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Review Article

The pharmacological basis for application of cannabidiol in cancer chemotherapy

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Abstract

Chemotherapy is one of the therapeutic approaches for cancer treatment and has demonstrated great success with the introduction of selectively acting molecules against specific biomarkers of some types of tumors. Despite this success there is a large unmet need for novel therapies that provide effective control on the progression of advanced or drug-resistant cancer diseases. In this review, we briefly summarized our knowledge of cannabinoids and the endocannabinoid system, as possible agents for cancer therapy. We analyzed the anticancer properties and mechanism of action of cannabidiol (CBD), the main non-psychoactive cannabinoid received from hemp of *Cannabis* plant. Despite of data for pleiotropic effects of CBD, we here present the results for the efficacy of CBD in the modulation of different stages of cancer development. The analysis of the anticancer properties of CBD is made in relation to the proposed or newly discovered molecular targets of action. Thereafter, we consider the specific effects of CBD on primary tumors, their invasiveness and metastases, whether the influence on identified tumor markers in different types of tumors reflect the therapeutic potential of CBD. The studies reviewed herein indicate that CBD elicit activity through the cannabinoid receptor dependent and independent pathways. The processes such as ceramide production, ER-stress, autophagy and apoptosis, angiogenesis and matrix remodeling also appear to regulate the anticancer activity of CBD. So, the pharmacological basis for therapeutic application of CBD is constructed on the scientific data for its antitumor activity, extensively provided studies in vitro and in vivo in animal tumor models, and available data on the safety profile of clinically approved CBD products. We also try to reduce the deficits of our understanding in relation of pharmacological synergistic interactions of CBD with cytostatic drugs, where data remains limited. It is recognized that more studies for defining the specific molecular and signaling mechanisms of anticancer action of cannabinoids, particularly CBD, requires further evaluation. We believe that the therapeutic advantages of CBD are associated not only with its non-psychoactive behavior, but also are related to its influence on the important biochemical pathways and signal molecules, defining the genome instability and specific changes of the malignant tumor cells.

Keywords

anticancer effect, cannabidiol, mechanism of action, pharmacological interactions, safety profile

Introduction

In the recent decade many investigators have been trying to establish a scientific base for the therapeutic application of cannabinoids for different diseases including malignant tumors. Interest in the anticancer properties of cannabinoids was renewed after the discovery of the Endocannabinoid system (ECS) which was realized with

the cloning of specific cannabinoid receptors (Zou and Kumar 2018). The ECS is a signalling system comprising the cannabinoid CB1 and CB2 receptors, their intrinsic lipid ligands, endocannabinoids, and the associated transporters, biosynthetic and degradative enzymes. Both cannabinoid receptors are G protein-coupled receptors: CB1 are highly distributed in the central nervous system (CNS), with low to moderate expression in the periphery, whereas CB2 receptors are high in the immune system, and have a moderate expression in other tissues, including the cardiovascular system, gastro-intestinal tract, liver, adipose tissue, bone, and reproductive system (Howlett et al. 2002). Two major known endogenous ligands are the anandamide (AEA) and the 2-arachidonoylglycerol (2-AG). Both are arachidonic acid derivatives produced from phospholipid precursors through activity-dependent mechanism of specific phospholipase enzymes. Apart from their binding to CB1 and CB2 receptors, they may bind to other receptors as the vanilloid receptor type 1 (TRPV1); the 'orphan' G protein-coupled receptor, GPR55, and the peroxisome proliferator-activated receptor, PPAR (Kano et al. 2009).

In 1975 Munson et al. (1975) obtained that Tetrahydrocannabinol (Δ^9-THC, THC) and Cannabidiol (CBD), the main cannabinoids in *Marijuana sativa* inhibit the growth of Lewis lung carcinoma after oral administration in mice. Since then the anti-proliferative and pro-apoptotic effects of several natural and synthetic cannabinoids in cancer cell lines and in some cases in animal tumor models were evaluated (Galve-Roperh et al. 2000; Sánchez et al. 2001; Casanova et al. 2003; Blázquez et al. 2006). Moreover, studies showed the potential of these compounds to inhibit tumor invasion, cell migration and metastasis (Freimuth et al. 2010). However, the clinical use of THC and synthetic agonists of the cannabinoid receptors is limited by their unwanted psychoactive side effects. So, this area of research is quite controversial and debatable. The interest of the researchers is now oriented to several phytocannabinoids, which have no psychoactive effects, especially CBD. It was suggested that they may be used in various pathological conditions, including inflammation and pain, cytostatic-induced emesis, cancer, narcotic addiction and epilepsy (Izzo et al. 2009; Grotenhermen and Muller-Vahl 2012). Review data of Massi et al. (2013) focus on the efficacy of CBD in the modulation of tumor growth and progression in some general types of cancer as breast, lung, colon, and lympho-proliferative malignant diseases as one group. Additional data in the recent years gives us a reason to make predictable pharmacological analysis for tumor cytotoxicity and mechanisms of action of CBD in the context of its application alone or in combination with cytostatic drugs in cancer chemotherapy.

Chemical structure

As it is shown in figure 1, CBD is cyclohexene which is substituted by a methyl group at position 1, a 2,6-dihydroxy-4-pentylphenyl group at position 3, and a prop-1-en-2-yl group at position 4. It is a member of resorcinols, an olefinic compound, and a phytocannabinoid (Mechoulam and Hanus 2002). CBD is normally taken to refer as a naturally occurring (-)- enantiomer metabolite. (+) CBD has been synthesized, but received little attention because it has been shown to have only a modest affinity to CB1 and CB2 receptors unlike (-) CBD. Both of the enantiomer compounds inhibit anandamide hydrolysis and stimulate the vanilloid receptor type 1 (TRPV-1) at which capsaicin acts as well. The (+)-CBD isomer was more active than the (-)-CBD-isomer as an anticonvulsant agent in a mouse seizure model. However, to date, there is no substantive evidence as to whether (+)-CBD is likely to cause THC-like psychoactive effects.

Cannabidiol (INN) is the non-psychoactive compound derived from *Cannabis* species that has proposed therapeutic benefits. Cannabidiol is one of some 113 identified cannabinoids in cannabis plants, accounting for up to 40% of the plant's extract (Marks et al. 2009). The legal criteria for non-psychoactive hemp (also commonly-termed industrial hemp) is any part of the *Cannabis* plant, whether growing or not, which contain a Δ-9 tetrahydrocannabinol concentration of no more than 0.3% on a dry-weight basis, and CBD levels exceeding 10% by dry weight (State of Colorado 2018). Several industrial hemp varieties can be legally cultivated in Western Europe, and a variety such as „Fedora 17" has a cannabinoid profile consistently around 1%, with THC less than 0.1%. The difference between marijuana and hemp is based on chemical composition, relates to the concentration of THC, the primary intoxicating compound found in *Cannabis*. Hemp is legally defined as a cultivar of *Cannabis sativa* with low concentrations of THC, although limitations on its concentrations differ internationally.

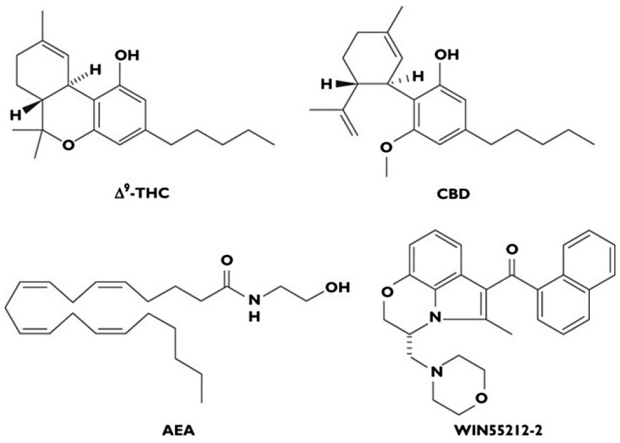

Figure 1. Chemical structures of Δ9-tetrahydrocannabinol (Δ9-THC), cannabidiol (CBD), anandamide (AEA) and synthetic cannabinoid agonist WIN55212-2. Chemical name of CBD: 2-[1R-3-methyl-6R-(1-methylethenyl)-2-cyclohexen-1-yl]-5-pentyl-1,3-benzenediol; IUPAC name: 2-[(6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1- yl]-5-pentylbenzene-1,3-diol.

Safety profile and drug interactions

Cannabidiol is evaluated as well tolerated compound with a good safety profile. To date, there is no evidence of recreational use of CBD or any public health related problems to be associated with the use of pure CBD. Reviewed data of the World Health Organization for cannabis-related substances, including cannabidiol, are based on the evaluation of the Expert Committee on Drug Dependence (WHO 2017). These data show that CBD has no effect on a wide range of physiological and biochemical parameters or significant effects on animal behaviour unless extremely high doses are administered (more than 150 mg/kg IV as an acute dose or in excess of 30 mg/kg orally daily for 90 days in monkeys). The results from studies in humans and animals show, that CBD have very different effects from those of THC (Iffland and Grotenhermen 2017). In mice, CBD failed to produce the behavioral characteristics (e.g. suppression of locomotor activity, hypothermia, antinociception) associated with CB1 activation, whereas THC generate all of the effects which occur when CB1 is activated (Pertwee 2008; Izzo et al. 2009; Long et al. 2010). Tolerance to the effects of THC was observed, however no tolerance to CBD at any of the dosages was observed (Hayakawa et al. 2007). No studies of the physical dependence potential of CBD in animals were identified. It also failed to produce significant effects in a human study of abuse potential. Neuroimaging studies in humans and animals show that CBD has effects which are generally opposite to those of THC (Batalla et al. 2014). In contrast to THC, CBD has no effect on heart rate or blood pressure under normal conditions, but in animal models of stress CBD reduces heart rate and blood pressure (Sultan et al. 2017). CBD has no effect on embryonic development (limited research). Effects on the immune system are unclear; there is evidence of immune suppression at higher concentrations, but immune stimulation may occur at lower concentrations (Kaplan et al. 2008).

Adverse reactions are documented in clinical trials of Epidiolex (Cannabidiol, INN), and they are included in the characteristic of the product, approved for treatment of Dravet and Lennox-Gastaut syndromes which are both treatment-resistant seizure disorders (GW pharmaceuticals 2017). The clinical evaluation is based on a lot of data for a good safety profile. Rarely, the following are observed: drowsiness, tiredness, unusual lack of energy and decreased appetite, decreased weight, or diarrhea. A very serious allergic reaction to this drug is rare, but it is possible to have rash as a sign to stop the treatment. A small number of people who take anti-seizure drugs for any condition (such as seizure, bipolar disorder, pain) may experience depression, suicidal thoughts/attempts, or other mental/mood problems (Bergamaschi et al. 2011). Many of these reactions are due to possible interactions of CBD with a simultaneously received antiepileptic drug, as it is shown below.

Cannabinoids are metabolized with the cytochrome P450 enzyme system and inhibit predominantly the enzymes CYP3A4 and CYP2D6. THC and CBD have been found to inhibit CYP1A1, 1A2 and 1B1 enzymes during *in vitro* studies (Jiang et al. 2011; Stott et al. 2013). In addition CBD is a potent inhibitor of CYP2C1P and CYP3A4 (Geffrey et al. 2015). Theoretically, CBD may increase the blood concentration of many other medications received simultaneously. That is about 60% of all pharmaceuticals on the market, including common antipsychotics, antihistamines, antiretrovirals, steroids, anticoagulants, and others. The summarized data for interactions of THC and CBD with some medications are presented in table 1. Many of these data are theoretical or derived from *in vitro* studies. Some of the interactions presented in the table are associated with smoked cannabis. These unwanted interactions may not be present with cannabis-based medicinal products when taken orally because oral products realize low bioavailability. It is known that cannabis products are contraindicated, or should not be used, in people with acute psychosis or unstable psychiatric conditions (Chetty et al. 1994), and in combination with benzodiazepines, opioids and phenobarbital (Rong et al. 2018). CBD may also interact with the ECS through direct or indirect mechanisms such as enhanced action of the anandamide. Then the blockade of anandamide reuptake and the inhibition of its enzymatic degradation was observed (Arellano et al. 2017).

Table 1. Drug interactions with cannabinoids THC and CBD*.

Drugs	Effect of the Interaction	Research data
Antiplatelets / anticoagulants	Increased risk of bleeding	*In vitro* studies found that THC and CBD may inhibit platelet aggregation. In a case study smoking cannabis significantly raised the INR of a patient prescribed warfarin after a mechanical heart valve replacement (Formukong et al. 1989; Yamreudeewong et al. 2009)
Ketoconazole	Increased concentration of CBD and THC	Ketoconazole inhibit CYP3A4, and increased the Cmax of CBD by 89% and THC by 27% *Theoretically* other inhibitors of CYP3A4 such as clarithromycin or itraconazole might increase the risk of adverse effects of CBD and THC (Stout et al. 2014)
Rifampicin	Reduction of CBD and THC concentration	Rifampicin induce activity of CYP3A4 and reduce the Cmax of CBD by 52% and THC by 36% (Stout et al. 2014).
Anti-convulsants	Increased levels of anticonvulsants and hepatotoxicity after valproates	CBD (Epidiolex*) increase bioavailability of topiramate, rufinamide, zonisamide. In addition AST/ALT levels were significantly increased in patients concurrently received valproate and CBD (Gaston TE et al. 2017; Yamreudeewong W et al. 2009).
Clobazam	Increased concentration of clobazam	After four week treatment of children with clobazam and CBD are observed significant increasing of levels of its active metabolite norclobazam and side effects such as drowsiness, ataxia and irritability at 77% of patients. (Geffrey AL et al. 2015).
Phenytoin	Increased concentration of phenytoin	*Theoretically* CBD as an inhibitor of CYP2C19 may increase plasma concentrations of phenytoin (Rong C et al. 2018).

*Theoretically, interactions of the cannabinoids with psycho-suppressive drugs, anticoagulants, antifungal, anti-diabetes and antiepileptic drugs are clinically important.

Target receptors and signal pathways

The identified molecular targets of CBD and other cannabinoids include numerous classical ion channels, receptors, transporters, enzymes, and newly identified signal

proteins (reviewed data of Katsidoni et al. 2013; Bih et al. 2015; Pyszniak et al. 2016). According to analysis of Bih et al. (2015) receptor targets of CBD account for only 15% of the known different molecular targets of cannabinoids described in the literature. But authors comment that many of these studies are provided at supraphysiological concentrations *in vitro*, rendering any contribution to behavioral effects unlikely. The recent evidence suggests that CBD has influence on cannabinoid CB1 receptor as a negative allosteric modulator of CB1 signaling, and can be used successfully for treatment of opioid abuse or THC intoxication (Straiker et al. 2018). CBD shows low affinity to CB2 receptors (McPartland et al. 2015). Despite of the limited data it has been proposed that ECS participates as a regulator of tumor cell malignancy, and the abnormal expression of CB receptors are defined in some tumors (Pyszniak et al. 2016). It is known that CB1 and/or CB2 receptors are coupled to several signaling pathways directly involved in cell survival, proliferation, and apoptosis, including p38 MAPK, cyclic AMP, PI3K-Akt, RhoA, JNK, EGF-R, ERK, and ceramide pathways (Sánchez et al. 1998; Cianchi et al. 2008). All cannabinoids induce sustained production of sphingolipid ceramide, which is commonly found in the cell membrane and is generated de novo by ceramide synthase or through sphingomyelin hydrolysis (Oesch and Gertsch 2009). Ceramide seems to be the key mediator of cannabinoid-mediated anticancer effects, as it is shown in osteosarcoma cells, glioma cells, and primary astrocytes through stimulation of ERK, MAPK, and/or JNK pathways (del Pulgar et al. 2002). In addition, there are several reports describing the influence of CBD and other phytocannabinoids on extracellular signal-regulated kinase (ERK) cascade in cancer. Although ERK is considered as a rather pro-proliferative signaling molecule, it has been shown that sustained activation of ERK induces apoptosis in astrocytes.

The identified target receptors are presented in figure 1; the signal target molecules and pathways are presented in table 2. As it is shown, CBD has affinity not only to CB receptors, but also to ion type vanilloid receptors, TRPV1, TRPV2 (Bisogno et al. 2000; Iannotti et al. 2014). TRP ion channels are present in the plasma membrane of a variety of cells in many tissues and act as ligand-gated, nonselective cation channels permeable to sodium, calcium, and magnesium ions. As targets for CBD they accounted 15% of the known molecular targets. CBD acts as an agonist at human TRPV1 channel expressed in HEK293 tumor cells, and induces increases in intracellular calcium ($[Ca^{2+}]_i$), but the potential role of these effects remains less well defined. The role of 'orphan' G protein-coupled receptors GPR55, GPR3, and GPR6 is also unknown (Pyszniak et al. 2016; Laun and Song 2017). The peroxisome proliferator-activated receptor (PPAR)γ, otherwise known as the glitazone receptor, is thought to be responsible for lipid storage and glucose metabolism, and some anticancer effects of CBD are thought to be mediated through interaction with PPARγ (Kano et al. 2009). PPARγ activation is becoming an important target in lung metastases and colon carcinogenesis. However the exact role of all these receptors in endocannabinoid signaling is still under discussion. Theoretically there is a general consensus that cannabinoids have multiple target molecules and signal pathways which participate in the control of the tumor growth and progression. It is diligent to note that the lipophilic nature of CBD and the membrane-bound nature of many of these targets reflected nonspecific interaction between them. Moreover, CBD acts on tumor growth and tumor progression by target oriented action on the signal molecules and pathways, and in many cases these effects are reached in receptor-independent manner.

Anticancer activity

A number of mutations that inhibit apoptosis have been found in tumors. In the first phase of tumor progression the cancer cells become locally invasive; in the second phase the most lethal attribute of cancer cells is their ability to disseminate and colonize secondary sites with metastases. Tumor progression is defined by irreversible changes in the tumor characteristics, reflecting genetically altered subpopulation of cells (Aguirre-Ghiso 2007; Welch and Hurst 2016). Despite these well-recognized facts, the majority of cancer research funding still focuses on primary carcinogenesis. In contrast, the investigations with phytocannabinoids, their synthetic derivatives, and endocannabinoids are oriented predominantly to the possibility to inhibit tumor progression, and are reviewed in Hermanson and

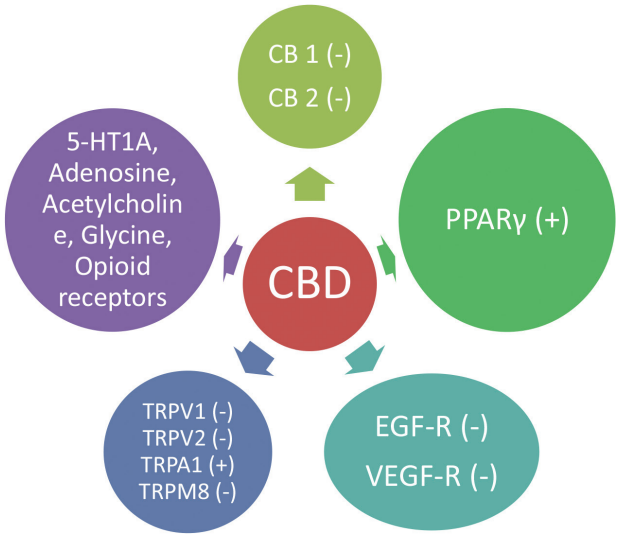

Figure 2. Some of the potential biological targets of Cannabidiol (CBD): cannabinoid receptors CB1, and CB2; ion channel receptors, incl. transient receptor potential vanilloid (TRPV) type 1 and 2; EGF-R, epidermal-growth factor receptor; 'orphan' G protein-coupled receptors, GPR55 and GPR3, GPR6; peroxisome proliferator-activated receptor, PPAR; vascular endothelial growth factor, VEGF-R; allosteric modulation and enhanced activity at αIγ glycine receptor; enhanced activity at the 5-HT1a, adenosine and N-acetylcholine receptors; inhibiting activity on mu and delta opioid receptors. Note: (+) stimulation; (-) inhibition.

Marnett (2011); Massi et al. (2013), Rocha et al. (2014), Ladin et al. (2016), and Śledziński et al. (2018).

As it is summarized in table 2, CBD have anti-proliferative and tumor-reductive effects in cell lines and tumor-bearing mice. In most of the cases CBD may cause these effects in receptor-independent manner, but the role of two signal pathways (ERK and ROS) is very important. Also, it is well known that the phosphatidylinositol 3 kinase (PI3K) pathway is one of the major pathways modulating cell growth, proliferation, metabolism, survival, and angiogenesis. Hyperactivation of this pathway is one of the most frequent occurrences in human cancer and is thus an obvious target for anticancer treatment.

CBD induces two forms of the programmed cell death: autophagy and intrinsic or mitochondria-mediated apoptosis, as it is shown on breast cancer cells by Shrivastava et al. (2011). Induction and accumulation of de novo synthesis of ceramide lead to an activation of endoplasmic reticulum (ER) stress-related signaling pathway. Interestingly, ROS generation is available in different cell lines after treatment with CBD, and seems to be needed for CBD-induced autophagy and apoptosis. The inhibition of tumor invasion in surrounding tissue after treatment with CBD is associated with the inhibition of Id-1 expression, as it is discovered in brain and breast cancer by McAllister et al. (2007, 2011). Additionally, intracellular adhesion anti-metastatic protein ICAM-1 participates in the realization of CBD anti-metastatic effects in lung cancer, discovered by Ramer et al. (2012).

Moreover, CBD induces endothelial cell cytostasis and inhibits angiogenesis *in vivo* by receptor-mediated manner (Hermanson and Marnett 2011).

Breast cancer

Breast cancer can be divided into three sub-types: hormone sensitive, HER2-positive, and triple negative breast cancer. CB1 receptors were reported to be present in 28% of all breast carcinoma patients, CB2 receptors were found in 72% of breast carcinomas and 91% of these tumors were HER2 positive. A correlation between CB2 receptor expression and breast cancer aggressiveness has been proposed (Qamri et al. 2009; Caffarel et al. 2010; Caffarel et al. 2012; Pérez-Gómez et al. 2015).

In 2006 for the first time Ligresti et al. (2006) demonstrated CBD's anti-proliferative effect on MCF7 and MDA-MB-231 breast tumour cell lines (IC_{50} between 6.0 and 10.6 mmol/L). It was shown that CBD exhibits the most potent antiproliferative action as compared to other cannabinoids. Additionally, CBD and the CBD-rich extract inhibit the growth of xenografts of human MDA-MB-231 cells, and reduce lung metastases. It was shown that CBD's antitumor effect is due to its capability to induce apoptosis via direct or indirect activation of cannabinoid CB2 and vanilloid receptors, with participation of the ROS (Bifulco et al. 2006). Later data for CBD inhibiting effect was shown on breast cancer progression (McAllister et al. 2007). For the first time in this study the important role of CBD for downregulation of the expression of key genes involved in the control of cell proliferation and invasion as Id-1 protein, of basic helix-loop-helix transcription factor, and regulator of cell growth and tissue-specific differentiation was discovered (Perk et al. 2005). It was found that overexpression of Id-1 in breast cancer cells is responsible for cancer progression. Four years later McAlister et al. (2011) discover that the CBD-induced effects on cell proliferation and Id-1 expression was mediated by the extracellular signal-regulated kinase (ERK) and reactive oxygen species (ROS) pathways. Moreover, these *in vitro* received data was confirmed *in vivo* in multiple breast cancer models including: two orthotopic, one genetically engineered mouse model and one TNBC xenograft model (Ligresti et al. 2006; McAllister et al. 2011; Murase et al. 2014; Elbaz et al. 2015). Furthermore, two of these studies which used genetically engineered and xenograft models proposed that CBD elicited these effects by inhibiting EGF-R activation, cytokine secretion, and Akt expression (McAllister et al. 2011; Elbaz et al. 2015). The anti-metastatic effect of CBD was defined *in vivo* with 4T1 breast cancer cells injected into the tail vein of syngeneic BALB/c mice. It was shown that 1 and 5 mg/kg CBD reduces primary tumor growth and the number of metastatic foci. Although CBD has negligible affinity for CB1 and CB2 receptors, CBD has been shown to control cell migration through the activation of ERK enzyme (Mo et al. 2004).

The excellent experiments provided by Shrivastava et al. (2011) highlighted the potential use of CBD as an anticancer agent. These authors showed that CBD induces a concentration-dependent cell death in two oestrogen receptor-positive and oestrogen receptor-negative breast cancer cells in a receptor-independent manner. They determined CBD-mediated autophagy and apoptosis by inducing endoplasmic reticulum stress in breast cancer cells and inhibiting AKT/mTOR/4EBP1 signaling. It is well known that these pathways are frequently activated in human cancers, and modulate breast cancer metastasis, cancer cell proliferation, and acquired drug resistance (Rosen and She 2006). Additionally, the authors obtained caspase-dependent apoptosis in MDA-MB-231 cells via the mitochondria-mediated signaling pathway. It was demonstrated that CBD-driven increase in ROS production is needed not only for apoptosis, as the impaired mitochondrial function is a result of increased ROS production (Zorov et al 2000), but also is associated with autophagy (Chen and Gibson 2008).

Glioma and Glioblastoma

Glioma is CNS brain tumor subtype from glial tissue and accounts for approximately 80% of all primary malignant brain tumors (Ostrom et al. 2015). These types of tumors are characterized with a high morphological and genetic heterogeneity, high proliferative rate, aggressive invasiveness and insensitivity to radio- and tra-

ditional chemotherapy (Rocha et al. 2014; Dumitru et al. 2018). There is a general consensus that high-grade gliomas, including glioblastoma (GBM), express high levels of CB2 receptors. Furthermore, CB2 expression positively correlates with the malignancy grade (reviewed in Ellert-Miklaszewska et al. 2013). Therefore, therapeutic strategies aimed at inhibiting the migration and invasion of glioma tumor cells are of great clinical relevance in the management of the disease (Velasco et al. 2007; Russo 2018).

There are many investigations with THC and synthetic cannabinoids, including a clinical trial. The pre-clinical results demonstrate specific cytotoxicity of cannabinoids, including CBD, in glioma cell line U87-MG and U373 and subcutaneous animal models through the induction of apoptosis (Massi et al. 2004, 2006). These investigators evaluate the anti-proliferative effect of CBD as cannabinoid- and vanilloid- receptors independent. It was shown that apoptotic cell death in glioma cells is due to the induction of de novo synthesis of ceramide with proapoptotic activity (reviewed in Śledziński et al. 2018). Most importantly, for the first time antitumor activity of CBD in glioma cells was associated with oxidative stress: increasing of ROS production, depletion of intracellular glutathione and increased GSH-associated enzyme activity (Massi et al. 2010; Singer et al. 2015). But CBD did not induce ROS production in non-transformed primary glial cells. The inhibitory effect of CBD in multiple GBM cell lines was confirmed by Marcu et al. (2010), and in animals orthotopically implanted with primary 3832 and 387 glioblastoma cells (Soroceanu et al. 2013). The mechanism of anti-proliferative effect of CBD is defined as inhibition of the Ras/Raf/MEK/ERK pathway in human glioblastomas. The other investigators (Solinas et al. 2012, 2013) show the anti-invasive effect of CBD on GBM even at low concentrations, which are not sufficient to induce cell death. This effect of CBD was attributed to the inhibition of Id-1 expression and Sox-2 protein. Several studies have shown that CBD and some other cannabinoids are capable to inhibit tumor neoangiogenesis on animal models and in patients with recurrent GBM (Blázquez et al. 2003, 2004; Blázquez et al. 2008a, 2008b; Solinas et al. 2012). Anti-angiogenic activity of CBD corresponds to downregulation of pro-angiogenic factors such as MMP2 and MMP9, endothelin-1 (ET-1), platelet-derived growth factor-AA (PDGF-AA) and some chemokines. In addition, CBD inhibits the hypoxia-inducible transcription factor HIF-1α, one of the most critical stimuli for cell survival, motility and tumour angiogenesis. Despite of these studies the role of cannabinoids and CBD in glial tumor cells migration and invasion is still poorly characterized.

Lung cancer

The expression of the cannabinoid receptors in non-small-cell lung cancer (NSCLC) was defined (24% – for CB1 and 55% – for CB2), which suggests the important role of these receptors in tumor development (Preet et al. 2011). The provided investigations of the scientific group of Ramer et al. (2010a, 2010b) evaluate the anti-invasive and anti-metastatic effects of CBD on human lung cancer cells (A549) that was reversed by antagonists to both CB_1 and CB_2 receptors as well as to TRPV-1. The decrease of invasion by cannabidiol appeared concomitantly with upregulation of tissue inhibitor of matrix metalloproteinases-1 (TIMP-1). It has been demonstrated that CBD decreases lung tumor cell invasion and metastasis via mechanisms related to the upregulation of the intercellular adhesion molecule 1 (ICAM-1) (Ramer et al. 2012). It is well known that local invasiveness requires a breakdown of the mechanisms that normally hold epithelial cells together. In other studies the role of PPARγ receptor for tumor growth was evaluated (Keshamouni et al. 2004) and showed the inhibitory effect of CBD to be reversed by co-administration of PPARγ antagonists (Ramer et al. 2013). Viability analysis revealed a concentration-dependent cytotoxic action of CBD in primary tumor cells obtained from a brain metastasis of a patient with lung cancer. The significant cytotoxicity was obtained even at a concentration as low as 0.001 mmol/L (IC50 is 0.124 mmol/L). The investigations of Ramer et.al. are the first report to provide an inhibitor-proven tumor-regressive mechanism of CBD in vivo as well as a proapoptotic mechanism confirmed by the use of primary lung tumor cells. But, the relation between ECS, immune system and lung cancer development is not yet clear, and it is difficult to evaluate the possibility of CBD application for treatment of highly invasive lung cancer.

Colon cancer

It was established that there is a positive correlation between CB2 receptor expression and human colon cancer growth. So, the expression of CB2 receptor is a poor prognostic marker in advanced stages of colon cancer (Martinez-Martinez et al. 2015). *In vitro* studies support the beneficial effect of CBD in colorectal carcinoma cell lines: CBD protects DNA from oxidative damage, increased endocannabinoid concentrations and reduced tumor-cell proliferation. In chemically-induced azoxymethane colon carcinogenesis, CBD and *Cannabis sativa* extract (which contains high CBD content) reduced aberrant crypt foci formation and the number of precancerous polyps and tumors (Aviello et al. 2012; Romano et al. 2014). *In vitro* experiments suggested that the cytotoxicity was mediated by CB1, TRPV1, and PPARγ or CB2 receptors. The researchers propose that the effects of CBD are associated with the upregulation of phospho-Akt, iNOS and COX-2 and the downregulation of caspase-3. Cianchi et al. (2008) define the increase of ceramide production and apoptosis through tumor necrosis factor alpha. These results suggest that CBD might be worthy of clinical consideration in colon cancer prevention.

Pancreatic cancer

Pancreatic cancer is a type of cancer that has some of the lowest survival rates because there are very few, and mostly only palliative care, treatments available. It was discovered that the ECS plays an active role in pancreatic carcinogenesis. It was obtained that CB1 and CB2 receptor expression was elevated in human pancreatic tumors when compared to normal pancreas. Although the levels of endocannabinoids (AEA, 1-AG, 2-AG) were unchanged in pancreatic cancer compared to normal human pancreas, high levels of CB1 receptor expression and low levels of endocannabinoid degrading enzymes (FAAH and MAGL), are associated with shorter survival (Carracedo et al. 2006). The provided experiments of this scientific group showed that cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress-related genes. Recently, prof. Marco Falasca and colleagues have conducted a study on mice that had been genetically modified to develop pancreatic cancer. This study shows that a gene known as GPR55 is involved in the growth and multiplication of pancreatic cancer cells. This gene gives rise to proteins that sit in cell membranes and detect various substances, including cannabis-derived molecules. Most importantly, it was obtained that CBD hinders the development of resistance to gemcitabine, as it is shown below. This result is associated with the blocking action of CBD on the receptors produced by the GPR55 gene, preventing them from interaction with endogenic molecules which promote the cell proliferation and tumor growth (Ferro et al. 2018).

Prostate cancer

The available three common primary therapies for prostate cancer (chirurgical, radiotherapy and brachytherapy) showed a unique pattern of changes in quality of life related to urinary symptoms, sexual and bowel function, and vitality or hormonal function of patients. It was obtained for the first time that the levels of CB1 and CB2 receptor was elevated in prostate cancer compared to normal prostate tissue (Sarfaraz et al. 2005), and it is associated with poor disease outcome. *In vitro* experiments of de Petrocellis et al. (2013) on four prostate cell lines (PC-3, DU-145, 22RV1, and LNCaP) show that CBD decreased androgen receptor expression and may affect tumor growth. Additionally, CBD significantly increased the generation of ROS and pro-apoptotic CHOP10 expression in these prostate cancer cell lines. *In vivo* study obtained that CBD effectively decreased tumor growth in androgen-sensitive, PSA-positive LNCaP cells xenografts, but potentiated tumor growth of androgen receptor negative DU-145 xenografts. Additionally, other investigations with endocannabinoids (Sánchez et al. 2003a, 2003b; Olea-Herrero et al. 2009) try to obtain the relationship between ECS, androgen receptor signaling and cannabinoid efficacy but currently the mechanism of action is not yet understood. Limited data makes it impossible to evaluate the potential application of CBD for the management of prostate cancer as it is proposed by Sarfaraz et al. (2005).

Leukaemia/Lymphoma

The study of McKallip scientific group (2002) demonstrate that ligation of CB2 receptors can induce apoptosis in a wide range of cancers of immune-cell origin. After that Gallily et al. (2003) provided the first evidence of a possible use of CBD in the treatment of lymphoblastic diseases. They demonstrated that CBD treatment induces apoptosis, through caspase-3 activation in human acute myeloid leukaemia HL-60 cell line, whereas it had no effect on normal human monocytes. Later on, McKallip et al. (2006) in experiments with the murine EL-4 lymphoma cell line, the human Jurkat and Molt-4 leukaemia cell lines, demonstrate that CBD induce CB2 receptor-mediated decrease in the number of viable cells as well as the induction of apoptosis, both *in vitro* and *in vivo*. In Jurkat cells, exposure to CBD resulted in the activation of caspase-8, -9, and -3, the cleavage of poly (ADP-ribose) polymerase and the decrease in full-length of Beclin2 interaction protein (Bid). These data suggest a possible cross-talk between the intrinsic and extrinsic apoptotic pathways. Moreover, exposure to CBD led to the loss of mitochondrial membrane potential and subsequent release of cytochrome C. As in other tumour cells, CBD-induced apoptosis required an increase of ROS production. Finally, CBD decreased the levels of phospho-p38 mitogen-activated protein kinase (McKallip et al. 2006), and this effect was blocked by treatment with a CB2-selective antagonist or ROS scavenger as tocopherol. *Briefly*, the received results suggest that CBD, acting through CB2 receptors and ROS production, may represent a novel and highly selective treatment for lymphoblastic diseases.

Multiple myeloma

Multiple myeloma (MM) is a haematological B cell malignancy characterised by clonal proliferation of plasma cells and their accumulation in the bone marrow (Rajkumar 2011). MM cells exhibit mutations in the nuclear factor kappalight-chain-enhancer of activated B cells [NF-jB] pathway, and this family of transcription factors involved in the regulating of the MM proliferation, survival and chemoresistance. TRPV2 gene mutations (gain or loss of function) have been identified in haematological disorders such as MM (Fabris et al. 2007; Santoni et al. 2011, 2013).

The excellent investigations of Morelli et al. (2014) show for the first time that CBD induces cytotoxicity in MM cells and this effect was amplified in TRPV2-positive cells. CBD inhibits proliferation of TRPV2-transfected cells and increased the percentage of cells in the sub-G1 and G1 phases compared with untransfected cells. They found that the effect of CBD on TRPV2-transfected MM cells was independent of the CB1 and CB2

receptors, TRP ion receptors and PPARγ. The researchers demonstrate also that CBD and proteasome inhibitor drug bortezomib alone inhibit ERK activation in TRPV2-transfected and untransfected MM cells, albeit at lower levels. In addition, CBD and bortezomib strongly abrogated Akt phosphorylation (approximately 80% inhibition in TRPV2-transfected MM cells). Finally, the investigated compounds induce mitochondrial and ROS-dependent necrosis in MM cell lines.

Combination and adjuvant therapy

Many *in vitro* and *in vivo* studies have shown the anticancer activity of CBD, with reports advocating for investigations of combination therapy approaches that could better leverage these effects in clinical translation. In fact, the administration of CBD together with some anticancer drugs has been shown to increase the susceptibility of glioblastoma cells to the cytotoxic effects of drugs (Nabissi et al. 2013). The studies of Morelli et al (2014) demonstrate that CBD and bortezomib (using the lowest effective dose for each component) synergistically reduced the viability of TRPV2-transfected and untransfected MM cell lines (CI≤1). The authors found that cannabidiol, applied alone or simultaneously with bortezomib, kills multiple myeloma cells, particularly when TRPV2 was expressed. In addition, the growth of CD34+ cells isolated from healthy blood donors is unaffected by this combination. Triggering of the TRPV2 ion channel by cannabidiol sensitizes glioblastoma cells to cytotoxic chemotherapeutic agents (Nabissi et al. 2013). These data suggest that treatment with CBD may help sidestep the problem of patients developing resistance to bortezomib.

The scientific group of prof. M. Falaska demonstrated some striking experimental evidence regarding CBD and combination chemotherapy. Mice with pancreatic cancer survived nearly three times longer when their cytostatic treatment was combined with the cannabis-derived compound. Gemcitabine and synthetic cannabinoids combinations trigger autophagy in pancreatic cancer cells through a ROS-mediated mechanism (Donadelli et al. 2011). These data highlighted the possibility for simultaneously application of CBD and gemcitabine, both currently approved for medicinal use in the UK and USA, in patients with pancreatic cancer as novel promising treatment. Strong et al. (2018) evaluate in vitro the anti-proliferative effect of CBD and some new inhibitors used for treatment of two aggressive forms of Non-Hodgkin lymphoma. Synergistic potential of CBD with Bruton's tyrosine kinase inhibitors such as ibrutinib and proteasome inhibitors such as carfilzomib is observed. Data shows a marked reduction in viability of DLBCL and MCL cell lines after combination treatment. The exposure to CBD and ibrutinib lowered the cell viability to under 25% as compared to control whereas, individually the drugs never fall under 75% of control.

Synergistic pharmacological effects are observed also for cannabinoids and paclitaxel in gastric cancer cell lines (Miyato et al. 2009); cannabinoids and temozolomide against glioma cell lines (Torres et al. 2011). The studies of Aviello et al. (2012) show that CBD in combination with paclitaxel produces additive to synergistic inhibition of colon cancer cell viability. Our investigations with CBD and epirubicine show that combination treatment of sensitive and resistant myeloid HL-60 cell lines has advantages in relation to the anti-proliferative effect reached in smaller concentration. Additionally, we observe pro-oxidant and antioxidant effects of epirubicine and CBD in dependence of applied concentration (Zhelyazkova et al. 2019; and unpublished data). These results confirm the hypothesis that CBD could enhance positively the activity of first-line antitumor drugs.

Available pre-clinical data for combination treatment with CBD and cytostatic agents are very limited. Additionally, the experiments are provided with different methodical approaches and there is a difficulty to make a comparative analysis. There is an urgent need to apply standard procedure for quantitative assay of the combination treatment as recommended by Chou TC (2007). But, it is clear, that combination therapy utilizing non-psychoactive cannabinoid CBD and conventional treatment may be a beneficial option for patients with advanced or resistant cancer.

Another direction for using cannabinoids is as adjunctive drugs. The aim of this treatment is to prevent or reduce cytostatic-induced side-effects. In particular, THC (Marinol), its analog nabilone (Cesamet), and buccal spray Sativex (Nabiximol, containing THC and CBD 1:1) were brought onto the market in several countries owing to their ability to inhibit chemo- and radiotherapy-induced side effects (Chakravarti et al. 2014), despite of the fact that it is not recommended by NICE (UK Medicines Information 2018). Sativex is approved for muscle spasticity in patients with multiple sclerosis but is used for neurological pain in cancer patients. Cesamet is indicated for prevention of chemotherapy-induced emesis.

The most terrible unwanted effect of some cytostatic drugs, including taxanes, platinum agents and Vinca alkaloids is drug-induced peripheral neuropathy. This side effect occurs in 30–40% of patients but incidences can reach 75% with certain regimens of chemotherapy. The pre-clinical investigations of Ward et al (2014) show that CBD in doses 2.5 and 5 $mg \cdot kg^{-1}$, administered only before each of the four paclitaxel injections of a standard dosing regimen for inducing neuropathy pain in rodents, prevents the development of paclitaxel-induced mechanical sensitivity in female C57Bl/6 mice. This effect is in part mediated by the serotonin 5-HT_{1A} receptors as it proposed by Russo et al. (2005). Another investigation shows that CBD attenuates cisplatin-induced nephrotoxicity by decreasing oxidative/nitrosative stress (Pan et al. 2009). These results indicate that CBD is a potent adjuvant to chemotherapy for the purposes of patient comfort, ultimately improving

Table 2. Effects of cannabidiol on different types of cancer cells*.

Effects	Target receptors	Autophagy / apoptosis		ROS	Cell signaling pathway and target signal molecules
Breast cancer					↓ pro-survival pathways
↓ proliferation	TRPV1; EGF-R	NC	+	↑	PI3K/Akt** and
↓ viability	CB2-R;	+	+	↑	Raf1/MEK/ERK
	non-CB1-R.				↓ EGF; ↓ Id-1; ↑ cytochrome C;
↓ invasion*		NC	NC	↑	Bid translocation.
Glioma, Glioblastoma					↓ Ras/Raf/MEK/ERK
↓ proliferation	non-CB_1;	NC	+	↑	(↓ p-ERK; ↓ p-Akt);
	non-TRPV1;				↑ Caspase activity; ↑ ceramide
↓ invasiveness*	CB_2; TRPV2			NC	↓ HIF-1α; ↓ MMP-2,-9
↓ migration*					↓ Id-1; ↓Sox-2 (protein)
↓ angiogenesis	VEGF-R?			NC	↓ VEGF and other factors
Lung cancer					↓ PPARγ and COX-2
↓ proliferation	CB-R	+	+	↑	↑ p-p38; ↑ p-ERK
	TRPV1				
↓ invasiveness*					↑ ICAM-1; ↑ TIMP-1 (protein)
↓ metastases*	PPARγ	NC	NC		↓ MMP-9.
Colon cancer					↑ *caspase-3 activity; COX-2*
↓ proliferation	CB1/CB2;	NC	+	NC	↑ *ceramide;* ↓ *Akt;* ↑ *2-AG;*
Chemoprevention	TRPV1; PPARγ				*TNFα-mediated apoptosis.*
Pancreatic cancer					
↓ proliferation	GPR55	NC	+	NC	*ER-stress-related genes*
	CB1, CB2 ?				*ECS pathway ?*
Prostate cancer					
↓ or ↑ proliferation	CB1, CB2 or	NC	+	↑	*ECS pathway ?*
	other receptors	(with other cannabinoids)			↓ *enzymes (FAAH, MAGL)*
					↑ *CHOP10 (protein)*
Leukaemia/Lymphoma					*caspase-3,-8,-9 activation*
↓ viability;	CB2	NC	+	↑	↓ *p-38 MAPK*
cytoreduction					↓ *Bid translocation*
					↑ *cytochrome C*
Multiple myeloma		Mitochondrial and ROS-mediated			↓ *ERK activity*
↓ proliferation	TPRV2	necrosis		↑	↓ *p-Akt*
					Cell cycle arrest in G1

* Study on orthotopic and subcutaneous animal models; other data are received in vitro; 2-AG, 2-arachidonoyl glycerol; Bid, Beclin2 interaction protein; CB, EGF-R, TRPV, PPARγ, VEGF-R, as in fig.1; ERK, extracellular regulated kinase; ER, endoplasmic reticulum; FAAH, fatty acid amide hydrolase; HIF-1α, hypoxia-inducible transcription factor; ICAM, intracellular adhesion anti-metastatic (protein); MAPK, mitogen-activated protein kinase; MAGL, monoacyl glycerol lipase; MPP, matrix metalloproteinase; ROS, radical oxygen species; TIMP, tissue inhibitor of MMPs; VEGF, vascular endothelial growth factor. Note: NC = not checked; ↑ increase; ↓ decrease.

overall quality of life in multiple ways. Additionally, the integrated approach for using CBD to prevent clinically important side effects and the inhibitory effects of CBD on tumor progression make it a potential valuable therapeutic option for the treatment of cancer patients undergoing treatments with first-line agents.

In conclusion

The available scientific pre-clinical data show that CBD may be applied in cancer therapy. Its low toxicity and non-psychoactive profile of action are a good starting point for clinical trial and suggest possible exploitation for prolonged treatment. CBD has anticancer activity in different type malignant tumors and more interesting this cannabinoid has influence on tumor progression. Significantly important are data for its synergistic anticancer activity with other cytostatic drugs, its tumor-sensitizing or protective effects which create a possibility for application of CBD as a component of combination schedule of chemotherapy or as adjunctive drug. In the light of its safety record and considering that CBD is currently used in clinical practice, the findings here summarized suggest that CBD might be worthy of clinical consideration for cancer therapy. It may be proposed that cannabinoid effectiveness of CBD is directed against the changes in the tumor cells received in the different stages of cancerogenesis, reducing the expression of the Id-1 gene, and some other signal molecules that are over-expressed in aggressive forms of cancer (Alberts et al. 2002; Ladin et al. 2016). Though some important achievements have been made in our understanding for cannabinoids, their immunosuppressive effect and relation between ECS and other cell signal pathways are still unknown. The information for interactions of CBD with clinically applied anticancer drugs must be well identified on pre-clinical and clinical levels. But the route of administration appears more problematic since CBD oral absorption is slow and unpredictable. The available studies and observed problems lead us to the conclusion, that further profound studies in some directions are doubtlessly needed to verify the rational idea of introducing cannabidiol into the cancer chemotherapy.

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