightened activity of eCB signaling pathways and increased expression of eCB receptors in various cancer types, often in correlation with prognosis [40].

Preclinical models propose that cannabinoids contain anti-oncogenic effects, notably by inhibition of tumor proliferation, vascularization, and metastasis. The cannabinoids cannabidiol, AEA, 2-AG and endocannabinoid transport inhibitors have been shown to induce cancer cell death through apoptosis and to inhibit proliferation and migration in numerous murine and human tumor cell lines including glioma, oligodendroglioma, glioblastoma multiforme, astrocytoma, neuroblastoma, breast cancer, prostate cancer, colon carcinoma, uterine cervix carcinoma, thyroid cancer, leukemia and lymphoid tumors; additional research has shown inhibited growth *in vivo* in murine models of lung carcinoma, glioma, thyroid epithelioma, lymphoma, and skin carcinoma. [41]

Conflicting reports have shown oncogenic cannabinoid activity as well. Hart et al. demonstrated that while high concentrations of cannabinoids have antiproliferative effects on tumors, treatment of lung, brain and genitourinary carcinoma cell lines with low concentrations results in rapid epidermal growth factor receptor and metalloprotease-dependent cancer cell proliferation [42]. In cholangiocarcinoma cell lines, while anandamide shows an *in vitro* antiproliferative effect, 2-AG stimulates growth, and the effects are apparently due to stabilization of lipid rafts and not mediated by CB receptors [43]. Finally, multiple studies report pro-cancer effects of cannabinoids in association with immunological mechanisms, as will be further discussed below.

Several well-studied cell signaling pathways and biological processes are implicated in the connection between the eCB system and cancer. Importantly, the pathways associated with cyclic adenosine monophosphate, mitogen-activated protein kinase, protein kinase B, ceramide accumulation, reactive oxygen species, Id-1, tissue inhibitor of matrix metalloproteinase-1, and the epidermal growth factor family of protein ligands will be reviewed. Cancer stem cells and the biological interaction between cannabinoids and conventional oncological agents will be discussed as well.

4.1.1. Cyclic adenosine monophosphate (cAMP)

CAMP is a second messenger used for intracellular signal transduction that is key to many biological processes, such as transferring hormones like glucagon and adrenaline as well as activating protein kinases. The cannabinoid cannabidiolic acid has been shown to inhibit migration of breast cancer cell lines via inhibition of cAMP-depended protein kinase A, alongside activation of a small GTPase – suggesting a role in inhibition of metastatic spread [44].

4.1.2. Mitogen activated protein kinase (MAPK)

This signaling pathway causes the activation of transcription factors needed for cell growth, proliferation, and survival. Activation of $CB_1/_2$ receptors demonstrates modulation of the MAPK pathway. AEA inhibits adenylate cyclase, activating the Raf/ERK/MAP pathway in ER+/PR+ breast cancer cells [14]. Leukemia and lymphoma subtypes are known to overexpress endocannabinoid receptors. Studies have shown that the addition of Δ9-THC to cytotoxic agents induces apoptosis by MAPK/ERK pathway [45]. Finally, gastric cancer cell lines show decrease in cell viability and proliferation after cannabinoid agonist administration, via G1 cell cycle arrest mediated by MAPK and Akt pathways [46].

4.1.3. Protein kinase b (Akt)

This serine/threonine kinase is responsible for inhibition of apoptosis and stimulation of cell proliferation. Inhibition of this pathway is implicated in numerous mechanisms of cannabinoid-induced antineoplastic effects in breast, prostate, lung, and skin cancer models [47]. Modulation of Akt has a central role in apoptosis, anti-proliferation, anti-angiogenic and anti-invasive effects in breast cancer cell lines treated with cannabinoids and selective cannabinoid agonists [48]. In lung cancer, selective agonists inhibit *in vitro* chemotaxis and chemoinvasion and *in vivo* tumor growth and lung metastasis, by inhibiting Akt and matrix metalloproteinase 9 expression, and these effects are reversed with selective antagonists [49]. Inhibition of Akt alongside ERK 1/2 is implicated in glioma [50] and prostate [51] cell lines.

4.1.4. Ceramide

Ceramides are a family of lipid molecules found within cell membranes that take part in regulating differentiation, proliferation and programmed cell death of cells. Cell lines of prostate cancer treated with the cannabinoid AEA demonstrated accumulation of ceramide alongside downregulation of epidermal growth factor, and a CB_2 agonist triggered its de novo synthesis, leading to induction of cell death [52]. Ceramide also has a role in cannabinoid-induced apoptosis in pancreatic cancer cell lines via the CB_2 receptor and ceramide dependent gene upregulation [53]. Additionally, antineoplastic effects of cannabinoids on gliomas appear vitally tied to ceramide levels. Highly aggressive, malignant and treatment-resistant brain tumors, gliomas express endocannabinoid receptors abundantly and are thereby common targets for cannabinoid research. Studies have shown that growth inhibitory effects of both selective and nonselective agonists are prevented by blocking ceramide synthesis [54]. Lastly, apoptosis associated with ceramide accumulation is also implicated in lymphoma cell lines [55].

4.1.5. Reactive oxygen species (ROS) and id-1

ROS is a key by-product of energy metabolism in the mitochondria and its increased production has been associated with inducing apoptosis. Id-1 modulates the metastatic potential of various malignancies by inhibiting basic transcription factors. CBD regulates ROS pathways, causing downregulation of Id-1 expression. The cannabinoid arachidonoyl cyclophosphamide induces AMPK-mediated autophagy in pancreatic cancer cell lines, in association with a ROS-dependent increase of AMP/ATP ratio, thus inhibiting energy metabolism [56]. Reduction in tumor mass as well as number and size of metastatic foci, in a mechanism involving ROS, Id-1, and ERK, is also shown in mammary metastatic cell lines after CBD administration [57]. Activation of CB_2 receptors by a CBD analog reduces gene expression of Id-1, associated with breast cancer metastases, and also increases survival [58]. Moreover, cannabidiol has

been shown to downregulate expression of the Id-1 gene along with associated glioma cell invasiveness and self-renewal, as well as glioma progression *in vivo* [59].

4.1.6. Tissue inhibitor of matrix metalloproteinase-1 (TIMP-1)

TIMP is a calcium-dependent zinc-containing endopeptidase capable of degrading extracellular matrix proteins and is thought to play a key role in cell proliferation, migration, angiogenesis, and apoptosis. It is upregulated in invasive cancer cell lines treated with cannabinoids both *in vitro* and *in vivo* in association with inhibition of cell invasion [60].

4.1.7. Epidermal growth factor (EGFR) family

The EGFR family of extracellular protein ligands includes the receptor tyrosine kinases EGFR, human epidermal growth factor receptor 2 (HER2/Neu), Her 3, Her 4. EGFR is an important transmembrane protein, as mutations in its expression may result in cancer, and inhibition of its signaling pathways prevent tumor spread. Fatty acid amide hydrolase (FAAH), a serine hydrolase that metabolizes N-acylethanolamines like AEA, OEA, and PEA, is known to be overexpressed in certain cancer cells and its inhibition can enhance patient survival. Blockage of FAAH raises the level of AEA, inhibiting the EGFR signaling pathway and leading to cell arrest and apoptosis [61]. Both *in vivo* and *in vitro*, activation of CB2 receptors decreased migration and invasion of estrogen positive and negative breast cancer cells by suppressing EGFR and insulin-like growth factor tumorigenic pathways [62].

HER2/neu is a protein kinase oncogene with a role in the development and progression of certain types of cancer, most notably breast cancer. When amplified or overexpressed, it is a potent biomarker and target for treatment. More than 90% of HER-2-positive tumors were found to overexpress CB_2 receptors, in correlation with poor prognosis, as opposed to better prognosis in other forms of breast cancer with CB_2 receptors [63].

4.1.8. Cancer stem cells (CSC)

CSCs are distinct tumorigenic cells found within tumors that possess the ability to give rise to all cell types. They are thought to persist despite treatment and cause relapse and metastasis. Cannabinoid receptors may be involved in the differentiation of neural progenitors. $CB_{1/2}$ receptor activation modulates proliferation of daughter progenitors, as cannabinoids were shown to induce cytotoxicity in embryonal carcinoma cells [64]. Similar results were shown in glioma stem-like cells, where cannabinoids helped in neural differentiation and blocked CSC mediated gliomagenesis [65].

Fiore et al. created 3D cultures of primary colon CSC and showed strong synergism between rimonabant, an inverse agonist of CB_1 receptors, with 5-fluorouracil in HTC_{116} cells, as well as slightly increased 5-fluorouracil efficacy but antagonism with oxaliplatin in GTG7 cells [66].

4.1.9. Synergism between cannabinoids and conventional cancer treatment

The use of cannabinoids in conjunction with chemotherapy was explored in leukemia cell line models and found to have improved oncological potency when chemotherapy preceded cannabinoid use as opposed to chemotherapy alone or in the reverse order [67]. When administered with the chemotherapeutic agent gemcitabine, synergistic inhibition of pancreatic adenocarcinoma cell growth was shown by a ROS-mediated autophagy [68]. In gastric carcinomas, AEA enhanced the pro-apoptotic effect of paclitaxel [69]. Moreover, cannabinoids modulate the expression of ABC efflux pumps responsible for resistance to chemotherapy [70], thereby suggesting a potential role in increasing sensitivity to chemotherapy. Holland et al. demonstrated that the administration of Δ9-THC and CBD potentiates the cytotoxicity of vinblastine via this very mechanism [71]. Finally, cannabinoids were found to enhance efficacy when combined with irradiation in a murine glioma model, suggesting CBMs prime glioma cells to respond to ionizing radiation or that they prevent oxidation damage [72].

4.2. Immunological effects

Cancer growth and development is rooted in inflammation and immunology, and immunotherapy has become an emerging pillar of cancer care. A large body of evidence from preclinical animal models confirms the immunosuppressive properties of cannabinoids, specifically through activation of peripheral CB_2 receptors on splenic macrophages, B-lymphocytes and nerve terminals, causing T-cell suppression. Researchers found suppressed splenic T-cell responses after Δ9-THC administration, and reduced ability to respond to T-cell mitogens. Multiple reports demonstrate differential suppression of CD8 T-cells [73]. In brain tumor models, CB_2 agonists cause downregulation of inflammatory pathways such as NP-kB, reduction of cytokines like IL-2, TNF alpha, INF-gamma in T lymphocytes and inhibition of adhesion molecules and chemokines [47]. McKallip et al. found that Δ9-THC increases tumor growth in breast carcinoma cell lines by suppression of the anti-tumor immune response, notably a malignancy with low expression of cannabinoid receptors in most subtypes [74]. Similarly, by activating CB_2 receptors, Δ9-THC increases production of IL-4 and IL-10, stimulating a Th-2-type immune response and inhibiting the Th-1 response, resulting in a pro-cancer effect [75].

5. Human studies with Cannabis – is it possible?

5.1. Cannabis as an anti-cancer agent

Despite extensive preclinical research and data, antineoplastic efficacy in humans is still mostly anecdotal. Basic and preliminary studies alongside accumulating case reports support the need for large formal RCTs, especially in the treatment of brain tumors and leukemia. In a pilot phase I trial in 2006 where intracranial Δ^9-THC was used on nine patients with refractory glioblastoma multiforme (GBM), drug delivery was safe and in two patients, associated with decreased proliferative biomarker expression [76]. In 2011, an article reported spontaneous regression of incompletely resected astrocytomas in two teenagers who were regular consumers of cannabis, and suggested the possible role of cannabis in tumor regression, based merely on the temporal correlation [77]. In 2013, another article reported the case of a child with acute lymphoblastic leukemia for whom different cannabis preparation appeared to have a dose-dependent effect on the number of circulating blasts [78]. More recently, a Phase 2 placebo-

controlled study examining a Δ9-THC: CBD [1:1] preparation given in conjunction with temozolomide (TMZ) in 21 patients with recurrent GBM found that the drug was well tolerated and associated with survival advantage, however, the early findings in 2017 have yet to be formally published in a peer-reviewed article [79]. Another phase 1/2 study in a similar patient population assessed concomitant administration of nabiximols and TMZ but has not yet reported results [80]. Finally, two Phase I trials tested dexanabinol, a synthetic cannabinoid derivative that acts as an NMDA receptor antagonist, in patients with advanced solid tumors and brain cancer, respectively, and these, too, have not yet reported results [81,82].

5.2. Immune modulation and interaction with immunotherapy

Ensuing strong data taken from animal models, human studies exploring possible immunological interactions suggest that cannabinoids may suppress an active or overactive immune system [2]. Researchers investigated possible effects on immune competence in HIV patients and found reduced levels of CD4+ and CD8 + T-cells. Additionally, several small studies observed a decrease in the production of multiple inflammatory cytokines in healthy individuals under regular exposure to Cannabis [2]. That said, shortcomings in trial design preclude drawing reliable conclusions from data.

A recent retrospective study in our institution studied the combination of immunotherapy with cannabinoid administration. The cohort consisted of 140 patients treated with the immune checkpoint inhibitor, nivolumab, with or without simultaneous cannabinoid treatment. Two homogenous groups of patients with non-small cell lung cancer, melanoma, and renal clear cell carcinoma were included. In a multi-variant model, the authors found significantly reduced response rate to immunotherapy while using CBMs, without a difference in overall or progression-free survival, after taking into account confounders such as performance status and Cannabis composition. They suggest a possible interaction between the two treatment modalities [83].

6. And yet – limitations

6.1. Associated adverse effects

Side effects associated with cannabinoids vary largely from patient to patient and are generally mitigated by limiting drug dosage. They are generally short-term and include somnolence, nausea, dizziness, dry mouth, and disorientation, as well as euphoria, anxiety and hallucination. Memory and cognition problems, addiction, and exacerbation or provocation of nascent psychiatric illness, such as depression and anxiety disorders, have also been associated with Cannabis use [84]. A small prospective study did not find cognitive impairment in cancer patients on chemotherapy while on CBMs [85]. adverse events are mostly attributed to Δ^9-THC, while the opposing cannabinoid CBD is thought to alleviate its effects, and rather to facilitate learning, prevent psychosis and ease anxiety [9]. Street Cannabis notoriously contains high levels of Δ^9-THC and negligible CBD, in contrast to CBMs supplied for research or patient use [9].

Rare but severe events may develop in susceptible or naïve patients. Multiple reports link Cannabis consumption to cardiac toxicity, such as variability in heart rate, increased risk for myocardial infarction and other cardiovascular morbidity and mortality; these suggest reluctance in the prescription of Cannabis to patients with pre-existing heart disease or those using concomitant cardiotoxic drugs. Cannabis has also been reported to cause Cannabis hyperemesis, a variant of cyclical vomiting syndrome in the context of chronic Cannabis use, and finally toxic psychosis or paranoia [84]. A link between cannabis consumption and testicular cancer has been explored in several studies, the largest of which included 50,000 Swedish men and found higher incidence only in heavy cannabis users [86].

6.2. Potential barriers and limitations in academic research of Cannabis

A thorough investigation of research regarding Cannabis and associated drugs is hampered by high variability and lack of standardization in trial construction and drug formulation. Studies in CINV differ in timing of drug administration in relation to chemotherapy exposure, specific chemotherapy regimen, and cannabinoid composition and dosage. Furthermore, a varying pharmacokinetic profile for different cannabinoid products and subjects causes serious intra and interpatient inconsistency in terms of bioavailability of the drug, and consequently, in result interpretation. The dose delivery of smoked marijuana, for instance, varies by number and duration of inhalations and breath hold – determining the spectrum of reactions from lack of effect to toxicity. The palliative oncological patient population, in particular, may be especially vulnerable to toxicity, often exhibiting lowered muscle mass and tending to extremes in weight, resulting in unexpected pharmacodynamic interactions. Additionally, patients may limit the use of Cannabis due to stigma or lack of knowledge; conversely, others may neglect critical antineoplastic treatment in an attempt to self-medicate with Cannabis without medical monitoring. Finally, legislation barriers that accompany a drug regulated as an illicit narcotic cause difficulty in undertaking clinical research.

7. Conclusion

Cohort studies have added support to the growing body of knowledge on Cannabis use in oncology. However, these studies have many limitations. Promising data on pain, nausea and vomiting relief, as well as potential immunological and anti-cancer properties, alongside a relatively favorable safety profile, will allow for more focused research in the future. Moreover, intriguing drug interactions of which we still know relatively little should be further explored and uncovered. Meanwhile, carefully constructed clinical trials are needed to find the right constellation of drug composition, dose, and means of administration, to tailor specific Cannabis-based medicine per indication and per patient. With evolving legislation, improved education and training, and increasing availability, the effects of medical Cannabis are gradually becoming elucidated and integrating into standard, evidence-based oncology practice.

8. Expert opinion

8.1. Physician awareness of CBMs and how to prescribe

Extensive variability exists between the different cannabinoid-based products available today; starting from the quality of cannabis cultivation and relative proportions of cannabinoids to the drug formulations, routes of administration and habits of consumption [13,14]. Therefore, when a physician prescribes cannabis, there is little control over the specific product that the patient will eventually receive. Discrepancies in each step of cannabis production may make the difference between immense palliation and intolerable side effects. This lack of consistency has historically precluded the implementation of large-scale clinical trials investigating effects of cannabinoid-based products – and thereby limited the administration of cannabis as evidence-based medical practice.

Rising prevalence and demand for cannabis in recent years [3] has driven physicians to gain a basic understanding of its efficacy and side effect profile, as well as knowledge of novel mechanisms for drug delivery. A physician should prescribe cannabis only if a careful explanation can be provided, and follow up response evaluation, ensured. When starting cannabis, one should try the lowest dose and titer slowly. Oral Cannabis may be easier to dose compared with smoked Cannabis but with a longer effect and slower onset of action. Oral Cannabis contains variable bioavailability depending on the drug and patient characteristics. Smoked Cannabis should be avoided in smokers or those with lung disease due to respiratory side effects [13]. Novel mechanisms for drug delivery offer less toxic alternatives such as vaporizers or inhalers [16,17].

In oncology, sufficient evidence supports its use as add-on therapy for chemotherapy-induced nausea and vomiting to achieve a synergistic effect with conventional medicines [22], as well as for the treatment of refractory chronic or neuropathic pain [30]. Weak evidence supports use for weight gain, sleep, and mood disorders, and may certainly be given in certain populations [24]. Caution should be taken in susceptible patients, such as the elderly or those with cardiac and psychiatric comorbidities [84]. Importantly, the current state of evidence does not support the use of cannabis as an initial treatment, rather as an adjunct or advanced line of care; additionally, its use in other palliative or therapeutic indications is considered investigational, and should be described this way or reserved for clinical research trials [20]. It should be

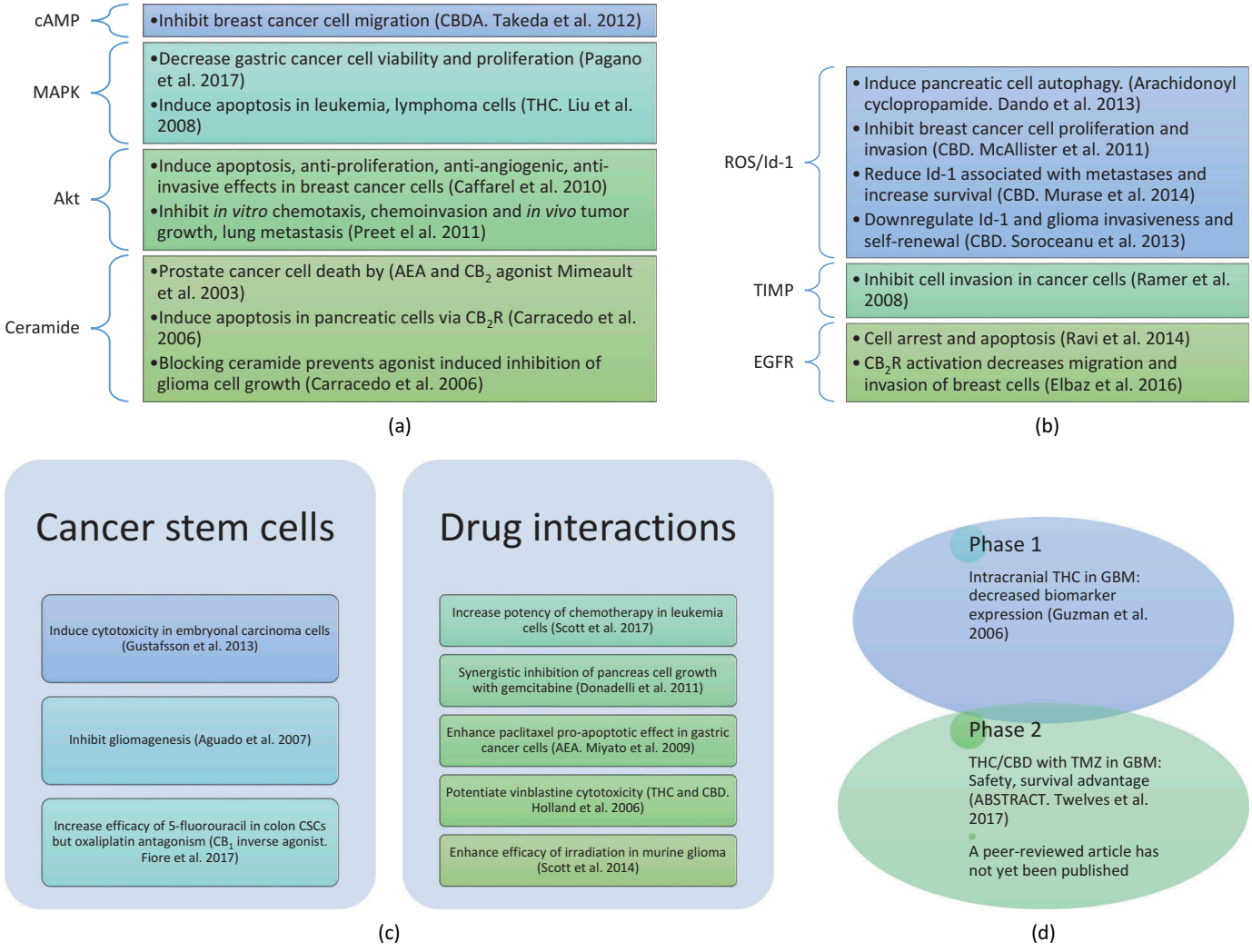

Figure 3. Antineoplastic effects of cannabinoids, examples.

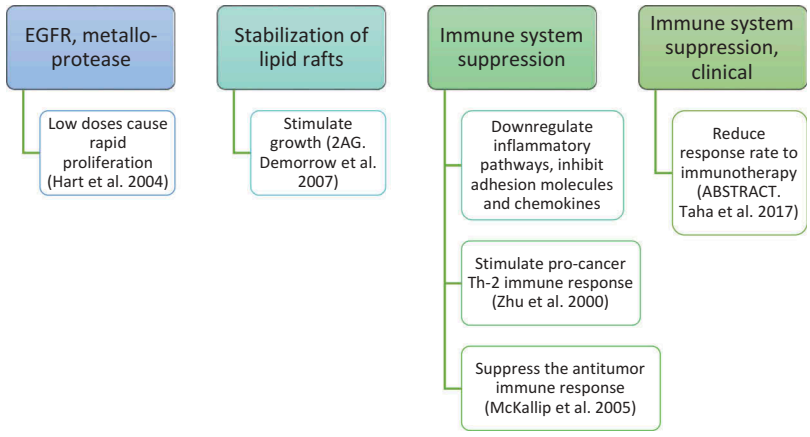

Figure 4. Pro-cancer effects of cannabinoids, examples.

noted that a serious limitation pertains to patient preconceived notions regarding cannabis. Often those who may benefit resist treatment due to stigma or fear of side effects. Contrastingly, other patient populations may demand treatment for recreational usage or due to false beliefs of a 'miracle drug' that could lead to self-medication with extremely high dosages in place of conventional treatment.

8.2. Immunosuppressive, anti-inflammatory and anti-neoplastic properties

These are well-established in preclinical models, demonstrating that specific cannabis varieties regulate different biological pathways, varying by cell type and tumor microenvironment, and may even augment or diminish the effects of other oncologic treatment modalities. Strong evidence exists for the endocannabinoid system's involvement in cancer growth. Implicated biological processes with promising data include cAMP, MAPK, Akt, ceramide accumulation, ROS, Id-1, TIMP-1, EGFR, and cancer stem cells [40,47]. [Figure 3,4] Synergism between cannabinoids and conventional cancer treatment has been shown, notably chemotherapy [71] and to a lesser extent, radiotherapy [72]. Conflicting reports have shown cannabinoid oncogenic activity as well, often in association with immunological mechanisms [74].

8.3 Current limitations and the future

Although robust, the main problem with anti-cancer research today is that it is still limited to cell lines and animal studies, precluding meaningful conclusions and extrapolations in human cancer. Somehow, despite the exponential rise in cannabis use in recent years, researchers have failed to construct and present significant clinical data; in fact, only a handful of trials have been documented [79–82] and the only one with published results was over a decade ago [76].

We expect that in the coming years, this information will shift from the theoretical and preclinical arena to concrete clinical research, by combining comprehensive cannabinoid data with those obtained from next-generation sequencing of tumors. In this way, potentially potent combinations of cannabis formulations and tumors with specific characteristics may be identified. Moreover, increased patient data will elucidate populations that are most responsive to Cannabis. We are currently undertaking a study to advance a deeper understanding of cannabis' role in oncological therapy. Three main sources of data will be investigated: the bioactive chemicals in a cannabinoid product will be isolated, their levels in patient serum determined, and finally, patient and physician reported drug effects analyzed. These data may determine which patients are responsive to which cannabinoid formulation, and ultimately lead to tailored treatment per patient and per indication. They will aid physicians in making effective evidence-based decisions in prescribing cannabinoids for patients. Moreover, they will be grounded on and built upon the rich scientific foundation of cannabis research available today.

Much is still unknown regarding this controversial plant, and quality, standardized clinical studies underway are pertinent to gaining a deeper understanding of the mystery behind cannabis. With increased standardization, more lenient legislation alongside realistic patient notions and expectations, we believe more patients will be recruited for clinical trials and their results will advance the field.

Funding

This paper was not funded.

Declaration of interest

The authors have no relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript. This includes employment, consultancies, honoraria, stock ownership or options, expert testimony, grants or patents received or pending, or royalties.

Reviewer disclosures

Peer reviewers on this manuscript have no relevant financial or other relationships to disclose

References

Papers of special note have been highlighted as either of interest (•) or of considerable interest (••) to readers.

1. Abel EL. Marijuana, the first 12,000 years. In: Cannabis in the ancient world. Springer Science+Business Media, New York: Plenum Press; 1980. p. 3–35.
2. National Academies of Sciences. The health effects of cannabis and cannabinoids: the current state of evidence and recommendations for research. Washington, DC: The National Academies Press; 2017.
3. Abuhasira R, Shbiro L, Landschaft Y. Medical use of cannabis and cannabinoids containing products – regulation in Europe and North America. Eur J Intern Med. 2018;49:2–6.
4. Devinsky O, Cross JH, Laux L, et al. Trial of cannabidiol for drug-resistant seizures in the dravet syndrome. N Engl J Med. 2017;376(21):2011–2020.
5. Yeshurun M, Shpilberg O, Herscovici C, et al. Cannabidiol for the prevention of graft-versus-host-disease after allogeneic hematopoietic cell transplantation: results of a phase II study. Biol Blood Marrow Transplant. 2015;21:1770–1775.
6. Naftali T, Mechulam R, Lev LB, et al. Cannabis for inflammatory bowel disease. Dig Dis. 2014;32:468–474.
7. Shevyrin V, Melkozerov V, Endres GW, et al. On a new cannabinoid classification system: a sight on the illegal market of novel psychoactive substances. Cannabis Cannabinoid Res. 2016;1:1, Mini-review
8. Bar-Sela G, Avisar A, Batash R, et al. Is the clinical use of cannabis by oncology patients advisable? Curr Med Chem. 2014;21(17):1923–1930.
9. Curran HV, Freeman TP, Mokrysz C, et al. Keep off the grass? Cannabis, cognition and addiction [Review]. Nat Rev Neurosci. 2016;17(5):293–306.
10. Di Marzo V, Bifulco M, De Petrocellis L. The endocannabinoid system and its therapeutic exploitation. Nat Rev Drug Discov. 2004;3(9):771–784.
11. Alexander SP, Christopoulos A, Davenport AP, et al. Concise guide to pharmacology 2017/2018: G protein-coupled receptors. Br J PHarmacol. 2017;174(Suppl 1):S17–S129.
12. Ttsuboi K, Uyama T, Okamoto Y, et al. Endocannabinoids and related *N*-acylethanolamines: biological activities and metabolism. Inflamm Regen. 2018;38:28.
13. MacCallum CA, Russo EB. Practical considerations in medical cannabis administration and dosing. Eur J Intern Med. 2018;49:12–19.

•• **Authors provide a comprehensive, highly detailed and helpful practical guide for the administration of cannabinoid-based medicines in a wide range of patient populations.**

14. Hazekamp A, Ware MA, Müller-Vahl KR, et al. The medicinal use of cannabis and cannabinoids—an international cross-sectional survey on administration forms. J Psychoactive Drugs. 2013;45(3):199–210.
15. Martin JH, Schneider J, Lucas CJ, et al. Exogenous cannabinoid efficacy: merely a pharmacokinetic interaction? Clin Pharmacokinet. 2018;57(5):539–545.
16. Lanz C, Mattsson J, Soydaner U, et al. Medicinal cannabis: in vitro validation of vaporizers for the smoke-free inhalation of cannabis. PLoS One Public Lib Sci. 2016;11:e0147286.
17. Eisenberg E, Ogintz M, Almog S. The pharmacokinetics, efficacy, safety, and ease of use of a novel portable metered-dose cannabis inhaler in patients with chronic neuropathic pain: a phase 1a study. J Pain Palliat Care Pharmacother. 2014;28:216–225.
18. Van Sickle MD, Oland LD, Ho W, et al. Cannabinoids inhibit emesis through CB_1 receptors in the brainstem of the ferret. Gastroenterology. 2001;121:767–774.
19. Himmi T, Dallaporta M, Perrin J, et al. Neuronal responses to delta 9-tetrahydrocannabinol in the solitary tract nucleus. Eur J Pharmacol. 1996;312(3):273–279.
20. National Comprehensive Cancer Network. Antiemesis (version 3.2018) https://www.nccn.org/professionals/physician_gls/pdf/antiemesis.pdf Last accessed April 25, 2018.
21. Machado RFC, Stefano SC, Haiek RC, et al. Therapeutic use of Cannabis sativa on chemotherapy-induced nausea and vomiting among cancer patients: systematic review and meta-analysis. Eur J Cancer Care (Engl). 2008;17(5):431–443.
22. Tramèr MR, Carroll D, Campbell FA, et al. Cannabinoids for control of chemotherapy induced nausea and vomiting: quantitative systematic review. BMJ. 2001;323(7303):16–21.
23. Ben Amar M. Cannabinoids in medicine: a review of their therapeutic potential. J Ethnopharmacol. 2006;105(1–2):1–25.
24. Whiting PF, Wolff RF, Deshpande S, et al. Cannabinoids for medical use: a systematic review and meta-analysis. JAMA. 2015;313(24):2456–2473.
25. Lane M, Vogel CL, Ferguson J, et al. Dronabinol and prochlorperazine in combination for treatment of cancer chemotherapy-induced nausea and vomiting. J Pain Symp Manage. 1991;6(6):352–359.
26. Meiri E, Jhangiani H, Vredenburgh JJ, et al. Efficacy of dronabinol alone and in combination with ondansetron versus ondansetron alone for delayed chemotherapy-induced nausea and vomiting. Curr Med Res Opin. 2007;23:533–543.
27. Duran M, Perez E, Abanades S, et al. Preliminary efficacy and safety of an oromucosal standardized cannabis extract in chemotherapy-induced nausea and vomiting. Br J Clin Pharmacol. 2010;70:656–663.
28. Parker LA, Kwiatkowska M, Mechoulam R. Delta-9-tetrahydrocannabinol and cannabidiol, but not ondansetron, interfere with conditioned retching reactions elicited by a lithium-paired context in Suncus murinus: an animal model of anticipatory nausea and vomiting. Physiol Behav. 2006;87(1):66–71.
29. Fine PG, Rosenfeld MJ. The endocannabinoid system, cannabinoids, and pain [Review]. Rambam Maimonides Med J. 2013;4(4):e0022.
30. Hill KP. Medical marijuana for treatment of chronic pain and other medical and psychiatric problems: a clinical review. JAMA. 2015;313(24):2474–2483.
31. Nugent SM, Morasco BJ, O'Neil ME, et al. The effects of cannabis among adults with chronic pain and an overview of general harms: a systematic review. Ann Intern Med. 2017;167(5):319–331.
32. Noyes R Jr, Brunk SF, Avery DA, et al. The analgesic properties of delta-9-tetrahydrocannabinol and codeine. Clin Pharmacol Ther. 1975;18(1):84–89.
33. Portenoy RK, Ganae-Motan ED, Allende S, et al. Nabiximols for opioid-treated cancer patients with poorly-controlled chronic pain: a randomized, placebo-controlled, graded-dose trial. J Pain. 2012;13(5):438–449.
34. Johnson JR, Lossignol D, Burnell-Nugent M, et al. An open-label extension study to investigate the long-term safety and tolerability of THC/CBD oromucosal spray and oromucosal THC spray in patients with terminal cancer-related pain refractory to strong opioid analgesics. J Pain Symptom Manage. 2013;46(2):207–218.

• **One of the few studies to evaluate long term responses to cannabinoids, this research supports the effectiveness and stability of their use in pain management, without severe side effects or addictive qualities, limiting the need for alternative analgesics.**

35. Bar-Sela G, Vorobeichik M, Drawsheh S, et al. The medical necessity for medicinal cannabis: prospective, observational study evaluating treatment in cancer patients on supportive or palliative care. Evid Based Complement Alternat Med. 2013; 2013: 510392.
36. Beal JE, Olson R, Laubenstein L, et al. Dronabinol as a treatment for anorexia associated with weight loss in patients with AIDS. J Pain Symptom Manage. 1995;10(2):89–97.
37. Jatoi A, Windschitl HE, Loprinzi CL, et al. Dronabinol versus megestrol acetate versus combination therapy for cancer-associated anorexia: a north central cancer treatment group study. J Clin Oncol. 2002;20(2):567–573.
38. Strasser F, Luftner D, Possinger K, et al. Comparison of orally administered cannabis extract and delta-9-tetrahydrocannabinol in treating patients with cancer-related anorexia-cachexia syndrome: a multicenter, phase III, randomized, double-blind, placebo-controlled clinical trial from the cannabis-in-cachexia-study-group. J Clin Oncol. 2006;24(21):3394–3400.
39. Brisbois TD, de Kock IH, Watanabe SM. Delta-9-tetrahydrocannabinol may palliate altered chemosensory perception in cancer patients: results of a randomized, double-blind, placebo-controlled pilot trial. Ann Oncol. 2011;22(9):2086–2093.

40. Velasco G, Hernandez-Tiedra S, Davila D, et al. The use of cannabinoids as anticancer agents [Review]. Prog. Neuro-Psychopharmacol. Biol Psychiatry. 2016;64:259–266.
41. Pacher P, Batkai S, Kunos G. The endocannabinoid system as an emerging target of pharmacotherapy. Pharmacol Rev. 2006;58 (3):389–462.
42. Hart S, Fischer OM, Ullrich A. Cannabinoids induce cancer cell proliferation via tumor necrosis factor α-converting enzyme (TACE/ADAM17)-mediated transactivation of the epidermal growth factor receptor. Cancer Res. 2004;64:1943–1950.
43. DeMorrow S, Glaser S, Francis H, et al. Opposing actions of endocannabinoids on cholangiocarcinoma growth: recruitment of Fas and Fas ligand to lipid rafts. J Biol Chem. 2007;282:13098–13113.
- **The complex interaction between cannabinoids and cancer pathways is explored, with inspection of the molecular cross-talk and elucidation of the potential for opposing effects, depending on type of cannabinoid, specific mechanism of action and biological pathway.**
44. Takeda S, Okajima S, Miyoshi H, et al. Cannabidiolic acid, a major cannabinoid in fber-type cannabis, is an inhibitor of MDA-MB-231 breast cancer cell migration. Toxicol Lett. 2012;214(3):314–319.
45. Liu WM, Scott KA, Shamash J, et al. Enhancing the in vitro cytotoxic activity of Delta9-tetrahydrocannabinol in leukemic cells through a combinatorial approach. Leuk Lymphoma. 2008;49(9):1800–1809.
46. Pagano E, Borrelli F. Targeting cannabinoid receptors in gastrointestinal cancers for therapeutic uses: current status and future perspectives. Expert Rev Gastroenterol Hepatol. 2017;11(10):871–873.
47. Chakravarti B, Ravi J, Ganju RK. Cannabinoids as therapeutic agents in cancer: current status and future implications. Oncotarget. 2014;5(15):5852–5872.
48. Caffarel MM, Andradas C, Mira E, et al. Cannabinoids reduce ErbB2-driven breast cancer progression through Akt inhibition. Mol Cancer. 2010;9:196.
49. Preet A, Qamri Z, Nasser MW. Cannabinoid receptors, CB_1 and CB_2, as novel targets for inhibition of non-small cell lung cancer growth and metastasis. Cancer Prev Res Phila. 2011;4(1):65–75.
50. Ellert-Miklaszewska A, Kaminska B, Konarska L. Cannabinoids down-regulate PI3K/Akt and Erk signaling pathways and activate proapoptotic function of Bad protein. Cell Signal. 2005;17(1):25–37.
51. Sarfaraz S, Afaq F, Adhami VM, et al. Cannabinoid receptor agonist-induced apoptosis of human prostate cancer cells LNCaP proceeds through sustained activation of ERK1/2 leading to G1 cell cycle arrest. J Biol Chem. 2006;281(51):39480–39491.
52. Mimeault M, Pommery N, Wattez N, et al. Anti-proliferative and apoptotic effects of anandamide in human prostatic cancer cell lines: implication of epidermal growth factor receptor down-regulation and ceramide production. Prostate. 2003;56(1):1–12.
53. Carracedo A, Gironella M, Lorente M, et al. Cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress-related genes. Cancer Res. 2006;66(13):6748–6755.
54. Carracedo A, Lorente M, Egia A, et al. The stress-regulated protein p8 mediates cannabinoid- induced apoptosis of tumor cells. Cancer Cell. 2006;9(4):301–312.
55. Gustafsson K, Sander B, Bielawski J, et al. Potentiation of cannabinoid-induced cytotoxicity in mantle cell lymphoma through modulation of ceramide metabolism. Mol Cancer Res. 2009;7(7):1086–1098.
56. Dando I, Donadelli M, Costanzo C, et al. Cannabinoids inhibit energetic metabolism and induce AMPK-dependent autophagy in pancreatic cancer cells. Cell Death Dis. 2013;4:e664.
57. McAllister SD, Murase R, Christian RT, et al. Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis. Breast Cancer Res Treat. 2011;129(1):37–47.
58. Murase R, Kawamura R, Singer E, et al. Targeting multiple cannabinoid anti-tumour pathways with a resorcinol derivative leads to inhibition of advanced stages of breast cancer. Br J Pharmacol. 2014;171:4464–4477.
59. Soroceanu L, Murase R, Limbad C, et al. Id-1 is a key transcriptional regulator of glioblastoma aggressiveness and a novel therapeutic target. Cancer Res. 2013;73(5):1559–1569.
60. Ramer R, Hinz B. Inhibition of cancer cell invasion by cannabinoids via increased expression of tissue inhibitor of matrix metalloproteinases-1. J Natl Cancer Inst. 2008;100(1):59–69.
61. Ravi J, Sneh A, Shilo K, et al. FAAH inhibition enhances anandamide mediated anti-tumorigenic effects in non-small cell lung cancer by downregulating the EGF/EGFR pathway. Oncotarget. 2014;5 (9):2475–2486.
62. Elbaz M, Ahirwar D, Ravi J, et al. Novel role of cannabinoid receptor 2 in inhibiting EGF/EGFR and IGF-I/IGF-IR pathways in breast cancer. Oncotarget. 2017;8:29668–29678.
63. Fraguas-Sanchez AI, Martin-Sabroso C, Torres-Suarz AI. Insights into the effects of the endocannabinoid system in cancer: a review. Br J Pharmacol. 2018;175(13):2566–2580.
64. Gustafsson SB, Wallenius A, Zackrisson H, et al. Effects of cannabinoids and related fatty acids upon the viability of P19 embryonal carcinoma cells. Arch Toxicol. 2013;87(11):1939–1951.
65. Aguado T, Carracedo A, Julien B, et al. Cannabinoids induce glioma stem-like cell differentiation and inhibit gliomagenesis. J Biol Chem. 2007;282(9):6854–6862.
66. Fiore D, Ramesh P, Proto MC, et al. Rimonabant kills colon cancer stem cells without inducing toxicity in normal colon organoids. Front Pharmacol. 2017;8:949.
- **Three-dimensional cultures mimic colon cancer and strong synergism is shown with specific chemotherapeutic agents, suggesting a realistic and useful area of further research.**
67. Scott KA, Dalgleish AG, Liu WM. Anticancer effects of phytocannabinoids used with chemotherapy in leukaemia cells can be improved by altering the sequence of their administration. Int J Oncol. 2017;51:369–377.
- **An additional clinically useful area for further research – what should be the timing and sequence of the multidrug reservoir given to patients.**
68. Donadelli M, Dando I, Zaniboni T, et al. Gemcitabine/cannabinoid combination triggers autophagy in pancreatic cancer cells through a ROS-mediated mechanism. Cell Death Dis. 2011;2:e152.
69. Miyato H, Kitayama J, Yamashita H, et al. Pharmacological synergism between cannabinoids and paclitaxel in gastric cancer cell lines. J Surg Res. 2009;155:40–47.
70. Holland ML, Allen JD, Arnold JC. Interaction of plant cannabinoids with the multidrug transporter ABCC1 (MRP1). Eur J Pharmacol. 2008;591:128–131.
71. Holland ML, Panetta JA, Hoskins JM, et al. The effects of cannabinoids on P-glycoprotein transport and expression in multidrug resistant cells. Biochem Pharmacol. 2006;71:1146–1154.
•• **Well researched data on drug transporters raises important questions regarding drug interactions and toxicity, and should be reviewed before pursuing cannabinoid-chemotherapy combination studies.**
72. Scott KA, Dalgleish AG, Liu WM. The combination of cannabidiol and delta9-tetrahydrocannabinol enhances the anticancer effects of radiation in an orthotopic murine glioma model. Mol Cancer Ther. 2014;13(12):2955–2967.
73. Eisenstein TK. Effects of cannabinoids on T-cell function and resistance to infection. J Neuroimmune Pharmacol off J Soc Neuroimmune Pharmacol. 2015;10:204–216.
74. McKallip RJ, Nagarkatti M, Nagarkatti PS. Delta 9 tetrahydrocannabinol enhances breast cancer growth and metastasis by suppression of the antitumor immune response. J Immunol. 2005;174 (6):3281–3289.
•• **This research has been heavily cited and built upon in various models as one of the first to show the vital interaction with the immune system.**
75. Zhu LX, Sharma S, Stolina M, et al. Delta-9-tetrahydrocannabinol inhibits antitumor immunity by a CB2 receptor-mediated, cytokine-dependent pathway. J Immunol. 2000;165:373–380.

76. Guzman M, Duarte MJ, Blazquez C, et al. A pilot clinical study of delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. Br J Cancer. 2006;95(2):197–203.
•• **Although simple in construction and limited for purpose of extrapolation, this clinical study has not yet been recreated.**
77. Foroughi M, Hendson G, Sargent MA, et al. Spontaneous regression of septum pellucidum/forniceal pilocytic astrocytomas – possible role of Cannabis inhalation. Childs Nerv Syst. 2011;27:671–679.
78. Singh Y, Bali C. Cannabis extract treatment for terminal acute lymphoblastic leukemia with a Philadelphia chromosome mutation. Case Rep Oncol. 2013;6:585–592.
79. Twelves C, Short S, Wright S. A two-part safety and exploratory efficacy randomized double-blind, placebo-controlled study of a 1:1 ratio of the cannabinoids cannabidiol and delta-9-tetrahydrocannabinol (CBD:THC) plus dose-intense temozolomide in patients with recurrent glioblastoma multiforme (GBM). 15_suppl.2046. J clin oncol. 2017 May 20;35(15_suppl):2046.
80. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2016 Aug 11. Identifier NCT01812603. A Safety Study of Sativex in Combination With Dose-intense Temozolomide in Patients With Recurrent Glioblastoma. Last accessed Apr 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT01812603
81. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017 Feb 9 . Identifier NCT01489826. A Phase 1 Study of Dexanabinol in Patients With Advanced Solid Tumours. Cited on April 25, 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT01489826?cond=dexanabinol+cancer&rank=3
82. ClinicalTrials.gov [Internet]. Bethesda (MD): National Library of Medicine (US). 2017 July 7. Identifier NCT01654497. Dexanabinol in Patients with Brain Cancer. Cited on April 25, 2018. Available from: https://clinicaltrials.gov/ct2/show/NCT01654497?cond=dexanabinol+cancer&rank=1
83. Taha T, Talhamy S, Wollner M, et al. Abstract 1545PD: the effect of cannabis use on tumor response to nivolumab in patients with advanced malignancies. Ann Oncol. 2017 September 1;28(Issue suppl_5): mdx388.005.
84. Hoch E, Bonnet U, Thomasius R, et al. Risks associated with the non-medicinal use of cannabis. Dtsch Arztebl Int. 2015;112:271–278.
85. Bar-Sela G, Tauber D, Mitnik I, et al. Abstract: cannabis-related cognitive impairment: prospective evaluation of possible influences on cancer patients during chemotherapy treatment. MASCC/ISSO 2018 e-poster.
86. Callaghan RC, Allebeck P, Akre O, et al. Cannabis use and incidence of testicular cancer: a 42-year follow-up of Swedish men between 1970 and 2011. Cancer Epidemiol Biomarkers Prev. 2017;26:1644–1652.