Advances in Biological Regulation xxx (xxxx) xxx

Contents lists available at ScienceDirect

Advances in Biological Regulation

journal homepage: www.elsevier.com/locate/jbior

Therapeutic potential of cannabinoids in combination cancer therapy

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ARTICLE INFO

Keywords:
Cannabinoids
Cannabinoid receptors
Endocannabinoid system
Cancer
Chemotherapy
Polytherapy

ABSTRACT

Derivatives of the plant *Cannabis sativa* have been used for centuries for both medical and recreational purposes, as well as industrial. The first proof of its medicinal use comes from ancient China, although there is evidence of its earlier utilization in Europe and Asia. In the 19th century, European practitioners started to employ cannabis extracts to treat tetanus, convulsions, and mental diseases and, in 1851, cannabis made its appearance in the Pharmacopoeia of the United States as an analgesic, hypnotic and anticonvulsant. It was only in 1937 that the Marijuana Tax Act prohibited the use of this drug in the USA. The general term *Cannabis* is commonly used by the scientific and scholar community to indicate derivatives of the plant *Cannabis sativa*. The word cannabinoid is a term describing chemical compounds that are either derivate of Cannabis (phytocannabinoids) or artificial analogues (synthetic) or are produced endogenously by the body (endocannabinoids). A more casual term "marijuana" or "weed", a compound derived from dried Cannabis flower tops and leaves, has progressively superseded the term cannabis when referred to its recreational use. The 2018 World health organisation (WHO) data suggest that nearly 2.5% of the global population (147 million) uses marijuana and some countries, such as Canada and Uruguay, have already legalised it. Due to its controversial history, the medicinal use of cannabinoids has always been a centre of debate. The isolation and characterisation of Δ^9 tetrahydrocannabinol (THC), the major psychoactive component of cannabis and the detection of two human cannabinoid receptor (CBRs) molecules renewed interest in the medical use of cannabinoids, boosting research and commercial heed in this sector. Some cannabinoid-based drugs have been approved as medications, mainly as antiemetic, antianorexic, anti-seizure remedies and in cancer and multiple sclerosis patients' palliative care. Nevertheless, due to the stigma commonly associated with these compounds, cannabinoids' potential in the treatment of conditions such as cancer is still largely unknown and therefore underestimated.

1. Introduction

More than 480 different cannabinoids have been identified so far; out of these, 110 are classified as phytocannabinoids. Recreational cannabinoids are used to provide a psychomimetic state, which is described as a particular mixture of relaxation and exultation. Acute intoxication may cause subjective symptoms, varying from alterations in the perception of time, color or acoustic stimuli,

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https://doi.org/10.1016/j.jbior.2020.100774
Received 3 December 2020; Received in revised form 7 December 2020; Accepted 10 December 2020

increased appetite for certain foods, short term memory loss, mouth dryness, reduced movements and, at very high dosage, panic attacks, paranoia and hallucinations (Agrawal et al., 2014). Moreover, over 140 distinct and chemically diverse synthetic cannabinoids in herbal mixtures have been discovered to be available as recreational drugs, causing more severe symptoms among users such as vomiting, tachycardia, hallucinations, anxiety, disorientation and, in some cases, myocardial ischemia and hearth attacks (Tait et al., 2016).

The psychoactive effects of cannabis are due mainly to THC, which acts by imitating endogenous agonists. Although it has anti-emetic, analgesic and anti-inflammatory properties, its psychotropic characteristics impede its medicinal use (Śledziński et al., 2018). Its concentration varies according to different preparations. For instance, hemp contains <0.3 percent, herbal cannabis has 2–20 percent while hash oil has 10–30 percent of THC. In addition, the route of administration affects the pharmacokinetic and pharmacodynamic properties of THC (Toennes et al., 2008; Mcgilveray, 2005; Grotenhermen, 2003). Another cannabis compound, cannabidiol (CBD), has drawn medical attention due to its non-psychotropic nature and its ability to neutralise the effects of THC (Zuardi, 2008; Zuardi et al., 1982; Bhattacharyya et al., 2010; Hudson et al., 2019). Some studies have shown CBD's potential role in the treatment of pain and inflammation (Carrier et al., 2006) and as a neuroprotective compound thanks to its anti-oxidant and anti-inflammatory properties (Scuderi et al., 2009). Additionally, CBD has potential effectiveness in palliation and disease modulation of neurological conditions such as epilepsy, seizure (Jones et al., 2010), anxiety (Bergamaschi et al., 2011), Huntington's disease, amyotrophic lateral sclerosis and multiple sclerosis (Iuvone et al., 2009; Lakhan and Rowland, 2009). There has been an increasing interest in the medicinal properties of cannabinoid compounds for the treatment of Tourette syndrome, multiple sclerosis, epilepsy, digestive disorders, HIV, schizophrenia, Parkinson's disease, Alzheimer, atherosclerosis and myocardial infarction, glaucoma, hypertension, osteoporosis and cancer (Goyal et al., 2017; Cristino et al., 2020; Alfulaij et al., 2018; Uchiyama et al., 1991). In malignancies, the antitumor function of cannabinoids has been assessed in several cancers including pancreatic, prostate, colon, lung and breast cancer (Massi et al., 2013; Hermanson and Marnett, 2011; Ferro et al., 2018).

The first step in re-allowing the use of medicinal cannabis in the USA was made in 1996 in California, where a popular law permitted the use of cannabis for the treatment of various diseases. More states followed this example during the following years, with a total of 33 states allowing its medical use by 2020 in the USA and in many other countries throughout the world. By 1975, THC was recognised as a potential anti-neoplastic agent (Caffarel et al., 2006). However, it was not until the last two decades that cannabinoids were extensively studied. This article aims to evaluate the chemotherapeutic potential of cannabinoid compounds. As a part of this review, the plausibility of clinical application will also be addressed.

2. The endocannabinoid system

The endocannabinoid system (ECS) encompasses endogenous ligands (endocannabinoids), cannabinoid receptors (CBRs) and their metabolic enzymes. Interestingly, both the endocannabinoid and the opioid systems have remained conserved for more than half a billion years of human evolution. Endocannabinoids are lipids utilised as bioactive signalling molecules by different cell, such as

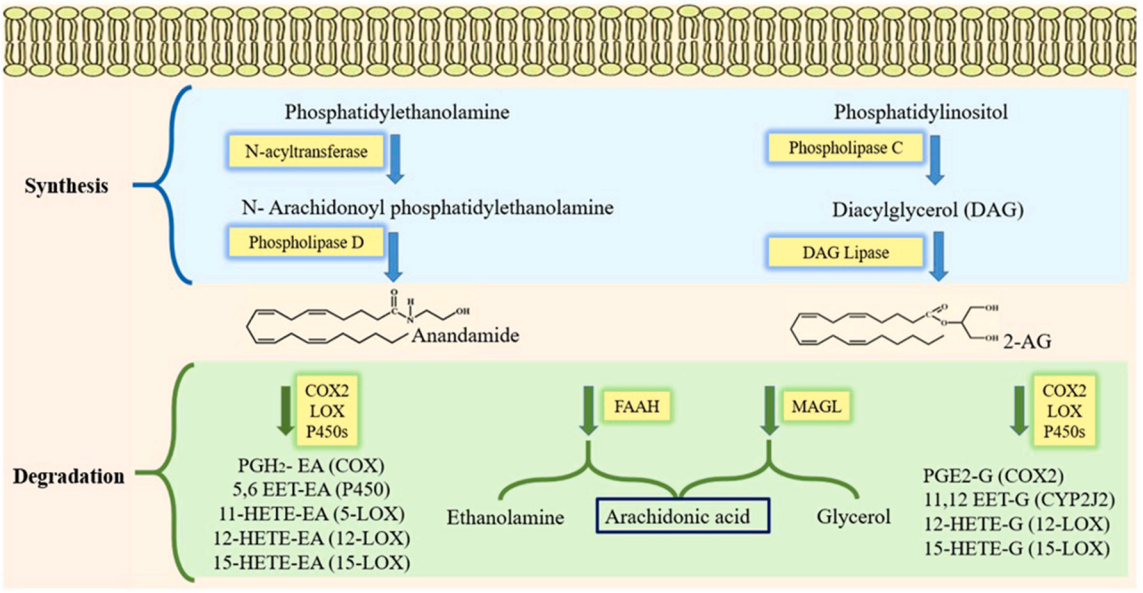

Fig. 1. Synthesis and Metabolism of endocannabinoids. Apart from FAAH and MAGL, COX, LOX and P450s also participate in the metabolism of endocannabinoids. Fatty acid amide hydroxylase (FAAH); monoacylglycerol lipase (MAGL); Cyclooxygenase (COX); Lysyl oxidase (LOX); cytochrome P450; prostaglandin ethanolamide (PG-EA); hydroxyeicosatetraenoyl-ethanolamide (HETE-EA); epoxyeicosatrienoyl-ethanolamide (EET EA); prostaglandin E2 glycerol ester (PGE2-G); epoxyeicosatrienoic acid glycerol ester (EET-G); hydroxyeicosatetraenoic glyceryl ester (HETE-G).

neurons (Moine and Vitale, 2019). The most investigated endocannabinoids are N-arachidonoyl ethanolamine, also referred to as Anandamide (AEA) and 2-arachidonoyl glycerol (2-AG) (Pertwee et al., 2010; Lu and Mackie, 2016). These compounds are lipid signalling molecules biosynthesised from phospholipids. AEA is synthesised from phosphatidylethanolamine and metabolised by fatty acid amide hydrolase (FAAH) enzyme. In contrast, 2-AG originates from inositol phospholipids and is degraded by monoacylglycerol lipase (MAGL). Cyclooxygenase (COX), Lysyl oxidase (LOX) or cytochrome P450 mediated oxidation can also metabolise these endocannabinoids (Maccarrone, 2017; Baggelaar et al., 2018) (Fig. 1).

The effects of cannabinoids and endocannabinoids are mainly mediated by two G-protein coupled receptors (GPCRs), cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) (Matsuda et al., 1990; Munro et al., 1993). These receptors are not only expressed on the extracellular surfaces of the cell but also in intracellular organelles such as the nuclei, Golgi apparatus and the mitochondria. CB1 receptors are expressed in both the central (CNS) and peripheral nervous systems (PNS). The olfactory bulb and hippocampus have the highest CB1 receptor expression in the brain. These receptors are also expressed in basal ganglia, cortex, septum, both dorsal and ventral horn of the spinal cord (Mackie, 2005) and thus account for the psychotropic properties of cannabinoids. In addition, they sparsely populate the brain stem indicating their neutral impact on the respiratory system. CB1 is also present in peripheral organs such as liver, skeletal muscles, blood vessels, pancreas, adipose and reproductive tissues (Maccarrone et al., 2015; Izzo and Sharkey, 2010). In contrast, CB2 receptor expression is predominant in immune cells and moderate in peripheral tissues (Pertwee et al., 2010). Predominantly, CB1 and CB2 receptor signalling arbitrate the neuro-modulatory and immunomodulatory functions respectively. However, lower levels of CB2 receptor have also been reported in the brain (Gong et al., 2006). Activation of CB1 and CB2 suppresses adenyl cyclase activity consequently decreasing intracellular cyclic adenosine monophosphate levels (Felder et al., 1998; Bayewitch et al., 1995; Slipetz et al., 1995). Furthermore, these receptors activate both Mitogen activating protein kinase (MAPK) (Derkinderen et al., 2001; Kobayashi et al., 2001) and phosphoinositide 3-kinase (PI3K) signalling pathways (Gómez Del Pulgar et al., 2000). CB1 is also implicated in the suppression of voltage-gated calcium channel-mediated calcium influx (Szabó et al., 2014).

Cannabinoids vary in their affinity to interact with cannabinoid receptors. While 2-AG can interact moderately with both CB1 and CB2 (Ben-Shabat et al., 1998; Mechoulam et al., 1995), AEA acts as a partial agonist for CB1 (Mechoulam et al., 1995; Lin et al., 1998). The effects of other endocannabinoids such as oleamide, O-arachidonoyl ethanolamine (Virodhamine), N-arachidonoyl dopamine and 2-AG ether (Noladin) are not well understood (Kovalchuk and Kovalchuk, 2020). While Virodhamine (Porter et al., 2002) acts as an antagonist of CB1, both 2-AG ether (Hanus et al., 2001), and N-acyldopamine (Bisogno et al., 2000) act as CB1 agonists. Phytocannabinoids include cannabigerol (CBG), cannabidiolic acid (CBDA) and Δ^9 tetrahydrocannabinolic acid (THCA). Δ^8-THC and

Endocannabinoid expression profile in cancer

AEA	↑	Glioma, meningioma, lymphatic metastasis, pituitary adenoma, hepatocellular carcinoma, Prostrate cancer, colon cancer
	↓	Glioma, meningioma
	=	Breast cancer, endometrial carcinoma
2-AG	↑	Colon cancer, endometrial cancer, Meningioma, Glioma, pituitary adenoma
	=	Colon cancer, Glioma

Endocannabinoid receptor expression in cancer

CB1	↑	Pituitary adenoma, prostrate, breast, cervical, ovarian, glioma, pancreatic, hepatocellular carcinoma, Hodgkin lymphoma, Tongue cancer
	↓	Glioma, colon, endometrial cancer
	=	Endometrial cancer, meningioma
CB2	↑	Glioma, Tongue, colon, pancreatic, breast, prostrate, cervix, endometrial cancer
	↓	Endometrial cancer

Other receptor expression in cancer

GPR55	↑	Pancreatic cancer, melanoma
TRPV1	↓	Prostate cancer, melanoma

Endocannabinoid metabolising enzymes

FAAH	↑	PDAC, Prostate
	↓	Glioma
MAGL	↑	PDAC, ovarian, melanoma, and prostate cancer
	↓	Glioma, endometrial cancer, lung, ovarian, breast and stomach cancer

Fig. 2. ECS expression profile in different cancers. The different outcomes of studies in same cancer highlight the heterogeneous nature of the expression profile.

Δ^9-THC act as partial agonists of CB1 and CB2 receptors. CBD acts as an antagonist for both cannabinoid receptors (Kovalchuk and Kovalchuk, 2020). Synthetic cannabinoids were initially developed to serve as pharmacological probes for the ECS. These cannabinoids can either be synthetic analogues of phyto- or endocannabinoids or newly synthesised compounds (Le Boisselier et al., 2017) with a varying affinity for cannabinoid receptors.

Despite the partial (44%) homology between CB1 and CB2 receptors, ligands do not differentiate between these two receptors (Moreno et al., 2020). Other receptors such as transient receptor potential channel subfamily V member 1 (TRPV1), calcitonin gene-related peptide (CGRP), G-protein receptor 55 (GPR55), GPR119 and Peroxisome proliferator-activated receptor gamma (PPARγ) are also susceptible to cannabinoids (Moreno et al., 2020; De Petrocellis et al., 2011a). Oleoylethanolamide (OEA), an endogenous lipid molecule, is reported to activate GPR119 and is referred to as a novel CBR (Overton et al., 2006). In addition, both CBD and Δ^9-THC are also known to interact with GPR55, GPR18 and PPARγ (Kovalchuk and Kovalchuk, 2020). Lysophosphatidylinositol receptor GPR55 has been associated with cancer progression (Falasca and Ferro, 2016; Piñeiro and Falasca, 2012; Ruban et al., 2014) and GPR119 activation (Arifin et al., 2018). Furthermore, it has been proposed to be a part of the ECS and is activated by various cannabinoids. However, its pharmacology is currently under investigation (Falasca and Ferro, 2016; Piñeiro et al., 2011). Apart from these receptors, cannabinoid compounds are also known to interact with gamma-aminobutyric acid (Naderi et al., 2005), opioids (Tsang et al., 2020) and noradrenergic systems (Muntoni et al., 2006).

3. ECS profile in cancer

The ECS plays a very important role in maintaining homeostasis and is subtly regulated in both physiological and pathological states. This multifaceted system participates in modulating the neural, immune, cardiovascular, metabolic and digestive system. A transient change in the ECS appears to be an adaptive mechanism to establish equilibrium. However, in certain conditions such as cancer, dysregulated ECS might exacerbate the disease and contribute to its progression (Di Marzo, 2008). Several studies have reported dysregulated expression of ECS components in several cancer types (Fig. 2).

Endocannabinoid levels are altered in disease tissue in comparison to normal tissue. Higher levels of AEA has been reported in glioma, meningioma (Petersen et al., 2005), lymphatic metastasis (Chen et al., 2015), pituitary adenomas (Pagotto et al., 2001), hepatocellular carcinoma (Mukhopadhyay et al., 2015) and prostate cancer (Schmid et al., 2002) in comparison to normal tissue. Ligresti et al. found both 2-AG and AEA levels were increased by two to three times in colon cancer tissue in comparison to the healthy tissue (Ligresti et al., 2003a). The increased expression of endocannabinoids is considered as the body's internal anti-cancer response. The same authors reported an increase in the endocannabinoid expression in precancerous polyps in comparison to full-blown colon carcinoma, suggesting their role as potential endogenous cancer growth inhibitors (Ligresti et al., 2003a). The protective functions of AEA in cancer have also been reported in several cancers including breast, prostate, lung, glioma and gastric adenocarcinoma (Ramer et al., 2019). In contrast, some studies have reported only a marginal change or decrease in endocannabinoid levels in cancer samples when compared to control. In glioma, some studies have reported lower AEA expression in comparison to normal tissue (Maccarrone et al., 2001; Wu et al., 2012). While Chen et al. reported increase in AEA in colon cancer, no change was reported in the level of 2-AG (Chen et al., 2015). Furthermore, in breast tumour, Schmid et al. reported no increment in the AEA levels but an increase in the AEA precursor, N-Arachidonoly phosphatidylethanolamine (NAPE) (Schmid et al., 2002). In endometrial carcinoma, although Guida et al. reported increased levels of 2-AG, no significant change in AEA was reported (Guida et al., 2010).

The expression profile of cannabinoid receptors is suggested to affect endocannabinoid levels. In pituitary adenoma, Pagotto et al. revealed a positive correlation of elevated AEA and 2-AG levels with CB1 receptor expression. Higher endocannabinoid expression was demonstrated in samples with higher CB1 receptor and vice versa (Pagotto et al., 2001). Altered expression of CBRs has been reported in cancer tissue in comparison to normal tissue. Many patient-derived cancer cells are known to express CBRs. Several studies have reported unregulated CBR levels in prostate (Orellana-Serradell et al., 2015), breast (Caffarel et al., 2010), cervix (Contassot et al., 2004), glioma (Wu et al., 2012), pancreatic (Michalski et al., 2008), hepatocarcinoma (Xu et al., 2006) and Hodgkin lymphoma cells (Benz et al., 2013) in comparison to non-malignant counterparts. However, there have been contrasting results in CBRs expression in cancer. While Cianchi et al. reported lower CB1 expression in colon cancer (Cianchi et al., 2008), Gustafsson found higher expression of CBRs expression and correlated it with poor outcomes (Gustafsson et al., 2011). In glioblastoma, lower expression of CB1 expression was reported (De Jesús et al., 2010), while in endometrial cancer lower (Ayakannu et al., 2014) or no change (Guida et al., 2010) in the CBRs expression has been described in comparison to normal. Besides CBRs, other cannabinoid interacting receptors are also reported to be activated in different cancers. Overexpression of TRPVI was observed in prostate cancer. The same study also reported a correlation between cell proliferation and TRPVI receptor expression (Morelli et al., 2014a). In addition, COX-2, TRPVI and GPR55 expression profiles were found to be overexpressed in a melanoma cell line (Adinolfi et al., 2013). Our group has previously reported higher GPR55 expression in prostate, ovarian and pancreatic cancer cell lines and pre-clinical mouse models (Ferro et al., 2018; Piñeiro et al., 2011).

The correlation between endocannabinoid receptors' expression and cancer progression has been extensively studied in different cancer types. Sanchez et al. demonstrated a higher CB2 expression in gliomas and suggested its correlation with the tumour grade (Sánchez et al., 2001). A murine model study illustrated that elevated CB2 expression predisposed the mice to develop leukaemia and might be involved in leukemogenesis (Joosten et al., 2002). Another investigation demonstrated the associated upregulated CB1 receptor expression with disease severity and poorer outcomes in prostate cancer (Chung et al., 2009). Michalski et al. connected upregulated CB1 receptor expression in pancreatic tumours with a shorter survival time (<6 months) in humans. On the contrary, low expression pancreatic tumours had a median survival time of 16 months (Michalski et al., 2008). In breast cancer, higher expression of CB2 is associated with the tumour grade and contributes to pro-oncogenic signalling of human epidermal growth factor (HER2)

(Pérez-Gómez et al., 2015).

Some studies have also demonstrated an inverse correlation between CBR overexpression and cancer development. Xu et al. demonstrated that increased levels of CB1 and CB2 in hepatocellular carcinoma (HCC) were linked to improved prognosis (Xu et al., 2006). In addition, silencing CB1 expression accelerates the growth and development of intestinal tumours (Wang et al., 2008). This idea is backed by studies demonstrating upregulated endocannabinoids and their metabolic enzymes in cancer. Taking the higher expression of endocannabinoids in malignant in contrast with healthy tissues into consideration, inhibition of the degrading enzymes could be speculated. Wu et al. reported a decrease in both MAGL and FAAH enzymes in glioma tissue as opposed to healthy brain tissue (Wu et al., 2012). Furthermore, the MAGL expression level was downregulated in endometrial cancer (Guida et al., 2010) and was later reported in lung, ovarian, breast, stomach and colon cancer (Sun et al., 2013). Interestingly, higher expression of MAGL reported in ovarian, melanoma, prostate and breast cancer corresponded with increased tumour invasion in ovarian, melanoma and prostate cancer (Qin and Ruan, 2014; Van Dross et al., 2013). In prostate cancer, higher expression of FAAH (Endsley et al., 2008) was also correlated with poor outcomes (Thors et al., 2010). However, in pancreatic ductal adenocarcinoma, higher expression of both MAGL and FAAH was associated with better prognosis (Michalski et al., 2008).

There is a lack of consensus on how the expression profile explains the heterogeneity of ECS in cancer. Highly heterogeneous cannabinoid receptor expression has been reported in several cancers. In HCC, 15/27 and 18/27 cases showed a higher immunoreactivity for CB1 and CB2 respectively (Xu et al., 2006). Interestingly in pancreatic cancer, only 13/37 and 19/37 samples showed a higher CB1 and CB2 immunoreactivity respectively, while the others were reported to have a lower level (Michalski et al., 2008). Blazquez et al. reported that 36/61 melanoma biopsies were immunoreactive for both CBRs (Blázquez et al., 2006). Hence, the ECS expression profile will depend on the site of tumour origin, growth and metastasis. Therefore, before considering the therapeutic efficacy of cannabinoids, it is important to comprehend that cannabinoids' targets are not ubiquitously expressed in all patients.

4. Anticancer properties of cannabinoids

Cannabinoid compounds have been reported to affect cell growth and survival in different cancer types. However, the underlying mechanisms involved may be heterogeneous and specific for different cells. Cannabinoids may target the tumour directly thus affecting signalling and cellular pathways that eventually induce cell growth arrest, cell death and inhibit migration. They can also indirectly mediate their effects through tumour microenvironment, immune response and/or by preventing vascularisation. These direct and indirect cannabinoid anti-cancer functions have been elegantly reviewed elsewhere (Śledziński et al., 2018; Hinz and Ramer, 2019; Velasco et al., 2016; Guzmán, 2003; Bifulco et al., 2006; Hermanson and Marnett, 2011).

4.1. Cannabinoids mediated anti-tumoral effect in a CBR-independent manner

It is now well established that cannabinoids can exert their anti-cancer properties also in a non-CBR (canonical receptors) dependent manner. This can be through targeting other receptors, which offer the potential for therapeutic intervention. Evidence supports the role of transient receptor protein family (TRP) in cannabinoid mediated anti-carcinogenic effects. CBD can activate both TRPV1 (Bisogno et al., 2001; Ligresti et al., 2006) and TRPV2 (Qin et al., 2008; Nabissi et al., 2015). While AEA acts on TRPV1 (Zygmunt et al., 1999), THC activates TRPV2 (De Petrocellis et al., 2011b). In addition, THC and CBD are also identified as activators of TRP melastatin type – 8 (TRPM8) and TRP ankyrin type −1 (TRPA1) respectively (De Petrocellis et al., 2008). AEA was found to induce cell death via TRPV1 activation in lymphoma, neuroblastoma (Maccarrone et al., 2000) and cervical cancer cell lines (Contassot et al., 2004). Cannabinoid mediated TRP receptor-dependent anti-carcinogenic roles involve the increased influx of intracellular calcium ions which consequently results in increased cell death, a higher level of intracellular reactive oxygen species (ROS), autophagy and cell cycle arrest (Rodrigues et al., 2016). CBD treatment resulted in decreased cell viability in breast (Ligresti et al., 2006) and colon cancer cells (Aviello et al., 2012) via TRPV1 stimulation. The same receptor was found to support CBD and AEA mediated toxicity in endometrial adenocarcinoma (Fonseca et al., 2018). In addition, TRPV2 activation contributed to cannabinoid treatment-induced responsiveness of tumour cells to chemotherapeutics (Nabissi et al., 2013; Morelli et al., 2014b).

Endocannabinoids AEA (Bouaboula et al., 2005), OEA and nodalin (Sun et al., 2007), along with endocannabinoid like molecules such as oleamide and PEA, are known to act as agonists for PPARα (Tellez et al., 2013; Lo Verme et al., 2005; Fu et al., 2003). Cannabimimetic compounds including CBD, THC, WIN-55,212–2, HU331 and JWH015 are known to activate members of the PPAR family (O'sullivan, 2016). The involvement of PPARs in the anti-carcinogenic roles of cannabinoids has been reported for WIN55212-2 (Giuliano et al., 2009; Hong et al., 2013) and THC in liver cancer (Vara et al., 2013), and for CBD in lung cancer (Ramer et al., 2013). As aforementioned, several studies have reported the carcinogenic roles of GPR55 receptor. Our group has previously reported that CBD (antagonist for GPR55) mediated pharmacological inhibition of GPR55 has anti-proliferative effects in pancreatic cancer. Furthermore, blocking the activity of GPR55 downregulated MAPK signalling and increased sensitivity to gemcitabine (Ferro et al., 2018).

There has been mounting evidence suggesting the existence of GPCRs, including CBRs and GPR55, as heteromeric form. Moreno et al. demonstrated that GPR55 and CB2 heteromerise in breast cancer cells and these heteromers have unique pharmacological and signalling properties (Moreno et al., 2014). In addition, CB2 and G-protein coupled chemokine receptor 4 (CXCR4) were found to heteromerise in both breast and prostate cancer cells (Scarlett et al., 2018; Coke et al., 2016). Coke et al. suggested that the presence of functional CB2-CXCR4 dimer resulted in decreased cancer cell function when agonists for both these receptors were added (Coke et al., 2016). This possibility of receptor dimerization might reveal novel pharmacological sites for therapeutic intervention in cancer.

Though not extensively studied, reports suggest that cannabinoids might exert their anti-cancer function through cell metabolism. Disrupted cellular metabolism is a characteristic feature of several cancers (Chen et al., 2014; Stäubert et al., 2015). Treatment of

pancreatic cancer cells with synthetic cannabinoids, GW405833 and arachidonoyl cyclo-propamide (APCA) blocked mitochondrial metabolism and induced cell death in AMPK dependent manner (Dando et al., 2013). Crosstalk between CBRs and AMPK has been elucidated in various tissues and has been associated with mitochondrial metabolism disruption (Tedesco et al., 2010). Altered mitochondrial function forces malignant cells to rely on glycolysis to meet their energy requirement. A study correlated energy metabolism inhibition and a switch from fatty acid oxidation to glycolytic pathway for energy in cancer cells to better prognosis and increased drug response. The authors showed that inhibiting glycolysis in cancer cells with mitochondrial defects resulted in significant cell death (Xu et al., 2005). Another study showed that niclosamide induced p53 independent mitochondrial uncoupling and further proposed this as an important strategy for targeting cancers with mutated p53 pathway. (Kumar et al., 2018). Furthermore, Rimmerman et al. observed that CBD treatment mediated cell death by blocking mitochondrial receptor voltage-gated anion channel 1 (VDAC1). Based on this observation, the authors further speculated the role of VDAC1 in anti-tumoral functions of CBD (Rimmerman et al., 2013). A recent study in glioblastoma suggested that CBD treatment mediated a decrease in prohibitin (PHB), a protein involved in chemoresistance and mitochondrial protection (Kosgodage et al., 2019). Although these studies suggest cannabinoid-cell metabolism interplay, further studies are required to validate the same.

4.2. Selective effects of cannabinoids on cancer cells

Most of the *in vitro* studies demonstrate the anti-carcinogenic effects of cannabinoid treatments in comparison to control treatment in cancer cells. Indeed, there is a growing body of evidence suggesting the selective effects of cannabinoids on cancer cells (Mcallister et al., 2005, Galve-Roperh et al., 2000a; Carracedo et al., 2004; Blázquez et al., 2003; Velasco et al., 2004). For instance, cell viability remained unchanged in astrocytes (normal glial cells) in comparison to glioma, post cannabinoid treatment (Carracedo et al., 2004, Mcallister et al., 2005). Furthermore, Carracedo et al. demonstrated protective function of cannabinoids in astrocytes (Carracedo et al., 2004). Treatment with 1–10 μM of WIN55212-2 did not affect cell viability of prostate epithelial cells but resulted in a significant dose-dependent decrease in cell viability of LNCaP cells (Sarfaraz et al., 2005). Another study reported the selective effects of cannabinoids in myeloma cell lines (Barbado et al., 2017). In animal models, anti-tumoral actions of cannabinoids have been reported in cancer cells while sparing the healthy tissues (Galve-Roperh et al., 2000a; Carracedo et al., 2006).

The mechanisms mediating cannabinoid selectivity are not fully understood. The different expression levels of CBR might account for selective cannabinoid responses. Treatment of mantle cell lymphoma cells with cannabimimetic compounds resulted in decreased cell growth but not in the CB1-lacking control cells (Flygare et al., 2005). Similarly, CB1 agonist Rimonabant was found to reduce cell proliferation in breast cancer cells in comparison to normal cells in CBR dependent manner (Sarnataro et al., 2006). Resistance to cannabinoid treatments has been reported in cancer models which do not express CBRs (Mckallip et al., 2005). Furthermore, it is unclear how the CBR expression profile is modulated in cancer. Rousseaux et al. demonstrated *lactobacillus acidophilus* mediated the modulation of CB2 receptor expression in colon cancer cell line (Rousseaux et al., 2007). Alternate splicing is also suggested to influence the differential and functional profile of CBRs in normal and tumour tissue (Ryberg et al., 2005). Notarnicola et al. suggested that oestradiol mediated CB1 receptor induction in colon cancer cell lines (Notarnicola et al., 2008). Since the CBR expression is heterogeneous in cancer, it will be interesting to evaluate the correlation between CBR expression and the effect mediated by the cannabinoid. While considering differential CBR expression-dependent cannabinoid selectivity in cancer cells, it is important to take into account their CBR-independent anti-cancer effects reported in several cancers.

Cancer cells' state of differentiation might affect their response to cannabinoid treatment. Ligresti et al. reported that cannabinoid treatments decreased cell viability in undifferentiated CaCo-2 cells (colon cancer cell line) via the CB1 receptor. In comparison to the undifferentiated cells, the differentiated CaCo-2 cells had lower levels of endocannabinoids, decreased FAAH expression and did not respond to cannabinoid treatments. It is interesting to note that the overall CB1 expression levels remained unchanged after differentiation. This study further suggests the possible role of altered CB1 receptor glycosylation in mediating cannabinoid selectivity based on the cell state (Ligresti et al., 2003b).

Differences in signalling pathways in cancer and normal cells might offer another plausible explanation for cancer-specific cannabinoid actions. Overexpression of ERK pathway is required for THC induced cell death in rat glioma cells (Galve-Roperh et al., 2000b). The differences in survival and signal transduction pathways might predispose the glioma cells to overexpression in comparison to healthy glial cells (Velasco et al., 2004). In addition, upregulation of CB2 receptors in glioma tumours (Sánchez et al., 2001) might play a role in facilitating overexpression of ERK in these cancer cells (Mcallister et al., 2005). Pulgar et al. demonstrated the role of cannabinoids in preventing ceramide stimulated cell death in astrocytes via phosphatidylinositol -3-kinase/protein kinase B pathway. This study also suggests the role of ERK in exerting this protective effect (Gómez Del Pulgar et al., 2002). However, it is also important to take into account that the different responses of transformed and non-transformed glial cells may be a consequence of ceramide synthesis following cannabinoid treatment (Pulgar et al., 2002).

On the contrary, a study investigated the anti-carcinogenic activity of CBD along with other chemotherapeutic agents in human and murine glioblastoma cell lines and further evaluated their toxicity in neural progenitor cells (Deng et al., 2017a). The authors reported the anti-proliferative and cytotoxic effects of CBD at micromolar concentrations. The mechanism involved in this activity did not preferentially target transformed cells and was associated with neural progenitor cell toxicity (Deng et al., 2017b). Blazquez et al. demonstrated that cannabinoid administration can decrease the cell viability of non-transformed cells, particularly those with a higher growth rate such as vascular endothelial cells (Blázquez et al., 2003). However, it can be argued that apoptosis of endothelial cells might facilitate inhibition of tumour angiogenesis. Therefore, it is important to evaluate the extent of cannabinoid-mediated toxicity in normal tissue when considering its therapeutic applications.

4.3. Targeting the endocannabinoid metabolic system in cancer

Since endocannabinoids upregulation is inversely correlated with cancer progression, attempts have been made to increase their local concentration in the tumour tissue either by inactivating endocannabinoid hydrolysing enzymes or preventing their transport.

Fatty acid-binding proteins (FABPs) participate in the delivery of endocannabinoids to intracellular targets. There are ten known subclasses of FABPs along with their tissue localisation (Thumser et al., 2014) and endocannabinoid binding capacity (Kaczocha et al., 2012; Sanson et al., 2014; Huang et al., 2016). Several studies have demonstrated their role in carcinogenesis (Schwarz et al., 2018). Inhibiting FABP5 has shown to decrease cervical cancer cell proliferation and invasion (Wang et al., 2016a). In line with this, downregulating FABP5 decreased cancer progression in prostate cancer (Kawaguchi et al., 2016) and mammary carcinoma (Kannan-Thulasiraman et al., 2010; Levi et al., 2013). However, the correlation between FABP expression and cancer progression is not firmly established. Upregulation of FABP3 induced cell death in a teratocarcinoma cell line (Song et al., 2012). Furthermore, Wang et al. demonstrated a direct association between FABP1 and better prognosis in hepatocellular carcinoma patients (Wang et al., 2014).

Although there are gaps in the literature concerning the role of FABPs as cancer inhibitors, studies have reported the role of these inhibitors, developed for metabolic syndrome, in the modulation of ECS (Wang et al., 2016b). Several other transport inhibitors have been studied in cancer. Administration of arachidonoyl-serotonin, a selective blocking agent for enzyme-mediated endocannabinoid breakdown, and VDM-11, an inhibitor for AEA cellular re-absorption, reduced tumour growth in xenograft models (Bifulco et al., 2004). Acyl-based AEA cellular uptake inhibitors, AM404, VDM11, UCM707, and OMDM2, resulted in a rapid decline in C6 glioma cell viability at pharmacologically relevant concentrations (De Lago et al., 2006).

Several studies have shown 2-AG breakdown inhibitors exert anti-cancer effects in ovarian, prostate, breast and melanoma cell lines (Mulvihill and Nomura, 2013; Motokura and Arnold, 1993). JZL184, a MAGL enzyme inhibitor, when administered to colon cancer cell lines, was found to exert anti-proliferative effects and increase sensitivity to 5-fluorouracil. The same study also suggested the role of JZL184 in decreasing migration by modulating epithelial to mesenchymal transition (EMT) (Ma et al., 2016). Ye et al. showed that downregulating MAGL, either using JZL184 or small interference RNA, could impair colorectal cancer growth and invasion (Ye et al., 2011). However, in contrast to this study, another independent study observed that PF-3845, a FAAH inhibitor, and not JZL184, mediated statistically significant reduction of colorectal cancer cell growth (Wasilewski et al., 2017). Furthermore, FAAH inhibitor URB597 was found to augment the anti-carcinogenic functions of AEA in lung cancer by inhibiting the activation of/EGF/EGFR signalling pathway (Ravi et al., 2014). The anti-proliferative effects of FAAH inhibitors have been demonstrated in colon (Proto et al., 2012) and lung cancer cells (Winkler et al., 2016). In melanoma, Hamtiaux et al. revealed the growth inhibitory role of URB597 in combination with N-palmitoylethanolamine in both *in vitro* and *in vivo* models (Hamtiaux et al., 2012). Another FAAH inhibitor CAY10401 was found to decrease cell viability and invasion in prostate cancer cell lines (Endsley et al., 2008).

The use of endocannabinoid enzyme inhibitors is also associated with unanticipated effects. For instance, in neuroblastoma cells, URB597 reduces cell viability indirectly by degrading ethanolamine, an AEA metabolite, and not by AEA upregulation (Matas et al., 2007). Another study demonstrated that treating colorectal cancer xenograft models with URB602 (MAGL inhibitor) decreased tumour growth by 52% in comparison to control. Although URB602-mediated anti-proliferative and antiangiogenic effects, its administration did not significantly change AEA, OEA and PEA levels *in vivo* (in both tumour and healthy tissue) thus indicating specificity of this inhibitor (Pagano et al., 2017). Furthermore, it is known that MAGL modulates endocannabinoid tone and CBR sensitisation (Chanda et al., 2010), but how its inhibitors affect the endocannabinoid system in various cancers is not well studied. A recent study indicated that JZL184 mediated the reduction of osteolytic bone metastasis in prostate and breast cancer and exerted anti-proliferative and metastatic effects in osteosarcoma models. However, in the absence of tumour, exposure to this inhibitor resulted in paradoxical bone volume reduction via CBR mediated effects thus indicating that activation of skeletal ECS might limit the use of MAGL inhibitors in osteo-protection (Marino et al., 2019). Whether cancer cell selectivity of these enzyme inhibitors is dose-dependent needs to be explored.

4.4. Exosomes - a target for cannabinoids in cancer therapy?

Exosomes are a subtype of extracellular vesicles that have a characteristic lipid bilayer structure and are produced and released by most eukaryotic cells. These vesicles mediate cell-cell communication and affect various physiological and pathological functions via delivery of biological compounds from their originating cells to recipient cells (Kalluri and Lebleu, 2020). They are present in body fluids including cerebrospinal fluid, saliva, urine, tears and blood (Saman et al., 2012; Michael et al., 2010; Keller et al., 2011; Lässer et al., 2011; Pisitkun et al., 2004). The molecular makeup of these vesicles depends on the cells of origin. Upregulated levels of exosomes have been reported in the blood of cancer patients (Ginestra et al., 1998; Zwicker et al., 2009). The release of exosomes from malignant cells contribute to cancer progression and chemotherapeutic resistance (Xu et al., 2018; Emmanouilidi et al., 2019). Recent investigations have demonstrated that pharmacological inhibition of exosome release can render the cancer cells predisposed to chemotherapeutic agents (Catalano and O'driscoll, 2020).

Non-toxic pharmacological agents have also been shown to selectively control the release of extracellular vesicles and may be applicable to pathological conditions including cancer (Lange et al., 2017). Kosgodage et al. demonstrated that administration of CBD to prostrate, breast adenocarcinoma and hepatocellular carcinoma cell lines significantly inhibited exosome release. Furthermore, the authors found altered mitochondrial function post cannabinoid administration and increased sensitivity to the chemotherapeutic regime. Based on this observation, the study suggests that cannabinoids might exercise their anti-cancer function by exerting regulatory effects on exosome production (Kosgodage et al., 2018). While exosomes contribute to oncogenesis in glioblastoma (GBM), and CBD is found to be an effective treatment strategy for the same, a more recent study from the same group demonstrated a link between

CBD and the extracellular vesicle secretion in GBM. This study reported that CBD treatment altered the extracellular vesicle profile (both production and cargo) in GBM cells. Its administration in GBM cells reduced the expression of pro-tumoral miR21 and increased anti-cancerous miR 126. Alteration of miR21 in GBM has been previously shown to affect cell survival and invasion. Furthermore, the combination of CBD with temozolomide downregulated miR21 in extracellular vesicles derived from GBM cells and in GBM cells in comparison to temozolomide administration alone (Kosgodage et al., 2019). This study backs up the growing evidence on the anti-cancer properties of cannabinoids and their use in combination therapy as discussed below. The mechanisms through which cannabinoid treatment targets exosomes release need to be fully elucidated.

5. Cannabinoids in combination with cancer therapies

The complex nature of cancer accentuates the need for considering treatment strategies in combination. These combinational therapies in cancer have several theoretical benefits over monotherapy. The main principle behind this approach is to target the tumour concurrently at various levels by employing drugs with different mechanisms of action (Liu, 2008). Most of the studies have shown that treatment with cannabinoids reduces tumour growth and does not eliminate it. Therefore, the focus is shifting on using cannabinoids in combination with other standard cancer therapies such as chemotherapy and radiation therapy.

5.1. Cannabinoids increase sensitivity to chemotherapeutic drugs

Poor chemosensitivity and development of resistance to chemotherapeutic drugs are key deterrents in therapeutic targeting of cancer. Cannabinoids can be combined with standard chemotherapeutic regimes to increase the sensitivity of cancer cells, thus making the chemotherapeutic drug more potent (Table 1). Furthermore, using drugs in combination might be a more effective method for achieving therapeutic efficacy at a less toxic dose. In myeloma, Morelli et al. reported increased sensitivity of cell lines to bortezomib (BORT) cytotoxicity upon the addition of 20 μM of CBD. In addition, the inclusion of CBD increased the effect of BORT, producing a response similar to that achieved by using higher BORT doses (Morelli et al., 2014b). A recent study showed that synthetic cannabinoid WIN-55212-2 increased the sensitivity of myeloma cell lines to chemotherapeutic drug melphalan or dexamethasone in combination (Barbado et al., 2017).

Therapeutic targeting of malignant brain tumours poses a major challenge. Nabissi et al. provided evidence that addition of CBD increased the susceptibility of human glioblastoma cells to chemotherapeutic agents carmustine (BCNU), doxorubicin (DOXO) and temozolomide (TMZ) (Nabissi et al., 2013). Furthermore, this study found that normal glial cells were refractory to the antineoplastic properties of CBD. In line with the previous investigation (Morelli et al., 2014b), integration of CBD with anti-cancer agents sustained high anti-cancer function at lower chemotherapeutic doses, thereby facilitating a reduction in side effects. (Nabissi et al., 2013). However, this study is limited by the use of a single glioblastoma cell line. A recent study demonstrated that co-application of DOXO and CBD enabled the entry of DOXO into tumour cells. This facilitated uptake might permit the use of lower concentration of this cytotoxic drug thus curtailing toxic side effects (Neumann-Raizel et al., 2019). In line with this approach, our group has demonstrated that the use of CBD in combination with cytotoxic drug gemcitabine could counteract the mechanisms involved in gemcitabine resistance in pancreatic cancer. Gemcitabine treatment increases ERK activation, a common mechanism to acquire chemoresistance both *in vitro* and *in vivo* (Adamska et al., 2018; Domenichini et al., 2019). CBD opposed this effect when used in combination with gemcitabine. This is the only study so far to have investigated cannabinoid in combination with a chemotherapeutic drug in transgenic mice models for pancreatic cancer (Ferro et al., 2018).

In leukaemia, Holland et al. demonstrated that exposing a multidrug-resistant cell line (CEM/VLB100) with higher P-glycoprotein (P-gp) expression to cannabinoids, THC and CBD, in combination with vinblastine, selectively downregulated the P-gp expression and increased the sensitivity of cells to vinblastine. Upregulated P-gp expression is associated with multidrug resistance and cancer relapse in leukaemia and lymphoma post-chemotherapy initiation. The study demonstrates a threefold reduction in IC50 value of Vinblastine at 10 μM concentration of THC and CBD (Holland et al., 2006). A similar study, showed that administration of sub cytotoxic dose of cannabinoids, CBD, CBN and THC increased the chemosensitivity of MEF3.8/Bcrp 1 A2 cell line to topotecan and mitoxantrone. Administration of CBD, CBN and THC (10 μM) in combination with Mitoxantrone decreased the resistance by four to six times by inhibiting the breast cancer resistance protein (BCRP/ABCG2) (Holland et al., 2007). Furthermore, Liu et al. demonstrated that adding 1 μM THC to the anti-leukaemia regime (cytarabine, vincristine and doxorubicin) could increase their cytotoxic effect in leukaemia cell lines in a pERK dependent manner. Based on this data, the authors hypothesise that adding THC might help lower the dose of chemotherapeutic drugs in leukaemia (Liu et al., 2008). As previous studies have suggested that the ERK pathway is a cell response determinant in THC stimulated cell death (Powles et al., 2005), this data further suggest the role of cannabinoids in synergism with chemotherapy.

5.2. Anti-neoplastic functions of cannabinoids in combination

Several studies have demonstrated that in addition to increasing cancer cell susceptibility, cannabinoids can synergise with chemotherapeutic agents and perform/or enhance the anti-neoplastic functions of chemotherapeutic drugs (Table 1). Administration of synthetic cannabinoid AM251 and celecoxib, a COX-2 inhibitor, in combination in a melanoma cell line (A375 cells) produced a greater effect on cell viability than that observed for each drug independently. On the contrary, selective and non-selective COX-2 inhibitors in combination with AM251, did not produce cytotoxicity in this cell line. This may be due to the molecular similarity in AM251 and celecoxib. However, this effect was investigated only in one cell line due to its upregulated COX-2 expression (Carpi et al.,

2015). The co-administration of BORT and CBD synergistically decreased proliferation of myeloma cell lines (Morelli et al., 2014b).

In gastric cancer, AEA was reported to induce cell death in HGC-27 cell line, which became more pronounced on combination with paclitaxel via potential activation of caspase. The paper further suggests synergism between paclitaxel and cannabinoids (Miyato et al., 2009). Another study illustrated the synergistic interaction between AM251 and 5-fluorouracil in pancreatic cancer (Fogli et al., 2006). Donadelli et al. reported a synergistic reduction in pancreatic cancer cell growth by gemcitabine in combination with ACPA, GW405833 and SR141716, via ROS supported autophagy. This study also shows that normal fibroblasts, in contrast to cancer cells, are significantly less susceptible to cannabinoid treatment, and adding gemcitabine does not result in further growth inhibition. Furthermore, intraperitoneal administration of SR141716 plus gemcitabine causes significant tumour growth inhibition in cancer xenografts (Donadelli et al., 2011). In line with this study, data from our combinational study show synergistic effects of CBD and gemcitabine both *in vitro* and *in vivo* (Ferro et al., 2018).

In glioma, Torres et al. demonstrated that the combination of THC with temozolomide (TMZ) inhibited tumour growth in a glioma xenograft model. Furthermore, combined treatment with these two agents exhibited much higher growth inhibition that each of them alone (Torres et al., 2011). In 2013, Nabissi et al. reported that co-administration of CBD (10 μM) with carmustine (200 μM) or TMZ (400 μM) resulted in synergistic anti-glioblastoma cytotoxic activity (Nabissi et al., 2013). Although there is evidence that cannabinoids potentiate the activity of chemotherapeutic agents, some studies suggest otherwise. An investigation in C6 glioma cells observed no synergistic effects of cannabinoids and tamoxifen, on cell proliferation (Jacobsson et al., 2000). Deng et al. reproduced the results by Nabissi et al. and found only a few concentration ranges showed synergistic effects. Interestingly, the authors observed additive effects in most concentration ranges and further showed that a substantial number of combinations caused antagonism (Deng et al., 2017b). Another study in leukemic cell lines reported lack of synergism between THC and chemotherapeutic drug cisplatin. However, the authors did not use isobologram analysis and dose-response curves to establish the extent of synergistic interactions (Powles et al., 2005).

5.3. Combining multiple cannabinoids with cytotoxic agents

Multiple cannabinoids can be combined with chemotherapeutic agents to scale up the antineoplastic responses. CBD and THC are the most investigated cannabinoids in this regard (Table 1). Both these cannabinoids interact differently with the receptors, thus combining them with anticancer treatments might be beneficial. For instance, the addition of CBD to THC resulted in decreased cell viability, cell cycle arrest and programmed cell death in two (U251 and SF126) out of three glioblastoma cell lines (Marcu et al., 2010). THC in combination with CBD was found to reduce cell viability in melanoma cell lines. Furthermore, 1uM of this combination and 5uM of each cannabinoid compound used alone had a comparable effect on apoptosis (Armstrong et al., 2015). As previously mentioned, CBD can help ameliorate the psychoactive effects of THC, thus offering an advantage on being co-administered.

Some studies have evaluated a combination of multiple cannabinoids with chemotherapeutic agents. In leukaemia cell lines, a study used multiple cannabinoid combinations to identify the most potent anti-cancer combination. They further reported that combining cannabinoids with CBD resulted in the most potent combination. The study found that the combination of CBD with THC was as potent as CBD with cannabigerol (CBG) in HL60 leukaemia cells. The authors further assessed CBD plus CBG and CBD plus THC in combination with anti-leukaemia chemotherapeutic agents vincristine and cytarabine. Although both cannabinoid pairs showed improved activity in combination with cytotoxic drugs, the results with the CBD-THC pair were more apparent. The latter investigation further highlights that the order of administration of these drugs in combination affects the overall results (Scott et al., 2017). Nabissi et al. reported on the combination of CBD-THC with carfilzomid, an immune proteasome inhibitor, in myeloma. This triple combination was found to decrease both cell viability and migration in multiple myeloma cell lines (Nabissi et al., 2016). Torres et al. observed that co-administration of CBD and THC at submaximal concentration with TMZ was found to elicit strong anti-tumour activity in both TMZ-resistant and sensitive tumours (Torres et al., 2011). In line with this study, Valero et al. demonstrated that oral administration of sativex, an oromucosal spray containing both CBD and THC (1:1), enhanced the effect of TMZ in glioma xenograft models (López-Valero et al., 2018b).

Evidence from *in vitro* and *in vivo* studies offers an excellent way of predicting and establishing treatment combinations with cannabinoids that have the strongest possibility for successful translation to clinic. However, clinical trials are required to test the value of these combinations in the cancer setting. Furthermore, the concentration of the cannabinoids to be combined with other cytotoxic drugs needs to be optimised before treatment. In another combination study, Valero et al. reported that a CBD concentration higher than THC (5:1 respectively), in combination with TMZ, targeted glioma stem cells much more efficiently than the sativex like formulation (López-Valero et al., 2018a). This is beneficial because the presence of a higher dose of CBD might lower the psychotomimetic effects of THC. Furthermore, the effect does not apply to all chemotherapeutic treatments even in a single cancer type. Co-administration of CBD-THC 1:1 and carmustine (BCNU), a drug with structural similarity to TMZ, did not enhance the anti-cancer activity in glioma xenografts (López-Valero et al., 2018b).

5.4. Cannabinoids in combination with radiation therapy for cancer

Few studies suggest the potential application of cannabinoids in combination with radiation therapy (Table 1). Emery et al. demonstrated the role of WIN55212-2 in enhancing the effect of radiation in breast cancer cells. The study found no significant effects of radiation on the cell cycle. However, on combination with WIN55212-2, radiation of cells resulted in a substantial increase in the sub G1 cell population (Emery et al., 2012).

Based on previous studies in glioma (Torres et al., 2011; De Lago et al., 2006; Nabissi et al., 2015; Sanchez et al., 1998), Scott et al.

Table 1
Effects of cannabinoids used in combination with standard therapy in cancer.

Cannabinoid	Treatment	Cancer/cell type	Remarks	Reference
CBD	Bortezomib	Myeloma	Increased the sensitivity of cell line as CBD BORT in combination produced a response similar to higher doses of BORT. Administration of this combination resulted in inhibition of cell proliferation, cell cycle arrest and cell death induction	Morelli et al. (2014b)
WIN-55212–2	melphalan or dexamethasone	Myeloma	Increases sensitivity of myeloma cell lines resistant to melphalan or dexamethasone Increased anti-cancer activity of melphalan or dexamethasone	Barbado et al. (2017)
CBD	Carmustine (BCNU) doxorubicin (DOXO) and temozolomide (TMZ)	Glioblastoma	Increased sensitivity of glioblastoma cells to BCNU, DOXO and TMZ cytotoxicity CBD lowered the dose of cytotoxic drugs required Synergistic anti-glioblastoma cytotoxic activity on the use of CBD in combination with BCNU and DOXO	Nabissi et al. (2013)
CBD	DOXO	Hepatocellular carcinoma	CBD potentiated the effect of DOXO Lower concentration of DOXO used in combination was able to decrease cell viability	Neumann-Raizel et al. (2019)
CBD	Gemcitabine	Pancreatic cancer	Increased sensitivity of cell lines to gemcitabine Synergistic effect of CBD and gemcitabine Could counteract the mechanisms involved in gemcitabine resistance in pancreatic cancer	Ferro et al. (2018)
CBD, THC	Vinblastine	Leukaemia	Downregulated P-glycoprotein Increased the sensitivity of cells to Vinblastine	Holland et al. (2006)
CBD CBN THC	Mitoxantrone, topotecan	Murine embryonic fibroblast	Co-administration increased chemosenstivity of MEF3.8/Bcrp1 A2 cell line. Decreased resistance by inhibiting ABCG2/BCRP	Holland et al. (2007)
THC	cytarabine, vincristine and doxorubicin	Leukaemia	Increased the cytotoxic effects of anti-leukaemia regime in pERK dependent manner.	Liu et al. (2008)
AM251	celecoxib	Melanoma	The coadministration had a greater effect on cell viability than each treatment independently	Carpi et al. (2015)
AEA	Paclitaxel	Gastric cancer	Pronounced cell death in cancer cells	Miyato et al. (2009)
AM251	5-fluorouracil	Pancreatic cancer	Pronounced growth inhibition in MiaPaca −2 cells	Fogli et al. (2006)
ACPA GW405833 SR141716	Gemcitabine	Pancreatic cancer	Combination increased cell growth inhibition compared to single treatment by ROS dependent autophagy	Donadelli et al. (2011)
THC CBD	TMZ	Glioma	Higher growth inhibition by combination than either of the treatments Submaximal dose of THC CBD with TMZ elicited strong anti-neoplastic activity in TMZ resistant and sensitive tumours	Torres et al. (2011)
CBD AEA THC	Tamoxifen	Glioma	Cannabinoids showed significant serum dependent effects No significant interactions between cannabinoids and tamoxifen reported	Jacobsson et al. (2000)
CBD	BCNU TMZ CDDP	Glioma	In mouse cells, TMZ/CBD combination trigger additive cell killing but antagonise in their cell growth inhibition responses In humans, combinations exhibit synergistic cell death but only additive anti-proliferative response	Deng et al. (2017a),b
THC	cisplatin		Small concentrations of THC did not enhance the cytotoxicity profile of THC Lack of synergism between combination treatments; only additivity reported	Powles et al. (2005)
CBD CBG THC	vincristine, cytarabine	Leukaemia	Combination reduced cell viability Suggest synergistic interaction between cannabinoids and vincristine Improved cytotoxic response Administration sequence dependent activity	Scott et al. (2017)
CBD THC	Carfilzomid	Myeloma	Triple combination synergistically decreases cell viability and invasion	Nabissi et al. (2016)
CBD THC (1:1)	TMZ BCNU	Glioma	CBD/THC enhance the effect of TMZ but not BCNU in glioma xenografts	López-Valero et al. (2018b)
CBD THC (5:1)	TMZ	Glioma	Higher concentration of CBD in the triple combination enhance the anti-tumour effect	López-Valero et al. (2018a)
WIN55212–2	Radiation therapy	Breast cancer cells	Increase in the cell population in G1 phase	Emery et al. (2012)
CBD THC	Radiation therapy	Glioma	Reduced tumour size in orthotopic glioma model	Scott et al. (2014)
Cannabinoids	Radiotherapy biomaterials	Pancreatic and lung cancer	Enhance efficiency Minimum inconvenience Minimum drug toxicity	Yasmin-Karim et al. (2018)

investigated whether cannabinoids could enhance the cytotoxic effects of irradiation. This study reported a remarkable reduction in tumour size post the use of triple combination (CBD, THC and radiation) in an orthotopic mouse glioma model. Interestingly, the proliferation marker Ki67 intensities were not altered post any treatment combination (Scott et al., 2014). A recent study assessed the potential to combined cannabinoids with radiation therapy or smart radiotherapy biomaterials to increase the therapeutic efficacy in lung and pancreatic cancer (Yasmin-Karim et al., 2018). In present clinical practice, radiotherapy biomaterials such as beacons, spacers and fiducials are commonly applied while performing radiation therapy on tumours (Cormack et al., 2010). The study proposed the replacement of these biomaterials with smart radiotherapy biomaterials loaded with cannabinoids for delivery in tumour with enhanced therapeutic efficacy, minimum patient inconvenience and drug toxicity. Although this study focuses on pancreatic and lung tumour, the authors suggest that this technique can be applied to other cancers as well (Yasmin-Karim et al., 2018).

Even though these studies indicate that cannabinoids enhance the response to radiation therapy in cancer, the mechanisms for this drug-radiation interaction are not fully understood. Using TUNEL staining, Scott et al. demonstrated the presence of apoptosis in the tumour but did not find significant differences between triple combination and cannabinoid treatment groups. Therefore, this study did not clearly state that the role of apoptosis in triple combination mediated tumour size reduction *in vivo*, but suggested its possibility. The authors further proposed that this combination might mediate the ant-cancer function by inhibition of angiogenesis (Scott et al., 2014). However, further research is required to fully understand how cannabinoids in combination with radiation improve the overall outcomes and which the most effective way to use them is.

5.5. Cannabinoids as palliatives for chemotherapy-associated side effects

Chemotherapeutic regimens are associated with side effects including pain, appetite loss, sleep disorders, neuropathy, nausea and vomiting. These effects can persist even after the treatment regimens are ceased, thus affecting the quality of life. Cannabimimetic compounds are a promising strategy for managing chemotherapy-associated side effects due to their multilateral biological functions in various tissues.

The ECS and cannabinoids have been extensively studied in palliative medicine. Dronabinol containing THC is available in the USA as an antiemetic and for treatment of AIDS-associated anorexia and weight loss (Badowski and Yanful, 2018). Sativex, is available for the symptomatic treatment of spasticity in non-responding MS patients. It might also be useful as an adjunctive analgesic in MS patients for relieving neuropathic pain (Patti et al., 2016). Sativex has also been licenced in Canada as an analgesic in cancer treatment. A synthetic THC equivalent, nabilone, was approved by the FDA as an antiemetic for cancer chemotherapy patients who fail to respond to conventional therapies. However, its use is restricted due to potential psychotomimetic effects in patients (Ware et al., 2008). In 2018, EPIDIOLEX (highly purified plant-derived CBD), an oral solution, has been approved by US food and drug administration (FDA) for the treatment of Dravet syndrome associated seizures in early age patients (Silvestro et al., 2019).

5.5.1. Cancer-associated anorexia and cachexia

Anorexia and cachexia represent a series of metabolic alterations starting from low-calorie intake and various magnitude of inflammation to a refractory stage promoting catabolism, which is further associated with decreased performance and lower survival (Jatoi et al., 2002; Aoyagi et al., 2015). Over 50% of patients have reported a loss of appetite and consequent weight loss. Cancer-associated appetite loss can be due to tumour-related factors such as bowel obstruction, inflammatory cytokines and compromised gut function due to tumour invasion. However, it can also be dependent on cancer treatment (Childs and Jatoi, 2019; Ezeoke and Morley, 2015). In the head and neck tumour, for instance, irradiation of the mouth as a part of radiation therapy affects the oral mucosa, alters taste sensation and this can cause appetite changes and weight loss (Asif et al., 2020). At present, the pharmaceutical therapies for stimulating appetite include corticosteroids and progestins. However, these therapies provide short-term improvement and are limited by adverse effects.

Early reports of dronabinol as an appetite stimulant and weight stabilizer in HIV encouraged research in cancer patients (Beal et al., 1995). There is low-quality evidence for the use of cannabinoids in the treatment of cancer-associated appetite loss. In a phase II trial, Nelson et al. reported a positive impact on appetite in cancer patients post administration of THC (Nelson et al., 1994). However, in phase III trials, Jatoi et al. administered dronabinol and megestrol acetate in 500 patients. The study found megestrol acetate was more effective than dronabinol in cancer-related anorexia. Furthermore, no additional benefit was reported in weight or appetite on the use of dronabinol and megestrol acetate in combination (Jatoi et al., 2002). In another phase III randomised control trial (RCT), THC, cannabis extract and placebo were administered in 243 cancer patients. This study reported no significant differences in appetite and quality of life between THC, cannabis extract and placebo or between cannabis extract and THC (Strasser et al., 2006). A smaller study group found changes in chemosensory perception and enhanced food taste in patients administered with THC (Brisbois et al., 2011). Bar and colleagues also reported improved appetite in cancer patients post THC administration, even though there was no significant difference in calorie intake (Bar-Lev Schleider et al., 2018; Brisbois et al., 2011).

5.5.2. Cancer-associated pain

More than 50 percent of cancer patients report moderate to severe cancer-associated pain (van den Beuken-van Everdingen et al., 2007). The interaction between sensory neurons (pain receptors) and cancer, as well as physiological, morphological and immunological alterations, sensitize the central and peripheral nervous system. However, these effects differ according to the type and location of cancer (Schmidt et al., 2010). Cannabis has served as an analgesic for a long time. Cannabinoid compounds can modulate pain transmission through CB1 receptor expressed on these pain receptors. Furthermore, CB1, which is expressed in the brain and spinal cord, modulates pain and its transmission. Therefore, therapeutic targeting of the CB1 receptor is a potential strategy in cancer-related

pain management. THC was found to mediate analgesic properties through both CB1 and CB2 receptors (Hudson et al., 2019; Davis, 2014). In addition, cannabinoids can also activate TRPV1 receptors, which perceive pain stimuli (De Petrocellis et al., 2011a).

Several preclinical studies have demonstrated the effectiveness of cannabinoids for cancer-related pain management. Guerrero et al. demonstrated that administration of WIN55212–2 and AM1241 increased the pain-perceiving threshold in cancer mice (Guerrero et al., 2008). Administration of AEA along with FAAH was found to decrease mechanical hyperalgesia in bone cancer mouse models (Khasabova et al., 2008). Cancer induced hyperalgesia was alleviated in mice post administration of WIN55212-2 (Potenzieri et al., 2008) and CP-55,940 (Hamamoto et al., 2007).

RCTs have been performed from as early as 1975 (Noyes et al., 1975) to validate the analgesic potential of cannabinoids in cancer. An observational study in 112 cancer patients reported pain alleviation post administration of nabilone therapy (Maida et al., 2008). In 2017, two reviews published on the analgesic properties of cannabis in cancer concluded that cannabimimetic compounds had the potential to alleviate both neuropathy and pain in cancer patients. However, both studies also highlight the potential side effects associated with the use of such as drowsiness, dry mouth, confusion, blurred vision and nausea (Blake et al., 2017; Bennett et al., 2017). Fallen et al. conducted two double-blind RCT for Sativex in patients with advance cancer pain unresponsive to opioid therapies. In comparison to the control arm, patients receiving the drug did not experience pain alleviation. However, a subgroup analysis found that the compound was effective in US patients ($P = 0.04$) in comparison to patients from other countries (Fallon et al., 2017). Bar et al. conducted a large-scale observational study in cancer patients to evaluate the efficacy of cannabinoid compounds. At baseline, 77% of the patients reported medium pain intensity and were offered 16 different CBD and THC compounds administered through either inflorescence or oil. Six months post-treatment, only 4.6 percent of the patient population reported a high intensity pain as opposed to 52.9 percent prior treatment. However, the study suffers from a lack of a control group. Therefore, it cannot be known whether the cannabinoid treatments reduced the pain or other factors, such as time, were involved (Bar-Lev Schleider et al., 2018). In another recent study, Casarett et al. demonstrated that 47% of participants experienced reduction in neuropathic pain post cannabinoid treatment. (Casarett et al., 2019).

Nearly 40% of cancer patients experience neuropathic pain. This type of pain may be a consequence of tumour burden and/or chemotherapy. There are few available therapies with limited efficacy for the management of cancer-related neuropathy. Preclinical research investigations have demonstrated the involvement of ECS in pain reduction in both rat and mouse models for cisplatin and paclitaxel-induced neuropathy (Mulpuri et al., 2018; Segat et al., 2017; King et al., 2017; Pascual et al., 2005). Clinical trials, demonstrating the efficacy of cannabinoid compounds for various conditions including cancer, have been conducted. However, pain is a heterogeneous feature of cancer and chemotherapeutic regimes, thus making it hard to target. For instance, the therapeutic strategy for radiation-induced pain might not be applicable for chemotherapy-based neuropathy. Not much is currently known about the physiological and biochemical effects of cannabis and cannabimimetic compounds as analgesics. Furthermore, the mechanism of action of these compounds in pain management needs to be explored in more detail. It is currently unclear whether cannabinoids exert their effects by reducing damage in peripheral nerves, by reducing the hypersensitivity of CNS, or both (Kleckner et al., 2019).

5.5.2.1. Cannabinoids in combination with opioids for pain management. The current pain management plan for cancer involves the use of opioids. However, their clinical use is associated with adverse effects, which might need additional symptomatic treatment. Opioid therapy has shown to promote emesis, seizures, convulsions, respiratory depression and abnormal renal function. In addition, sustained use of opioids is associated with increased hyperalgesia. Opioid use has also shown to encourage angiogenesis, inhibit apoptosis and promote cell cycle progression in breast cancer. On the contrary, cannabinoid treatments have been found to alleviate these side effects (Elikkottil et al., 2009). Both opioids and cannabinoids mediate anti-nociception through GPCRs. The co-localisation of opioid receptors, CBRs and TRPV1 channel, suggests a crosstalk between them for pain modulation (Zádor and Wollemann, 2015).

Many studies have explored the potential of using cannabinoids in combination with opioids for the management of cancer-related pain. Co-administration might further lower the dose of opioids and alleviate the symptoms associated with the use of opioid therapy. Smith et al. found anti-nociceptive activity equivalent to higher doses of morphine or THC when lower doses of both were used in combination in rats (Smith et al., 2007). The analgesic property of morphine was increased after pretreatment with HU-210 in rats (Wilson et al., 2008). Furthermore, knockout of the CB1 receptor was associated with reduced addiction and withdrawal to opioids in mice (Ledent et al., 1999). The analgesic actions of WIN55212-2 were enhanced when naltrexone was administered in ultra-low concentrations (Paquette and Olmstead, 2005). At present, no RCTs has been performed to compare the analgesic properties of opioid and cannabinoid in cancer patients. However, patients have reported the use of cannabis as a substitute for an opioid prescription (Lucas and Walsh, 2017).

Cannabinoids have been found to synergise with opioids when administered topically and systemically (Elikkottil et al., 2009). Co-administration of dronabinol with opioids reduced pain in chronic non-cancer patients (Narang et al., 2008). However, not all studies have reported synergism when these compounds are co-administered. In a double-blind randomised study, Seeling et al. reported no synergism on the use of THC adjunct to piritramide, an opioid agonist used in postoperative pain (Seeling et al., 2006). Anecdotally, the combination of cannabinoids and opioids has been used to achieve an opioid-sparing effect. Boehnke et al. reported improvement in the quality of life, decrease in opioid use by 64% and reduction in side effects in patients using cannabis for pain management (Boehnke et al., 2016).

5.5.3. Chemotherapy-induced nausea and vomiting

Nausea and vomiting are frequently reported side effects for chemotherapeutic regimes. Over 60% of the patients undergoing first chemotherapy cycle experienced chemotherapy induced nausea and vomiting (CINV). Moreover, 37.2 percent of the patients reported

impaired daily function due to CINV (Haiderali et al., 2011). Furthermore, results from an online survey showed that over 30% of the patients with adverse CINV might experience chemotherapy delay or discontinuation (Van Laar et al., 2015) thus, highlighting the burden of CINV in patients. The downregulation of 5-hydroxytryptamine receptor (5-HT) was a major advancement for the control of vomiting. The incidence of emesis was reduced by 70% when the 5-HT antagonist was used in combination with dexamethasone during chemotherapy. However, these medications were less effective in suppressing nausea. Furthermore, they were ineffective in reducing both delayed and anticipatory nausea and vomiting (Parker et al., 2011). More recently, antagonists for NK1 receptors have been reported to be effective for reducing not only emesis but also delayed emesis (Van Belle et al., 2002). Nevertheless, these drugs, alone or in combination with 5-HT antagonists, were found to be less effective in nausea (Slatkin, 2007).

The presence of CBRs in the central nervous system makes them targets for chemotherapy-associated nausea and vomiting. Several pre-clinical studies have suggested the anti-nausea and emesis properties of cannabimimetic compounds (Parker et al., 2011). Many reviews have evaluated the therapeutic potential of cannabinoids in CINV. A systematic review included 23 RCTs in adults that compared cannabimimetic compounds to either placebo or an anti-emetic medication. The authors concluded that cannabinoids were more effective than placebo but similar to conventional anti-emetic medications in alleviating CINV. However, these studies provide low-quality evidence for the use of cannabinoids in CINV (Smith et al., 2015). Another study addressed the safety and tolerability profile of cannabis in CINV and found that, although cannabinoids were more effective than placebo, they had a lower safety and tolerability profile than placebo and anti-emetics. Based on the results, the study did not recommend cannabinoids as the first or second-line intervention strategy for CINV when more effective and safer anti-emetics were available (Tafelski et al., 2016).

Most of the RCTs have a small and diverse population of cancer patients. There appears to be a variation in the anti-emetic effect of cannabinoids which may be further affected by the anti-emetic risk associated with the chemotherapeutic intervention strategy used for a particular patient, type of cancer in question, previous history of cannabis use, drug dose, formulation type and route of administration. In addition, most of these studies were conducted in the 1970s–1990s when there was a lack of standard care regime for emesis. Therefore, there is a need to evaluate the anti-CINV potential of cannabinoids in comparison to modern anti-emetic regimes. Furthermore, there is a lack of good quality evidence to recommend the use of cannabinoids in CINV (Tafelski et al., 2016; Smith et al., 2015). Paradoxically, cannabinoid hyperemesis syndrome, described as uncontrollable emesis episodes, is recognised as a symptom of cannabis episodes. Though it is often associated with the use of higher doses of recreational forms of cannabis, its aetiology is largely unknown and is anticipated to involve the ECS (Sorensen et al., 2017).

6. Translating cannabinoid treatments to the clinic

Data collected to date regarding the anti-cancer effects of cannabinoids is limited to the preclinical studies conducted in cell lines and animal models. The *in vitro* and the *in vivo* studies in cancer suffer from low predictive value, thus low translational power. In clinical practice, the use of cannabinoids is limited to palliation in a few diseases. From a practical perspective, several factors need to be considered for translation of cannabinoids as anti-cancer therapeutic agents alone and in combinational therapies. This section will focus on the key factors to be considered while using cannabinoids for therapeutic intervention in cancer.

6.1. Pro-tumorigenic and biphasic responses of cannabinoids in cancer cells

When considering cannabinoids for therapeutic intervention in cancer, it is important to take into account the bimodal effects of cannabinoids in the tumour. The studies discussed above would suggest the general anti-cancer effect of cannabinoids. However, this is not always the case. There are reports in the literature suggesting the activation of cannabinoid receptors can promote cancer. Hart et al. demonstrated that treatment of cancer cells with THC, HU-210, WIN55212-2 and AEA stimulated mitogenic signalling (Hart et al., 2004). In prostate cancer cells, Sanchez et al. demonstrated the mitogenic effects of Meth-AEA (0.1 μM) through enhanced 3-H thymidine incorporation in DNA (Sánchez et al., 2003).

The absence of CBR expression might account for the growth-promoting effects of cannabinoids. Treatment of breast cancer mice that do not express CBRs with THC resulted in increased tumour growth via inhibition of immune response (Mckallip et al., 2005). Evidence suggests that the growth-promoting and anti-cancer responses might depend on the dose of cannabinoids administered. In lung and brain cancer, although micromolar THC concentration induces apoptosis, nanomolar concentrations were found to encourage proliferation (Hart et al., 2004). Another study reported that only THC and HU210 could decrease cell viability in astrocytoma cells at higher concentrations. The IC50 value for THC and HU210 was determined to be 14.8 μM and 2.98 μM respectively. Endocannabinoids AEA and 2-AG, and another CBR agonists CP55,940 and WIN55212-2 did not result in a significant decrease in the cell viability at lower concentrations (<5 μM). In general, these results suggested poor efficacy of CBR ligands to induce cell death in astrocytoma cell lines (Widmer et al., 2008).

These opposite responses of cannabinoids may be explained by the concentration of serum used in these *in vitro* studies given that cannabinoids can bind to albumin. Jacobsson et al. investigated the effects of Tamoxifen and cannabinoid compounds on cell survival at different serum concentrations in C6 glioma cells. The study found that a decrease in FBS content from 10 percent (commonly used in cell culture) to 0.4 to 0 percent resulted in increased cell sensitivity to tamoxifen. Furthermore, a six-day incubation of C6 glioma cells with THC and CBD, but not endogenous AEA, in serum-free medium resulted in a modest decrease in cell viability (Jacobsson et al., 2000).

The potency of cannabinoids might vary in different cell lines for a particular cancer type. A study investigated the effect of AEA on three prostate cancer cell lines stimulated by the epidermal growth factor. Although the authors observed a dose-dependent decrease in cell proliferation in all the three cell lines (DU145, PC3 and LNCaP), the potential of AEA was found to considerably vary between the

cells. While in DU145 and PC3, a concentration of 5 μM of AEA was able to completely inhibit EGF induced cell growth, in LNCaP cell line, only a 30% reduction in cell growth was observed at this concentration (Mimeault et al., 2003). These observations can be a result of the distinct nature of cell lines or of a cell line dependent variation in AEA metabolism (Endsley et al., 2008; Ruiz-Llorente et al., 2004). Thus, in general, these studies highlight the high heterogeneity in cancer's ECS profile, lack of consensus on anti-cancer cannabinoid responses and the experimental variability. These factors need to be taken into account while considering the chemotherapeutic potential of cannabinoids and their use in cancer patients.

6.2. Cannabinoid formulation

The improvement of existing cannabinoid formulations is an exciting area of cancer research. Apart from the pure cannabinoids, different formulations prepared from cannabis have been investigated in cancer. A study compared the antioxidant enzyme expression and activity *in vitro* between supercritical fluid and ethanol extracts of hemp seeds. In comparison with the ethanol extract, the supercritical fluid extracts had more radical scavenging activity. The real-time PCR results of both extract-treated hepatocellular carcinoma cells (HepG2) showed a dose-dependent increase in antioxidant enzyme expression. At 500 μg/mL, the supercritical fluid extract exhibited more antioxidant enzyme expression activity than the ethanol extract. These findings suggest that hemp seed extracts blocked the oxidative stress and can be a potential therapeutic target. However, further research is required for the same (Hong et al., 2015).

In CHL-1 xenograft mice, Armstrong et al. found THC extracts to be more effective in reducing tumour growth in comparison to pure THC (Armstrong et al., 2015). Another study compared the effects of cannabinoid extracts to pure cannabinoids and observed a stronger effect of extracts on prostate cancer cell lines (De Petrocellis et al., 2013). A similar more recent study compared 12 cannabinoid extracts with their corresponding pure forms in 12 cancer cell lines. The authors found the extracts to be stronger than pure THC. In addition, the authors found that treatment with cannabinoid extracts containing similar concentration of THC resulted in different effects in the same cell line, thus suggesting that cannabinoid responses might be dependent on the characteristics of cell line being investigated and the composition of the formulation (Baram et al., 2019).

In glioma, Scott et al. compared the activities of less refined botanical drug substance (BDS) and pure forms of CBD and THC. While the BDS forms contained only 65% of each agent (w/w), the pure forms had no more than 5% impurities. The authors found that the efficacy of pure CBD was higher than its less refined form. Although it can be argued that the lower concentration of CBD in the BDS form might account for the lower efficacy recorded, the dose-response experiments performed by the authors did not support this entirely. On the contrary, the BDS forms of THC containing approximately 35% of impurities (non-THC cannabinoids) was more active than its pure formulation. These results indicate the complexity of cannabinoid interactions and further suggest concentration and type dependent activity (Scott et al., 2014).

It is well known that in addition to CBD, other cannabinoid compounds can help alleviate the psychoactive effects of THC (Pertwee, 2009). Therefore, based on this rationale, it is only ideal that, while investigating the chemotherapeutic potential of cannabinoids in cancer in pre-clinical models or clinical trials, studies comparatively evaluate pure and BDS forms of cannabis.

6.3. Resistance to cannabinoid treatments in cancer

The development of resistance to chemotherapeutic regimes is one of the major problems in cancer patients. Tumours can develop resistance to a variety of drugs with no functional or structural homology consequently disrupting therapeutic regimes. Studies have suggested the involvement of ECS in the modulation of chemotherapy-associated drug resistance. In glioma, Lorente et al. observed that susceptivity to THC was determined by differential expression levels of the gene rather than CBRs. The authors showed that Midkine aids resistance to anti-cancer actions of THC by activation of anaplastic lymphoma tyrosine kinase receptor (ALK), which impedes cannabinoid mediated activation of autophagy. Furthermore, Midkine or ALK inhibition in THC resistant glioma cell-derived tumour xenografts increases sensitivity to cannabinoid treatments. The findings support that activation of Midkine-ALK axis facilitates resistance to chemotherapeutic actions of cannabinoids and opens up avenues for the combined administration of Midkine inhibitors and THC (Lorente et al., 2011a, 2011b, 2011c). To that end, ALK inhibitors are being evaluated in clinical studies for cancers including Non-Small cell lung cancer (NCT01625234) and glioblastoma (Grande et al., 2011; Wu et al., 2016).

Interestingly, it appears that growth factors play a role in the development of resistance to chemotherapeutic activity of cannabinoids (Hart et al., 2004). In the previous studies, Lorente et al. showed that downregulating EGFR in glioma cells enhances anti-cancer actions of THC (Lorente et al., 2009). Evidence suggests the involvement of multidrug resistance protein 1 (MDR1/ABCB1), a member of the ATP binding cassette (ABC) transporters, in the development of resistance to chemotherapy (Gottesman et al., 2002). Another protein from the ABC family, BCRP/ABCG2, is known to facilitate multidrug resistance (Chen et al., 2010). Cannabinoid treatments have been suggested to modulate multidrug resistance in cancer. Arnold et al. found that 4-h incubation of T-lymphoblastic leukaemia cells with CBD and THC upregulated the MDR1 expression. However, longer incubation periods were reported to decrease the expression (Arnold et al., 2012). In breast cancer cells, CBD reportedly downregulated MDR1 but increased the BCRP expression (Feinshtein et al., 2013). The role of cannabinoids in chemoresistance has not been very well established. Some authors have reported that treatment with cannabinoids downregulated BCRP and MDR1 expression (Holland et al., 2007, 2008).

6.4. Clinical trials

Most of the evidence on the anti-cancer properties of cannabinoids in cancer patients is anecdotal. Despite the preclinical data, few

clinical trials have been conducted to determine the anti-cancer function of cannabinoids in cancer patients. The first pilot clinical study was performed in a cohort of nine adult patients presenting glioblastoma multiforme refractory to standard treatment. The study evaluated the anti-cancer potential and safety profile of THC in the cohort. Intratumoral administration of THC was found to be safe, as it did not result in overt psychomimetic effects. A decrease in tumour growth rate was observed in some patients. Furthermore, in two patients, THC administration was found to decrease cell growth and induced cell death. However, this observation affected the median survival only marginally (Guzmán et al., 2006). A recent randomised study evaluated the safety and efficacy of co-administering TMZ with sativex in patients presenting recurrent glioblastoma multiforme. This study confirms the validity of the strategy and provides evidence for the efficacy of this combination because the treatment arm had a higher one-year survival rate than the placebo (Twelves et al., 2017). This line of treatment might be beneficial in glioblastoma patients resistant to TMZ.

There are ongoing or recently completed clinical trials to evaluate the safety and efficacy of cannabinoids in cancer patients. One of the studies aims to determine the effects of using CBD as monotherapy in patients with confirmed solid tumours (NCT02255292). There are also currently ongoing investigations to evaluate the safety profile and effects of different doses of the synthetic cannabinoid dexanabinol in patients with solid tumours (NCT01489826) and brain cancer (NCT01654497). Furthermore, the safety profile and pharmacokinetics of its oral formulation are being evaluated in healthy patients (NCT02054754). An interventional study in pancreatic cancer is evaluating dexanabinol in combination with standard chemotherapeutic agents gemcitabine, nab-paclitaxel and sorafenib. This study aims to determine the efficacy and the maximum safe dose of dexanabinol in combination (NCT02423239). A double-blind trial will commence an investigation on the effects of smoked cannabis on pain and inflammation in lung cancer patients receiving radiotherapy (NCT02675842). Results from these studies will provide more evidence on the feasibility of the use of cannabinoid formulations in cancer patients.

7. Conclusion and future perspectives

There is a need to improve therapeutic intervention strategies for cancer, particularly for those without efficient therapeutic strategies. The ECS is found to be dysregulated in cancer cell lines and patients. Based on preclinical evidence, the use of cannabis and derivative compounds in cancer is a promising strategy. Since most of the preclinical studies demonstrate tumour reduction, cannabinoids may be combined with standard chemotherapeutic or radiation therapy regimes. However, only a few studies have investigated this line of approach. The use of cannabinoids for alleviating chemotherapy-associated side effects such as anorexia, cachexia, nausea, vomiting and pain has been extensively studied.

Translation of cannabinoids into the clinic is still in the initial phases. The heterogeneity of ECS should be taken into account while considering cannabinoids for therapeutic application. Since studies have demonstrated a dose-dependent, anti-carcinogenic and pro-carcinogenic activity of cannabinoids in cancer, it is important to determine the correct dose required for patients presenting a particular type of cancer. There are studies underway aiming to determine the dose-effect relationship in cancer patients. The route of administration to ensure maximum availability at the tumour site is another important aspect. Cannabinoid compounds have been administered as hemp oil, cannabis tea and through oral (capsule or oromucosal spray) or inhalation routes in cancer patients (Brown et al., 2019). Several parameters such as primary and secondary metabolism and their drug metabolising enzymes might affect an individual's tolerability to medicinal cannabis (Stout and Cimino, 2014). The tolerability can also be affected by the pharmacodynamics of previous cannabinoid users. The lipophilic nature of cannabinoids might influence their tolerability and analeptic outcomes. The absorption of these lipophilic compounds is improved when administered with polar solvents or fats (Huestis, 2007).

The lack of effective biomarkers and inability to evaluate how the body interacts with the drug makes it harder to accurately determine the cannabinoid dose. In addition, the sensitivity of methods of detection for pharmacokinetic data collection (non-invasive and invasive), indicate only a sign of the presence of the limited cannabinoid analytes (Schwope et al., 2011). Furthermore, the pharmacokinetic biomarkers for one route of administration cannot be applied to another (Vandrey et al., 2017). There is also a lack of biomarkers to effectively evaluate how administered cannabinoids modulate the ECS and exert their effects. Future studies should focus on investigating the best method of delivery, route of administration and dose-effect responses of cannabinoids in cancer patients. This will facilitate a better understanding of the effective application of cannabinoids in oncology.

CRediT authorship contribution statement

Pratibha Malhotra: Conceptualization, Data curation, Writing - original draft. **Ilaria Casari:** Conceptualization, Writing - review & editing. **Marco Falasca:** Conceptualization, Supervision, Writing - review & editing.

Declaration of competing interest

The authors declare no conflicts of interest.

Acknowledgements

This project is made possible by an Avner Pancreatic Cancer Foundation grant (http://www.avnersfoundation.org.au). M.F. acknowledges the infrastructure and staff support provided by CHIRI, School of Pharmacy and Biomedical Sciences, Faculty of Health Sciences, Curtin University. M.F. would also like to acknowledge the support of the Keith and Ann Vaughan Pancreatic Cancer Fund.

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