Cannabidiol as a chemotherapy adjunct in cancer treatment

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An overview of the potential of cannabidiol in combination with standard chemotherapy drugs for both the treatment of cancer and management of chemotherapy side effects.

Cancer care

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Abstract: Cannabidiol *(*CBD) is a non-psychoactive component of the cannabis plant that has garnered interest owing to its wide range of therapeutic qualities, where preclinical evidence has shown anti-tumour effects, as well as a potential role in the palliative care setting. Many of the signalling pathways that CBD targets modulate the hallmarks of cancer. Mechanistically, CBD elicits its activity through both cannabinoid receptor-dependent and independent pathways, in turn leading to ceramide production, endoplasmic reticulum stress, autophagy and apoptosis. Evidence has shown synergy when CBD is used in combination with standard chemotherapy drugs, which could be used to potentiate and leverage chemotherapy drugs, while also alleviating the harmful side effects normally observed in chemo-toxic regimens, making CBD an attractive molecule for adjunct therapy.

Key words: cannabidiol; endocannabinoid system; cannabinoids; phytocannabinoids; cancer; chemotherapy; drug delivery; side effects

Introduction

The endocannabinoid system (ECS) and its constituents, which include endogenous cannabinoids (i.e. endocannabinoids [naturally occurring lipid-based transmitters produced by the body]), synthetic cannabinoids and naturally occurring phytocannabinoids, such as cannabidiol (CBD), has gained tremendous interest in recent years for treating neurological- and cancer-related symptoms. Owing to the unwanted side effects of current cancer treatments, many patients have turned to cannabis-based products for medicinal use (CBPMs) to help ease cancer-related pain. CBPMs are compounds comprising CBD and/or tetrahydrocannabinol (THC) in various forms, including oils, tinctures, capsules, edibles,

topicals, patches and sprays. They have shown merits in alleviating chemotherapy-induced pain, nausea, vomiting, decreased appetite, cachexia, sleep disturbances and anxiety, thereby improving quality of life in palliative care[1].

Several countries have legalised medical cannabis because of public pressure of use, despite a lack of clinical data. The UK legalised CBPMs in 2018 for epilepsy, such as Epidiolex (CBD containing); multiple sclerosis, such as Sativex (THC:CBD containing); and chemotherapy-induced peripheral neuropathy (CIPN), such as Nabilone (THC containing) and Dronabinol (CBD containing)[2–4]. In the United States, 26 states have legalised cannabis, with varying state-dependent possession of quantity[5]. In 2019, Canada legalised cannabis for both recreational and medicinal use, such as for treating chronic pain, multiple sclerosis, CIPN, post-traumatic stress disorder, neuropathic pain and migraines[5].

Pre-clinical evidence has shown that CBD is able to modulate the hallmarks of cancer and, in doing so, has also shown synergistic benefits as an adjunct to standard chemotherapy agents.

In this article, we aim to highlight the pre-clinical evidence and available clinical trial data that support CBD as a potential chemotherapy adjunct, while emphasising the need for more clinical studies to translate from the bench to bedside. This article will:

- Provide an overview of the endocannabinoid system;
- Explain the mechanistic pathways/targets of CBD as an anti-cancer agent;
- Outline the current routes of administration and delivery of CBD;
- Explore the evidence of efficacy of CBD in management of cancer/side effects.

The endocannabinoid system in cancer

The ECS is named after the plant *Cannabis sativa*, from which cannabinoids were initially identified[6]. It comprises endocannabinoids, enzymes and cannabinoid receptors, such as cannabinoid receptor 1 (CB_1) and cannabinoid receptor 2 (CB_2; see Figure 1)[7]. The nature of the ECS highlights the fundamental role it plays in maintaining homeostasis throughout the body; in particular, its specific cannabinoid receptor localisation contributes to the governing of bodily functions, such as CB_1 expression in the brain, which regulates learning, memory and reward, and CB_2 found in the immune and peripheral system[6].

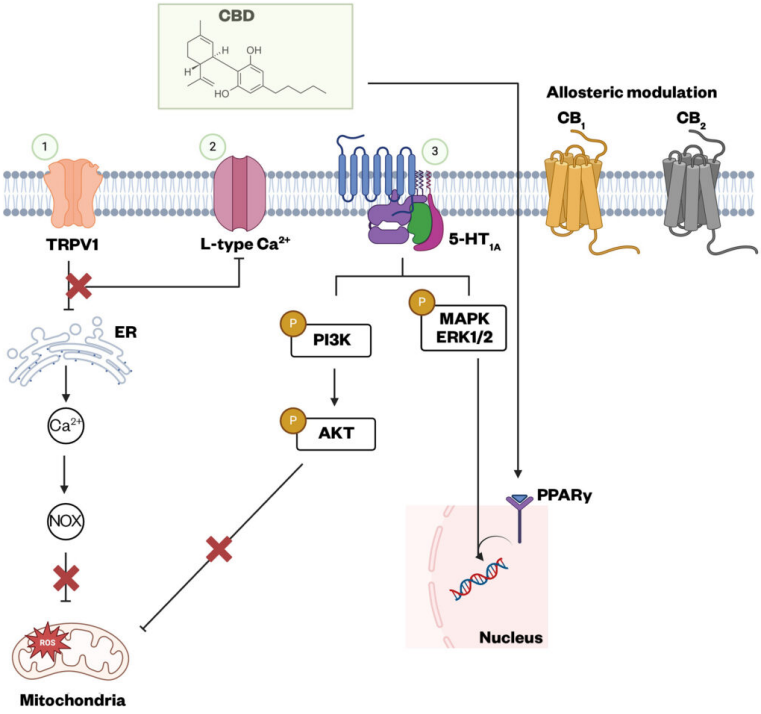

Figure 1: Summary of direct and indirect effects of CBD and intracellular signalling

CBD can interact with several cell surface and nuclear receptors, antagonising PI3K/AKT, MAPK/ERK, and JAK/STAT pathways. CBD can also inhibit, through the PPARγ receptor, modulating DNA transcription of pro-inflammatory mediators. In addition, CBD can modify membrane and organelle calcium channels, altering intracellular signalling. CBD can indirectly exert indirect effects on CB_1 and CB_2 receptors

Adapted from Naya et al, 2023 (Created with BioRender.com)

In 1964, chemist Raphael Mechoulam was the first to characterise the full chemical structure of THC as the main active compound, and therefore phytocannabinoid, in cannabis[8]. Endocannabinoids occur naturally within our body and are classified as lipid mediators. These include chemical messengers, such as anandamide (AEA or arachidonoyl ethanolamide) and 2-arachidonoylglycerol(2-AG), which, in synaptic retrograde signalling, are released from postsynaptic terminals and activate CB_1 receptors at presynaptic terminals (see Figure 2 for an overview of the ECS and its relevant signalling pathways)[9–18]. In some cancer models, such as breast cancer, AEA has been reported to have the anticancer effect of epithelial mesenchymal transition (EMT)[19]. The downstream receptor-mediated effects of endocannabinoids also contribute to the plasticity of the ECS, which overlaps with many of the components known to be involved in cancer progression[10].

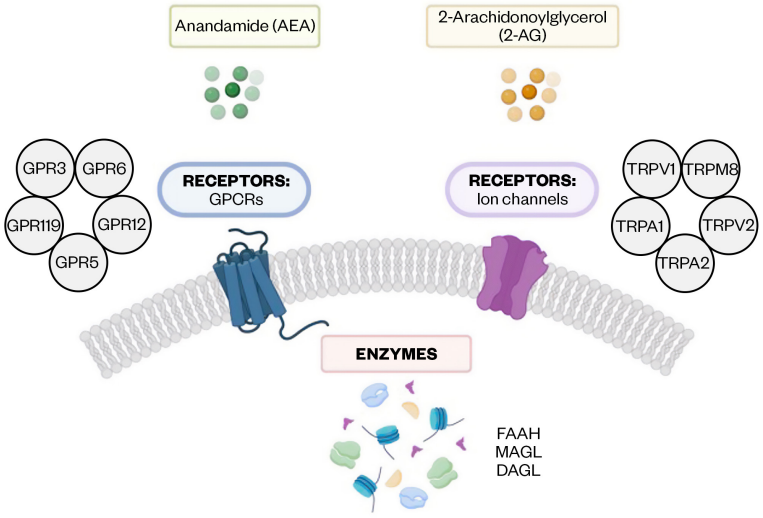

Figure 2: Overview of the endocannabinoid system, which comprises three main components that include endogenous endocannabinoids, enzymes and receptors (G protein coupled receptors [GPCRs] and ion channels). The two main enzymes that break down endocannabinoids are fatty acid amide hydrolase, which breaks down AEA, and monoacylglycerol lipase, which breaks down 2-AG. CBD acts through GPCRs, which are crucial for cell surface receptor signalling. CB1 (mainly located in the central nervous system) and CB2 (located on immune cells and areas of the GI tract) are the two most studied receptors, but it is now emerging that cannabinoids can interact with multiple orphan GPCRs, including GPR12, GPR18, GPR55, GPR119, in addition to ion channels, including TRP vanilloid, TRP ankyrin and TRP melastatin subfamilies, which have been reported to be biomarkers of prognostic value

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Mechanistic pathway/targets of CBD in cancer research in 2D and 3D models

Overall, the ECS and its components have been shown to have a role in blocking tumour growth by modulating the hallmarks of cancer; they induce apoptosis to inhibit proliferation, downregulate the vascular endothelial growth factor (VEGF) pathway, affecting angiogenesis, and dampen metastasis by inhibiting cell adhesion and migration through modifying matrix metalloproteinase (MMP2), tissue inhibitor of matrix metalloproteinase-1 (TIMP1), inhibitor of DNA binding 1 (ID1) and inducing endoplasmic reticulum (ER) stress [20–22]. There is increasing evidence that CBD can impair tumour growth through inhibiting the voltage-dependent anion channel 1 (VDAC1)[23]. CBD has been reported to mediate the anticancer effects of these pathways through CB receptors and GPR55, in addition to the *de novo* synthesis of ceramide[14].

Cancer signalling involves complex networks of molecular pathways that regulate fundamental cellular processes, such as growth, proliferation, differentiation and survival. Under normal cellular conditions, these signalling pathways maintain a balance, ensuring controlled behaviour[24,25]. However, in cancer, these pathways malfunction, leading to uncontrolled cell growth and tumour formation (see Figure 3)[23–26].

Cell cycle arrest

The cell cycle is a tightly regulated process that ensures the detection and repair of genetic damage for cell survival and correct division[27]. CBD can arrest the cell cycle and induce downstream apoptosis; a study investigating gastric cancer cells found that CBD could halt the cancer cells at the G0-G1 phase while upregulating the expression levels of *ATM* and *p53* and downregulating p21, CDK2, and cyclin E protein levels[28]. While CBD and THC are the most studied phytocannabinoids, cannabinol (CBN) has recently been reported to reduce the proliferative state of liver and breast cancer cell lines HepG2 and HCC1806, respectively [29]. The authors of this study report downregulation of p21 and p27, as well as cell cycle arrest at the G1 or S phase through a decrease in expression of CDK1, CDK2 and cyclin E1 [29]. This finding indicates that other phytocannabinoids may also conserve these anti-cancer effects and that more research is needed on their potential as additional alternatives/adjunct for cancer therapy.

Apoptosis

The induction of ceramide accumulation via CB receptors has been shown to lead to apoptosis in pancreatic, glioma, colon, and many other cancer cells[1,30]. Many of the cannabinoid signalling pathways result in reactive oxygen species (ROS) involvement and this has been widely observed in glioma and leukaemia[31–33]. In addition, ROS involvement is further supported by the involvement of N-acetylcysteine, a thiol antioxidant that scavenges ROS, or the NAD(P)H oxidase inhibitors that can attenuate the effects of cannabinoids[34]. CBD can interact with CB receptors that are differently expressed in neural and peripheral tissues, with transient receptor potential channels of the vanilloid type-1 (TRPV1), or directly with membrane microdomains rich in cholesterol named lipid rafts[35]. Often, the interaction of CBD with different receptor types leads to the same cell fate, even if different intracellular signalling cascades have been activated. Downstream events following ROS or ceramide induction has brought light to the involvement of ER stress. It has been observed *in vivo* that a high level of ROS induces ER stress, which is evidenced by the increase in levels of the specific ER-stress mediators; p8, CHOP, TRB-3 and GPR78, which activate the mitochondrial intrinsic apoptotic pathway[33]. Ceramide level increases have also been associated with ER stress in CBD-induced apoptosis in tumour cells[36,37]. The mitogen-activated protein kinase (MAPK) pathway has also been reported in numerous studies to be involved in CBD exposure[38]. Serine/threonine protein kinases are mainly involved in the pathway and act to convert extracellular stress into cellular responses,

including cell cycle arrest, apoptotic cell death and cytokine production via phosphorylation [39]. The involvement of this pathway in cancer has been largely reported in the literature and the duration of the stimulus has been reported to be important for the type of cellular response, whereby a brief activation of the ERK cascade leads to cell survival and proliferation, and a long-term activation leads to apoptosis[40,41].

The PI3K/AKT pathway has been reported to be involved in intracellular pro-survival signalling and regulates cell survival, growth, proliferation, angiogenesis, cell migration and invasion[42]. The downregulation of AKT is involved in CBD's anticancer effect and, in gastric cancer, induces cell cycle arrest, which is a consequence of AKT inhibition related to MAPK pathway activation[29]. In astrocytoma, CBD induces apoptosis in low CB receptor-expressing cells in comparison to high CB receptor levels, owing to the high levels of phosphorylated AKT present. This suggests that a high level of CB receptors, in addition to AKT, eliminates the ability of cannabinoids to induce apoptosis in astrocytoma cells[43]. The AKT pathway, therefore, stands as a potential target for clinical trials[44].

In a study investigating CBD in pancreatic cancer, the authors report anticancer effects via antagonisation of the GPR55 receptor through CBD[14]. They found that p53, a tumour suppressor gene, regulates GPR55 and modulates cell cycle and MAPK pathways[14]. Pancreatic cancer cell lines AsPc1, HPFA-II, BxPc3 and Panc1 were treated with CBD as well as an antagonist of GPR55, CID16020046 (CID), and found a reduction in cell growth with combinatorial CBD/CID and gemcitabine[14]. The study demonstrates a novel pathway by which gemcitabine may potentiate anticancer effects through inhibition of GPR55[14].

Autophagy

Autophagy is a mechanism by which unnecessary and dysfunctional components of a cell are removed and recycled via PI3K/AKT/mTOR and AMP kinase signalling; as a last resort of stress to the cell, autophagy can transition to cell death[45]. As above, ER stress can drive mitochondria-dependent apoptosis through activation of CHOP or determine cell survival by an increase in GPR78[46]. However, if the level of CHOP targeting TRB-3 significantly increases, ER stress then triggers autophagy[46,47]. In breast cancer, CBD induces ER stress and subsequent inhibition of AKT and mTOR signalling, suggesting the induction of autophagy[48]. Apoptosis and autophagy can co-exist — CBD, for example, can induce ROS production causing an inhibition of both processes; this is suggested by evidence from the effects of higher CBD concentration favouring cell death with a decreased association between beclin1 and Bcl-2, marking both autophagy- and CBD-mediated apoptosis[48].

The apoptosis and autophagy processes involved in cell death are complex, with overlapping features[49]. A third type of programmed cell death has been reported in a study investigating cannabinoids in mantle cell lymphoma[50]. The authors report a decrease in cell viability by CBD, without involvement of caspase-3, but insteadcycloheximide-sensitive

cytoplasmic vacuoles[50]. The lack of enhanced autophagosome formation and lysosomal contribution excludes the involvement of canonical autophagy. This indicates that there may be additional types of cell deaths activated by CBD.

Angiogenesis, invasion and metastasis

Cannabinoid receptor agonists are able to block the induction of angiogenesis by inhibition of the VEGF pathway[51]. Within this signalling cascade, cannabinoids act by targeting various elements, including VEGF receptors VEGFR1 and VEGFR2, which are downregulated upon treatment of gliomas, skin carcinomas and thyroid carcinomas[52]. Cannabinoid receptor activation in vascular endothelial cells leads to the inhibition of proliferation and migration and promotes apoptosis[51]. CB_1 and CB_2 agonists can reduce spontaneous metastasis of distant tumour masses *in vivo* and cause inhibition of adhesion, migration and invasiveness *in vitro* in glioma, lung and cervical cancers[53–55]. These anti-cancer effects have been reported to involve modulation of extracellular proteases, such as MMP2 and TIMP1[53,55].

Pharmacological inhibition of ceramide biosynthesis results in an anti-tumor and anti-angiogenic effect of CB_1 and CB_2 receptor agonists and decreases VEGF production both *in vitro* and *in vivo* in glioma[51]. Blocking ceramide biosynthesis and knock down of the p8 protein prevents inhibition of MMP2 expression and cell invasion in glioma[53]. However, CBD can reduce invasiveness and metastasis by acting independently of the CB_1 and CB_2 receptor, partly owing to downregulation of the helix-loop-helix transcription factor inhibitor of ID-1[56,57]. Emerging studies have proposed further pathways for the mechanism of action of cannabinoids. A recent study reports CBD could inhibit the release of exosome and microvesicles (EMV) from prostate, hepatocellular and breast cancers *in vitro*[58]. EMV release is associated with many diseases, such as cancer; Kosgodage *et al.* reported that an increase in EMV release may be the cause of chemoresistance[58]. In their study, they propose the regulatory effects of CBD on EMV biogenesis as a novel anti-cancer target, which may be used to sensitise cancer cells to chemotherapy[58].

A further 2019 study by Kosgodage *et al*. reported CBD-EV-mediated modulation of EV in glioblastoma[59]. Prohibitin (PHB) — an intracellular iron-binding protein — is involved in many roles, including cell metabolism, apoptosis, senescence, survival and immunity, and is crucial for mitochondrial function and integrity[60]. Increased PHB levels are associated with chemoresistance in cancers and are therefore a target of therapeutic interest. In this study, CBD was shown to reduce PHB protein levels and exchanged EV-mediated export of microRNAs to an anti-oncogenic signature in glioblastoma multiforme (GBM) cells[59].

A study investigating the effect of CBD on hypoxia inducible factor 1 subunit alpha (HIF-1α), a protein expressed in response to hypoxia that activates genes to increase oxygen, has shown that HIF-1α suppresses angiogenesis and stem cell-like properties of breast cancer by decreasing the expression of HIF-1α through the Src/von Hippel–Lindau tumour

suppressor protein (VHL) interaction[61]. Meaning CBD acts to inhibit Src (Proto-oncogene tyrosine-protein kinase) activity, which decreases HIF-1α through the degradation of VHL recruitment and the direct reduction of HIF-1α protein synthesis[61].

3D models

The use of 3D cancer models to study and evaluate the potency of drugs has proven to be an efficient tool for recapitulating the tumour microenvironment (TME) to better understand the cancer-drug interaction in real time. The majority of the pre-clinical investigations into CBD's oncological and synergistic effects with chemotherapy drugs have utilised 2D cell lines and animal models. In triple negative breast cancer (TNBC), Surapaneni *et al.* reported inhibitory concentrations (IC_{50}) of <3.5mM in 2D cell lines treated with CBD; however, a greater IC_{50} value of 75.36mM was observed in 3D organoids derived from a mouse model [62]. Another report showed that, following 48 hours treatment, 80mM of a CBD-rich extract exhibited cytotoxic effects in pancreatic ductal adenocarcinoma spheroids greater than gemcitabine at the same concentration[63]. These findings indicate further research is needed for evaluating CBD and chemotherapy drug combinations as potential TME-modulating therapies.

Drug administration and delivery

The current routes of administration for CBD include oral formulations, transdermal, pulmonary and transmucosal[64,65]. Although oral delivery is the preferred route of administration because of its ease of manufacturing and patient preference, it comes with many challenges, including poor bioavailability, variable pharmacokinetics, dosing and side effects, possible polymorphisms and drug–drug interactions[65].

Oral formulations have shown low bioavailability, which may be owing to slow and erratic absorption and degradation in the stomach[66]. The maximum plasma concentrations are usually obtained following one to two hours and can last up to six hours[65]. Self-emulsifying drug delivery systems have also been used in transporting CBD[67]. These are mixtures of oils, surfactants and solvents that produce nano-sized droplets when they encounter an aqueous solution in the gut and their small nature means that the surface area available for drugs to be dissolved and absorbed is increased[65,67]. An example of this includes the use of micelles, which are aggregate-like structures that are soluble in water. Micelles have shown a two-fold increase in first maximum activity peak when used as hosts for cannabinoid delivery via an oral aqueous formulation[68]. Most of these systems have been explored in epilepsy or pain and further studies into their uses in cancer treatment are warranted. Additionally, CBD soft gelatin capsules have been developed as an improved formulation, and, in combination with high fat/calorie foods, may increase the rate and degree of absorption[65,69].

CBD can be administered through a transdermal route for systemic effects or topically for localised effects in the skin [70]. These forms of administration have the benefit of bypassing the first-pass metabolism effect, which results in increased drug bioavailability and continuous release over a long period of time, with less adverse effects even at higher drug concentrations[70]. Many clinical studies have investigated this method for use in fibromyalgia, epilepsy, developmental and epileptic encephalopathy, fragile X syndrome, osteoarthritis, and even ocular ailments; however, in cancer and cancer-related pain, there remains a lack of investigation[71].

The use of nanotechnology to improve and enhance efficacy of CBD delivery *in vitro* and *in vivo* has shown promise; features include enhanced encapsulation efficiency, the presence of surface functional groups that can be modified to improve stability and controlled stimuli drug release[72]. Many studies have described utilisation of this strategy for delivery of CBD and ECS components as 'nanotherapeutics'[73]. In a syngeneic mouse model of triple-negative breast cancer, a nanomicellar formulation carrying a synthetic cannabinoid reduced tumour growth and psychoactive side effects[74]. In human glioblastoma cell lines, a lipid nanocapsule (NLC) containing CBD proved to be effective for prolonged release[75]. The blood–brain barrier (BBB) limits drug penetration into the brain; however, some studies have reported nose-to-brain administration shows a promising increased drug concentration in the brain[76]. Cannabinoids have also been loaded to poly lactic-co-glycolic acid (PLGA) nanoparticles and have shown reduced rates of tumour burden in an *in ovo* model of ovarian cancer[77].

CBD is highly unlikely to be used as a monotherapy for cancer treatment, but combination with chemotherapy has seen promising data in cell and mouse models of cancers; therefore, nano delivery should be considered as a tool for this synergistic therapy owing to its control of drug release reducing immunogenicity. An additional benefit of this system is the ability for conjugation of the object to the microenvironment and receptor-specific macromolecules, such as peptides, proteins and aptamers[78].

Efficacy of CBD in management of cancer and chemotherapy side effects

CBD's non-psychoactive nature has made it an attractive target to consider for its use in cancer patients to improve their quality-of-life factors, including chemotherapy-induced pain, nausea, appetite, sleeping and anxiety[79]. Currently, the majority of data from randomised controlled trials (RCTs) have come from CBD use in epilepsy, childhood seizure disorders and chronic pain[80,81]. There is a lack of published RCT data for CBD in the palliative setting; however, some trials are underway and described below. An up-to-date clinical trials summary is presented in supplementary Table 3.

Cancer and chemotherapy-induced pain is the most studied palliative symptom and there is strong anecdotal evidence of benefit; however, supporting data from clinical trials is limited. The mechanisms that have been suggested for the analgesic effects of CBD derive from mouse models of neuropathic and taxol-induced pain[82,83]. Many studies focus on THC and THC + CBD combination rather than CBD as a single agent, which limits understanding of CBD in cancer related-pain management. For example, a randomised, double-blind, crossover study investigating a topical CBD 250mg dose up to 4 times per day in neuropathic pain reported a significant decrease in intense, sharp, cold, and itchy feelings on the Neuropathic Pain Scale (NPS), in comparison to placebo[84]. This indicates a possible role for CBD in neuropathic pain; however, the study size was small and included several aetiologies, making it difficult to transfer relevance to cancer-related neuropathic pain. In another small cross-sectional study analysing THC and CBD use in outpatient palliative care, the authors report 14 out of 58 patients taking CBD felt improvements in their pain[85]. A study of 108 patients with cancer taking medication that was THC dominant (n=52), CBD dominant (n=19) and a mixture of the two (n=33) were compared over 1 month and showed no differences between the 3 groups in pain intensity[86]. The use of paclitaxel can cause chemotherapy-induced neuropathic pain. A study found that CBD *in vivo* could prevent paclitaxel-induced neurotoxicity, possibly through the 5-HT_{1A} receptor[83].

Anxiety and depression can co-exist in patients with cancer. Evidence over the years has shown CBD can reduce these symptoms. In a recent clinical trial, 14 patients with moderate-to-severe anxiety were treated for 4 weeks with a high-CBD containing sublingual solution (9.97mg/mL CBD, 0.23mg/mL THC) three times daily. Patients were aware that they were receiving CBD. The results showed a significant reduction in anxiety and improvements to mood, sleep, quality of life and cognition[87]. Although promising results were obtained, this data needs to be interpreted with caution — for example, the small cohort of patients consisted primarily of white women with above average IQ, which limits generalising, as gender and age can predominate anxiety[88]. Research has shown that sex differences significantly impact anxiolytic effects of THC, although for CBD this remains unclear and warrants the need for further investigation[89,90]. In addition, cytochrome P450 (CYP450) enzymes, which are involved in slowing drug metabolism and increasing drug effect, are also impacted by age, ethnicity and gender, which could affect metabolism of CBD[91]. CBD is also known to interact with CYP enzymes, which could cause interactions with other medications and side effects; therefore, more trials are needed to evaluate CBD's efficacy in managing anxiety, with consideration of wider representation of patient cohort, age, sex, and potential drug–drug interactions.

A common and distressing symptom of advanced cancer is cachexia, which involves muscle wasting, owing to decreased appetite, and can cause anorexia. Reports have shown that changes to inflammatory conditions produced by the tumour and host cause an imbalance of pro (TNF-a, IL-1, IL-6, interferon g and NF-kß) and anti-inflammatory cytokines, which play a role in maintaining adipocytes, cells, neurons and bone marrow[92]. Studies have focused on

use of THC + CBD or THC alone in cachexia rather than CBD alone[93–95]. One study reports a significant improvement in pre-meal appetite and a higher intake of calories consumed compared with placebo[94]. A systematic review, which analysed five studies, encompassing 934 participants taking THC alone and THC + CBD combination, found cannabis increased appetite but decreased quality of life. A possible explanation for this may be that, as CBD has anti-inflammatory properties, it may be playing a part in trying to regulate pro- and anti-inflammatory cytokines, while THC induces appetite through CB_1 receptors[96,97]. With limited data available, future trials are needed to determine CBD's role in modulating cachexia.

The ECS is known to regulate sleep; therefore, CBD and cannabis components may act as a potential therapy to aid with poor sleep, which patients with cancer can often experience. Observational studies have reported the effectiveness of CBD for improving sleep; however, RCT data is lacking[98]. Chemotherapy-induced nausea and vomiting (CINV) are common in oncology patients and cause major distress to their quality of life. CBD has shown promising effects in alleviating CINV. A randomised, double-blinded, placebo-controlled phase II trial aimed to evaluate the potential of a CBD: THC cannabis extract in preventing refractory CINV. The trial was carried out with a patient sample that experienced moderate-to-high CINV despite guideline-consistent anti-emetic prophylaxis. A total of 81 patients were randomised and given a preparation of oral CBD:THC capsules or a placebo. The researchers found that chemotherapy administration and a 2.5mg CBD/2.5mg THC dose three times daily was associated with less nausea and vomiting when compared to placebo. Overall, 31% of patients experienced sedation, dizziness and disorientation, but 83% of participants preferred cannabis to placebo and no serious adverse events were attributed to the treatment[99].

Does CBD usage affect potency of classic chemotherapy?

Evidence so far for the anticancer effects of CBD has included cytotoxic, anti-proliferative, apoptotic, autophagic and inhibiting metastasis pre-clinically. Some studies have additionally reported synergistic effects of CBD with chemo- and radiotherapy treatments. However, the mechanism for this synergy remains unclear and poses the question: does CBD usage affect the potency of these conventional anti-cancer therapies?

CBD is known to interfere and inhibit CYP450 enzymes[100]. A review by Buchtova *et al*. of chemotherapy drugs where CBD has reported effects separated them into the following groups: antimetabolites (small molecules mimicking standard nucleotides in DNA meaning they can synthesise DNA), alkylating agents (electron-rich atoms that can disrupt DNA function by transfer of alkyl groups), microtubule-targeting agents (bind to cytoskeletal components and can disrupt motility of the cell), anthracyclines (cause DNA damage), proteotoxic stress-inducing agents (damage protein turnover, activates unfolded protein response) and topoisomerase inhibitors (involved in DNA replication and repair damage)

[101]. CBD has also been reported to have both direct and indirect antioxidant effects, in addition to reducing ROS levels and pro-inflammatory cytokines, thus reducing inflammation, which could be beneficial in reducing inflammatory responses to chemotherapy drugs [102,103].

In a study analysing CBD's combination with paclitaxel in ovarian cancer cells, antiproliferative effects were reportedly increased with this combination and did not hinder the cytotoxic effect of chemotherapy[77]. Another report examining CBD in breast cancer cells showed a positive effect of CBD in protecting against paclitaxel-induced neurotoxicity, which was mediated partly by the 5-HT_{1A} receptor system[83]. CBD did not attenuate paclitaxel-induced inhibition of cancer cells viability[83]. In a cell line model of glioblastoma, CBD increased the sensitivity to chemotherapy agents temozolomide (TMZ), doxorubicin, cisplatin and carmustine[104]. Clinical trials have been limited in studying the combination of CBD and chemo/radiotherapies. However, a recent two-part randomised, double-blind, placebo-controlled study by Twelves *et al.* of 1:1 CBD/THC + TMZ was performed in recurrent GBM patients. The authors reported that median survival was improved with the CBD/THC group when compared to placebo (550 vs. 369 days) and concluded that 1:1 CBD:THC offers some efficacy and is safe and feasible when used as an adjunct to dose-intense TMZ[105].

Overall, the benefits of CBD in combination with therapeutic agents may be explained by its influence on transporter/receptor systems. TRPV are ion channels involved in sensation of heat and pain (nociception) and stimulated by CBD[106]. A report has shown that CBD can activate TRPV2, which causes an increase in influx and retention of certain chemotherapy drugs, including TMZ and cisplatin[107]. P-glycoprotein (p-gp) confers resistance by prevention of sufficient accumulation of anticancer drugs, avoiding their cytotoxic and apoptotic effects, and is another target of CBD's anti-tumour effects[108]. CBD has been shown to inhibit p-gp, which leads to increased accumulated levels of doxorubicin and vinblastine in cells overexpressing p-gp[109]. The multidrug resistance protein 1 (MRP1), encoded by ABCC1 and breast cancer resistance protein (BCRP)/ATP-binding cassette subfamily G member 2 (ABCG2), is an ATP-binding cassette (ABC) transporter**,** identified in multidrug resistance[110]. CBD can re-sensitise overexpressing cell lines to the cytotoxic effects of ABCG2 substrates, mitoxantrone and topotecan[110]. G protein-coupled receptors (GPCRs), such as GPR55, have been shown to regulate pancreatic cancer growth. In a study by Ferro *et al.,* inhibition of GPR55 via CBD, which acts as an antagonist to this receptor, was able to reduce pancreatic ductal adenocarcinoma growth in cells[16]. In a mouse model, the administration of CBD with gemcitabine increased survival by three times when compared to gemcitabine alone[16]. Additionally, the authors found gemcitabine-resistant markers, such as ribonucleotide reductase catalytic subunit M1 (RRM1), was also reduced after CBD treatment in cells[16]. This could be leveraged for gemcitabine-resistant tumours, where CBD therapy as an adjunct with gemcitabine would allow efficient metabolism of gemcitabine in cancer cells.

Future perspective

CBD and other cannabinoids have shown promising results in pre-clinical cancer studies as cytotoxic agents, in addition to the palliative setting, as they are not associated with the adverse effects that many drugs exhibit[7]. CBD is likely to be administered in combination with chemotherapy drugs and possibly epigenetic and immunotherapy treatments, making it probable that the future of CBD will steer in the direction of adjunct therapy[111]. Given the evidence so far, CBD as an adjunct has shown leverage of standard chemotherapy agents in aiding the reversal of chemoresistance, promoting wound healing and helping to alleviate the toxic side effects, while improving quality of life of oncology patients. These notable antiemetic, anxiolytic and analgesic properties therefore make it fundamental to understand CBD as an immunomodulator to help characterise which immunotherapy and chemotherapy combinations will have synergistic efficacy[1].

Clinical studies so far have been limited; however, a three-year randomised, controlled phase II trial of temozolomide with and without nabiximols (Sativex; GW Pharma; THC:CBD combination) spray in patients with recurrent glioblastoma has commenced in the UK (ARISTOCRAT)[3,112]. A major limitation in clinical trial studies that impedes the translation of this data to clinics can be grouped into the following: (i) inefficient formulations, (ii) most appropriate drug delivery method, (iii) dosage and intervals and (iv) lack of heterogenous populations analysed and duration of treatment studied[65]. Therefore, future work should focus on monitoring longer-term usage of CBD in patients with cancer, as cancer comprises a multitude of comorbidities and cellular and molecular abnormalities, particularly in the context of potential drug reactions and toxicities. Additional research that analyses the symptoms that are best treated by CBD, the dosage, and the route should also be completed in the palliative setting.

Conclusion

CBD's main reported mechanism of action has been through dysregulation of calcium homeostasis and mitochondrial calcium overload. However, CBD's other direct effects via TRP, 5-HT_{1A} and indirect effects (see Figure 1) on CB_1 and CB_2 are interesting avenues for exploration in cancer modulation. CBD's pharmacokinetic and pharmacodynamic information highlights the need for further clinical studies to better understand its mechanistic actions in combination with standard chemotherapy and immunotherapy drugs, while balancing this with maintaining a safe and optimal dosing effect. In summary, CBD has the potential to hinder the growth and division of cancer cells by altering MAPK/ERK signalling. CBD can impede the formation of blood vessels by VEGF signalling. CBD exhibits anti-inflammatory properties, which is significant considering the association of chronic inflammations with cancer development through changes to NF-kß signalling.

1. 1

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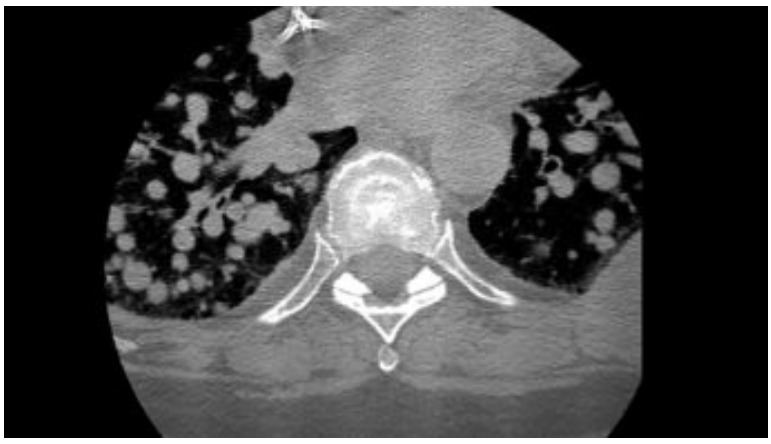

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