



Endocannabinoid system and anticancer properties of cannabinoids

PAWEŁ ŚLEDZIŃSKI*¹, AGNIESZKA NOWAK¹, JOANNA ZEYLAND¹, RYSZARD SŁOMSKI^{1,2}

1. Poznań University of Life Sciences, Faculty of Biochemistry and Biotechnology, Dojazd 11, 60-632 Poznań

2. Institute of Human Genetics, Polish Academy of Sciences, Strzeszyńska 32, 60-479 Poznań
E-mail: pawel717@gmail.com

ABSTRACT

Cannabinoids impact human body by binding to cannabinoids receptors (CB1 and CB2). The two main phytocannabinoids are Δ^9 -tetrahydrocannabinol (THC) and cannabidiol (CBD). THC interacts with CB1 receptors occurring in central nervous system and is responsible for psychoactive properties of marijuana. CBD has low affinity to CB1 receptor, has no psychoactive characteristics and its medical applications can be wider. CB receptors are part of a complex machinery involved in regulation of many physiological processes – endocannabinoid system. Cannabinoids have found some applications in palliative medicine, but there are many reports concerning their anticancer affects. Agonists of CB1 receptors stimulate accumulation of ceramides in cancer cells, stress of endoplasmic reticulum (ER stress) and, in turn, apoptosis. Effects of cannabinoids showing low affinity to CB receptors is mediated probably by induction of reactive oxygen species production. Knowledge of antitumor activity of cannabinoids is still based only on preclinical studies and there is a necessity to conduct more experiments to assess the real potential of these compounds.

KEY WORDS: cannabinoids, cancer, tetrahydrocannabinol, THC, cannabidiol, CBD

Introduction

Cannabinoids are diverse lipophilic compounds which interact with cannabinoid receptors (CBRs) in mammal body. This group of chemicals can be divided into three main classes: phytocannabinoids, endocannabinoids and synthetic cannabinoids. Phytocannabinoids naturally occur in

plants of *Cannabis* genus. More than 60 cannabinoids are identified in *Cannabis sativa*, of which the most abundant are Δ^9 -tetrahydrocannabinol (THC), cannabidiol (CBD), cannabichromene (CBC) and cannabigerol (CBG). THC is the main psychoactive component of marijuana – natural product obtained by

drying flowers and leaves of *C. sativa* and *C. indica*. THC strongly impacts central nervous system (CNS) by binding to CB1 receptors and exhibits euphoric, analgesic and antiemetic properties. Another important constituent of

Cannabis, cannabidiol (CBD) has low affinity to CB receptors and show no psychoactive characteristics (Fig. 1). Its effects are mediated by other receptor types.

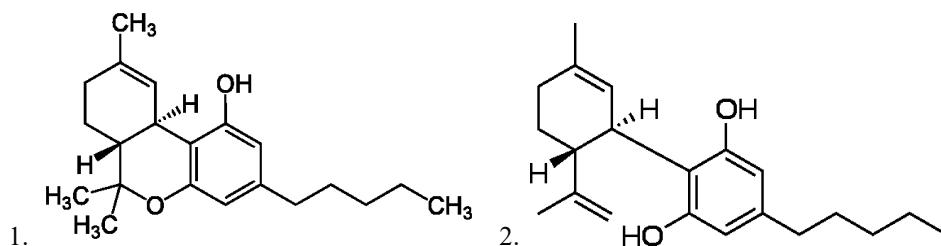


Figure 1. Examples of phytocannabinoids. 1 - Δ^9 -tetrahydrocannabinol (THC); 2 - cannabidiol (CBD).

Second main group, endocannabinoids includes endogenous ligands of CB receptors which are part of endocannabinoid system. Endocannabinoid system present in mammal body is involved in modulation

of many physiological processes, like inflammation, memory or pain modulation. The best characterized endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG) (Fig. 2).

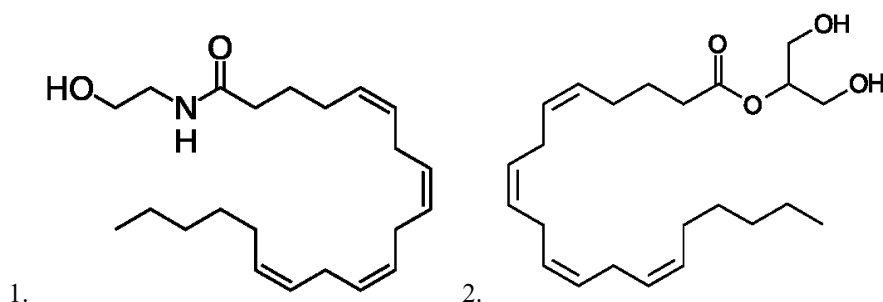


Figure 2. Examples of endocannabinoids. 1 - anandamide (AEA); 2 - 2-arachidonoylglycerol (2-AG).

Third group is constituted by synthetic cannabinoids, compounds which mimic properties of natural cannabinoids.

Variety of physiological processes in which endocannabinoid system is engaged causes that affecting its activity by phytocannabinoids or synthetic ligands of CBRs is a promising therapeutic strategy in many diseases.

Cannabinoids-based preparations have found some applications in palliative medicine. Nabiximols, oromucosal spray which contains THC and CBD in about 1:1 ratio is allowed in some countries for treatment of spasticity in multiple sclerosis. Dronabinol (synthetic THC in form of capsules) is allowed in USA and Germany for treatment nausea and vomiting associated with chemotherapy

and for anorexia in patients with AIDS. Nabilone (synthetic analogue of THC, capsules) can be used in USA, UK, Mexico and Austria also for nausea and vomiting associated with chemotherapy (Whiting *et al.* 2015).

Another important branch of cannabinoids research concerns their anticancer effects. First reports on the antiproliferative properties of THC comes from years 1975 and 1976. It has been shown that THC inhibits lung adenocarcinoma proliferation *in vitro* and tumor growth in murine model (Munson *et al.* 1975, White *et al.* 1976). Since that time there has been collected a lot of data referring to anticancer characteristics of cannabinoids, both *in vitro* and *in vivo* in cases of glioblastoma multiforme, breast, prostate, thyroid, colon, pancreas cancer or leukemia and lymphoma (Pisanti *et al.* 2009). It includes action of endocannabinoids (AEA, 2-AG), phytocannabinoids (THC, CBD) as well as synthetic cannabinoids (JWH-133, WIN 55,212-1-2). Many studies have shown that cannabinoids can inhibit proliferation of cancer cells, induce apoptosis/autophagy, inhibit angiogenesis and formation of metastasis (Velasco *et al.* 2012).

Mechanism of cannabinoids anticancer action is complex and many of its parts are still waiting to be fully elucidated.

Methods

Review of the available literature was done. We used PubMed database. Besides the latest reports, we consider also some older papers concerning the first discoveries of anticancer properties of cannabinoids.

Endocannabinoid system

Cannabinoids affect cells mainly through two classical receptors belonging

to the G Protein-Coupled Receptor (GPCR) superfamily: CB1 and CB2, which are part of the endocannabinoid system, involving cannabinoid receptors, their endogenous ligands (endocannabinoids) and enzymes engaged in synthesis, transport and degradation of cannabinoids (Hermanson & Marnett 2011). Activation of CB receptors leads to inhibition of adenylyl cyclase, which causes decrease in production of cyclic adenosine monophosphate (cAMP) and in turn activation of mitogen activated protein kinases (MAPK) and phosphoinositide 3-kinase (PI3K) pathways (Bowles *et al.* 2012).

Endocannabinoids act as retrograde transmitters: they are synthesized by postsynaptic cells in answer to binding neurotransmitters and diffuse through the synaptic gap to the presynaptic membrane where bind to CB receptors, which in turn leads to decrease in neurotransmitters release. Of note, endogenous cannabinoids are not stored in vesicles like other neurotransmitters. They are derived from arachidonic acid from plasma membranes (Stella *et al.* 1997).

As mentioned earlier, the two main endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). In predominant pathway of AEA biosynthesis, arachidonic acid (AA) is transferred from phosphatidylcholine (PC) to phosphatidylethanolamine (PE) by N-acyltransferase (NAT) enzyme, which leads to formation of arachidonoyl phosphatidylethanolamine (NAPE). Then, NAPE is hydrolyzed to AEA by NAPE-selective phospholipase D (NAPE-PLD) (Wang & Ueda 2009, Bisogno *et al.* 1999).

2-arachidonoylglycerol is generally formed by hydrolysis of phosphatidylinositol-4,5-bisphosphate (PIP₂) to diacylglycerol (DAG) by

phospholipase C- β (PLC- β). DAG is in turn hydrolyzed to 2-AG by diacylglycerol lipase (DAGL) (Hermanson & Marnett 2011, Murataeva *et al.* 2014).

Described endocannabinoids are degraded by hydrolysis to an arachidonic acid: AEA is hydrolyzed by fatty acid amide hydrolase (FAAH) and 2-AG by monoacylglycerol lipase (MAGL) (Hermanson & Marnett 2011).

CB1 and CB2 receptors belong to the A class (rhodopsin-like receptors) of G Protein-Coupled Receptor (GPCR) superfamily. Their amino acid sequence similarity is 44% (Pertwee *et al.* 2010). CB receptors are phylogenetically the closest related to lysophospholipid receptors (S1P, S1P1, S1P2, S1P3, S1P4, S1P5, LPA1, LPA2, LPA3), melanocortin 3 receptors (MC1-MC5), adenosine receptors (A1, A2A, A2B, A3) and the orphan receptors GPR3, GPR6 i GPR12 (Elphick & Egertová 2001, Fredriksson *et al.* 2003, Elphick 2007).

It is assumed that these groups of receptors emerged as a result of multiple duplications of one member of GPCR superfamily. Orthologous receptors were identified only in *chordata* phylum, therefore the duplication which led to a creation of CB receptors took place most likely in the common ancestor of *chordata* (Elphick 2002, Elphick 2007, Elphick *et al.* 2003, Elphick & Egertová 2005).

Mechanism of action of both cannabinoid receptors relies on activation of $G_{i/o}$ proteins causing adenylyl cyclase inhibition and on activation of MAPK pathway by $G_{\beta\gamma}$ complex. Furthermore, CB1 receptor inhibits voltage-dependent calcium channel (VDCC) (Pertwee *et al.* 2010, Hermanson & Marnett 2011).

CB1 receptor is expressed mainly pre-synaptical at central end peripheral neurons, especially in central nervous system regions engaged in control of

motility, memory and learning, emotions, perception, endocrine functions and analgesic effects (Velasco *et al.* 2012, Pertwee *et al.* 2010). It is responsible mainly for inhibition of neurotransmitters release. CB2 receptor is present mainly in immune cells and largely in microglia cells. It mediates modulation of cells migration and cytokine release (Pertwee *et al.* 2010, Cabral *et al.* 2008). Cannabinoid receptors are immunosuppressive.

Expression of CB receptors has been shown in many types of cancer cells, however its level is not always correlated with expression level in their tissues of origin (Fernández-Ruiz *et al.* 2007, Velasco *et al.* 2012).

Other receptors

Besides CB, there are many other, non-classical receptors which can interact with cannabinoids. The most important groups are vanilloid transient receptor potential cation channels (TRPV) and some orphan G protein coupled receptors.

TRPV1 receptors belong to the transient receptor potential (TRP) family of ion channels. They are formed by six transmembrane domains, contain cytosolic C- and N-terminal domains and non selective, kation-permeable region between fifth and sixth domains (Owsianik *et al.* 2006). Members of TRP family are engaged in many stimuli transduction, like temperature, electric potential, light, mechanic stimuli, flavor and savor, they mediate the effects of xenobiotic substances and endogenous lipids (Venkatachalam & Montell 2007). It has been shown that their expression level is frequently elevated in pathologically changed tissues (Nilius *et al.* 2007).

TRPV1 channel was firstly identified as capsaicin receptor, which is responsible for chilli pepper flavor

(Caterina *et al.* 1997). It is activated by many harmful factors as high temperature or low pH and is responsible for nociception (Caterina *et al.* 2000, Davis *et al.* 2000) TRPV1 receptor is localized mainly in sensory neurons but is also present in many others cells like lymphocytes or fibroblasts (Starowicz *et al.* 2007).

Some endocannabinoids and phytocannabinoids (CBD, CBG) can bind to TRPV1 receptors with high affinity and act as their full agonists (Starowicz *et al.* 2007, Bisogno *et al.* 2001, Ligresti *et al.* 2006). TRPV1 activation by cannabinoids can lead to the increase in concentration of reactive oxygen species and calcium, as well as cytochrome C release from mitochondria, which eventually leads to apoptosis (Maccarrone *et al.* 2000). It has been shown that activation of TRPV1 receptor by anandamide can induce apoptosis in neuroma, lymphoma and cervix cancer cells (Maccarrone *et al.* 2000, Contassot *et al.* 2004). Cannabidiol can exert anti-inflammatory effect through TRPV1 activation which causes inhibition of cyclooxygenase 1 and 2 (COX-1/2) (Hegde *et al.* 2011, Ruhaak *et al.* 2011)

G-protein-coupled receptors 55 are presumably a new group of CB receptors, but there is still not enough data about theirs interactions with cannabinoids to classify them as CBR. They belong to the A class of GPCR superfamily and have low sequence similarity to CB1 (13,5%) and CB2 (14,4 %) (Pertwee *et al.* 2010).

Cannabidiol acts as an antagonist of GPCR55 and competes with its endogenous ligand – lysophosphatidylinositol (LPI). Agonists of GPCR55 were shown to promote development of cancer in several model, therefore CBD can inhibit proliferation of cancer cells by preventing activation of these receptors (Andradas *et al.* 2016, Piñeiro *et al.* 2011, Hu *et al.* 2011). LPI

stimulates proliferation of cancer cells by initiation of ERK, Akt pathways and release of Ca^{2+} (Piñeiro *et al.* 2011). There are observations showing correlations between GPCR55 expression level and rate of cancer development (Andradas *et al.* 2011, Pérez-Gómez *et al.* 2012).

It has been shown that cannabinoid receptors are able to associate with other receptors of GPCR superfamily, like dopamine, opioid or orexin receptors, forming heteromeric complexes. These associations probably can influence agonist's effect through allosteric interactions (Pertwee *et al.* 2010). That phenomenon can be responsible for some of the cannabinoids' biological effects.

Endocannabinoids show also pronociceptive action being transformed into prostaglandins which interact with prostaglandin receptors (Davis 2014).

Anticancer properties of CB receptors agonists

There are number of ways in which cannabinoids can impact cancer cells and which at least partially underline their antiproliferative and proapoptotic properties. Firstly, activation of either cannabinoid receptors CB1 and CB2 leads to an activation of ceramide synthase, the enzyme that catalyzes synthesis of lipid molecules ceramides. Increase in ceramide concentration may be induced also by activation of sphingomyelinase, enzyme which causes release of ceramide from membrane sphingolipids (Calvaruso *et al.* 2012). Ceramides induce upregulation of an extracellular regulated kinase (ERK) signalling pathway which in turns causes apoptotic cell death (Sarfaraz *et al.* 2006, Sarfaraz *et al.* 2008). This process has been observed in gliomas, mantle cell lymphomas, colon and pancreatic cancers (Gustafsson *et al.* 2006, Guzmán *et al.*

2006, Cianchi *et al.* 2008, Carracedo *et al.* 2006).

Ceramide production leads also to endoplasmic reticulum stress (ER stress) which is connected with p8 protein expression (nuclear protein 1, Nupr1, transcription regulator involved in cancer development regulation), which in turn leads to the activation of TRIB3, inhibition of pAkt/mTOR and induction of apoptosis and autophagy (Velasco *et al.* 2012, Salazar *et al.* 2009, Sui *et al.* 2013, Salazar *et al.* 2013). Accumulation of ceramide causes also long-term activation of Raf1/ERK cascade and inhibition of JNK (Hermanson & Marnett 2011). In this pathway a crucial role is played by the mitogen activated protein kinases (MAPK), which are serine – threonine kinases. They take part in transduction of extracellular stimuli inside the cell and mediate in many diverse cellular responses, like cell cycle arrest, apoptosis or cytokine production. Much data has been collected confirming activation of kinases connected with response for extracellular stimuli in cases of proliferation inhibition of cancer cells by cannabinoids (Galve-Roperh *et al.* 2000). Long term upregulation of MAPK leads to activation of cyclin kinase inhibitor (p27/KIP1) which regulates signaling molecules crucial in cell cycle regulation (cyclins, cdk) and thereby induces cell cycle arrest and apoptosis (Kogan 2005, Sarfaraz *et al.* 2006, Sarfaraz *et al.* 2008). On the other hand in the cases of certain prostate and ovary cancer cell lines, activation of MAPK pathway by GPCR55 receptor can sustain proliferation (Piñeiro *et al.* 2011).

Ceramides also mediate in activation of a p38 mitogen-activated protein kinase (p38MAPK) pathway, upregulation of which also can lead to apoptosis through cytochrom C release from mitochondria or activation of caspases (Ramer & Hinz 2008).

Activation of apoptosis requires also inhibition of survival factors effects. Important signaling factor which mediate in action of survival factors is PI3K/Akt/mTOR pathway. This pathway is involved in many key processes, like cell survival, growth, proliferation, angiogenesis or cell migration (Hers *et al.* 2011). Inhibition of Akt kinase leads to cell cycle arrest and subsequently to apoptosis. Decrease in Akt activity is involved in cancer cell response to cannabinoids. This process has been observed in gastric cancer cells: CB receptors activation has led to MAPK pathway activation, Akt inhibition and cell cycle arrest (Park *et al.* 2011).

Another important issue is also that anticancer activity of cannabinoids can be stopped by pharmacological locking of each CB receptor in some cancer (gliomas) when in other tumors (pancreatic, breast, liver) it has been observed that only CB2 agonists have capacity to prevent induction of apoptosis (Galve-Roperh *et al.* 2000, Caffarel *et al.* 2006, Vara *et al.* 2011, Carracedo *et al.* 2006). These reports suggest that cannabinoids activate partially different metabolic pathways in different cancer types.

Anticancer action of non-psychoactive cannabinoids

Not all cannabinoids affect cells through CB receptors. Some cannabinoids do not bind with them at all or have very low affinity. The most widely studied is cannabidiol (CBD). It has low affinity to CB receptors, moreover, acts as a CB1 receptor antagonist. Therefore it shows no psychoactive properties by itself and blocks the psychoactive effect of THC and other CB1 receptor agonists. This characteristic makes this compound having high pharmacological potential

and in future can become valuable supplement in anticancer treatment.

Many CBD-binding receptors have been discovered but probably most of them do not mediate in its anticancer properties: GPR55, GPR18, 5HT1A, TRPV1, TRPV2, TRPM8, TRPA1, PPAR γ , VDAC1 channel or mitochondrial sodium-calcium exchanger (Rimmerman *et al.* 2013a, Fernández-Ruiz *et al.* 2013, De Petrocellis *et al.* 2011, O'Sullivan & Kendall 2010).

In contrast to THC molecular and cellular mechanism of action of CBD is still not fully elucidated. The most frequent proposed mechanism of CBD action *in vitro* is induction of reactive oxygen species (ROS) production (De Petrocellis *et al.* 2013, McAllister *et al.* 2010, Shrivastava *et al.* 2011, Ligresti *et al.* 2006). ROS are side products of oxygen metabolism and play important role in signaling and homeostasis. Their production is correlated with proliferation of healthy cells and takes part in activation of metabolic pathways connected with growth (Benhar *et al.* 2002). On the other hand, reactive oxygen species can induce programmed cell death. It has been shown that ROS stimulate many factors involved in activation of apoptosis, like MAP3K5, JNK, p38 and activation of p53 pathway (Laurent *et al.* 2005, Benhar *et al.* 2001). Type of effects induced by ROS probably depends on rate and way of their production and on activity of antioxidative enzymes (Laurent *et al.* 2005).

First reports of ROS mediation in cannabidiol action come from 2004 (Massi *et al.* 2004). It has been demonstrated that CBD inhibits viability of glioblastoma multiforme cells by induction of apoptosis and this effect was abolished in the presence of α -tocopherol (α -TOC, antioxidant). Increase of ROS

production was correlated with decrease in concentration of intracellular glutathione, that acts as important antioxidant. CBD effect was also selective – decrease in viability of healthy cells was not observed. Many later studies have shown similar mechanism of CBD action in other cancer cell lines, like breast cancer, prostate adenocarcinoma or leukemia (McKallip *et al.* 2006, Massi *et al.* 2006, McKallip *et al.* 2006). ROS mediation in cannabidiol effects was confirmed in many experiments with the use of antioxidants like α -TOC or acetylcysteine. At the same time most of reports suggest that CBD affects cells without interactions with classical CB receptors or TRPV1 receptor (McAllister *et al.* 2015).

The way of ROS induction by CBD is still insufficiently discovered, but it is frequently indicated that there is a correlation between ROS production and an increase in intracellular Ca^{2+} concentration leading to changes in mitochondrial membrane potential. This effect was observed in breast cancer cells, hippocampus cells, oligodendrocytes and microglia (Rimmerman *et al.* 2013b, Ryan *et al.* 2009, Ligresti *et al.* 2006, Mato *et al.* 2010). Studies have shown that increase in Ca^{2+} results from releasing it from intracellular supplies and that ROS production induced by CBD is inhibited by chelating factor BAPTA-AM, which confirms calcium mediation in described effects (Ligresti *et al.* 2006).

The phenomenon which occurs after ROS induction in metabolic cascade induced by CBD is endoplasmic reticulum stress (ER stress). It has been observed that high level of ROS induces ER-stress by elevation of activity of many mediators like p8, CHOP, TRB-3 or GRP-78, which in turn triggers the

intrinsic pathway of apoptosis (Malhotra & Kaufman 2007).

Endoplasmic reticulum stress is complex signaling pathway triggered in response to stimuli including oxidative damage, hypoglycemia, viral infections or exposition to anticancer drugs. This process leads to inhibition of protein load on endoplasmic reticulum as a result of temporal suppression of translation and concomitant elevation of protein folding related genes expression. If these changes fail to restore homeostasis in ER, cell runs apoptosis or autophagy (Schröder & Kaufman 2005, Verfaillie *et al.* 2010).

Autophagy is a process of enclosing parts of cytoplasm in membrane vesicles called autophagosomes. Autophagosomes undergo fusion with lysosomes which leads to degradation of their content by lysosomal enzymes. Autophagy can play different roles in different circumstances. It allows cell recycling of damaged organella or triggers cell survive pathways, but it can also coexist or substitute an apoptosis in process of cell death (Mizushima *et al.* 2008). There are many reports concerning induction of autophagy process by cannabinoids in various cancer models and they indicate that this process partially shares signaling pathways with apoptosis. Cannabinoids induced autophagy was observed in glioma, melanoma, breast cancer, pancreatic cancer and liver cancer cells (Calvaruso *et al.* 2012).

Discussion

Despite data collected in many pre-clinical trials which suggests that cannabinoids have certain medicinal and anticancer potential, and can be used as supplementary drug in many diseases, there were conducted only few clinical trials. One of the reasons is that in many countries law regulations are unfavorable in terms of medical applications of

cannabis. United States agency Drug Enforcement Administration (DEA) which controls use of substances with addictive potency, has placed marijuana and cannabinoids which are CB1 receptors agonists in the Schedule I in Controlled Substances Act, which means that these substances are illegal in the USA. Schedule I substances are characterized by high abuse potency, no medical applications and no sufficient safety level for medical use (Office of Diversion Control 2016). This group includes also drugs like heroin, MDMA (ecstasy) or LSD. This classification is one of the reasons for the difficulties in clinical trials of cannabinoids. Medical communities of the US recommend re-evaluation of cannabinoids and change in their classification in order to facilitate research on the medical use of cannabis and cannabinoids (Bowles *et al.* 2012). However, many states have attempted to legalize cannabis-based medicines and to date marijuana is allowed for medical applications in 24 states and the District of Columbia (Birdsall *et al.* 2016).

So far, no clinical trial concerning anticancer properties of cannabinoids was conducted (National Cancer Institute 2016). The only experiment conducted on human was small pilot study on patients with recurrent glioblastoma multiforme. THC was administrated intracranially directly into the tumor mass. It has been reported that this method was safe and no side effect was reported. In some patients temporal decrease of tumor growing was observed and activation of molecular mechanisms involved in apoptosis and in inhibition of proliferation of cancer cells were reported in two patients (Guzmán *et al.* 2006).

That study was too small to draw significant conclusions, but it shows a need to conduct subsequent studies in that field. It is necessary to assess

optimal patients selection, administration routes or interaction with other drugs.

Recently two safety clinical trials were conducted in human. In the first, Sativex in combination with temozolomide were studied in patients with glioblastoma multiforme and in the second, CBD for acute graft-versus-host disease in patients who have undergone allogeneic hematopoietic stem cell transplantation (ClinicalTrials.gov 2016a, ClinicalTrials.gov 2016b).

On the other hand the role of endocannabinoid system in carcinogenesis is still unclear. It has been shown that level of endocannabinoids and expression of cannabinoid receptors are elevated in many cancers, moreover, that seems to be correlated with the degree of malignancy (Guzman 2003). Increased concentrations of AEA and 2-AG were observed in cases of glioblastoma, prostate adenocarcinoma, colon cancer and pituitary adenoma (Pisanti *et al.* 2013). Elevated expression of CB1 receptor was demonstrated in ovary and colon cancers and in hepatocellular carcinoma (Messalli *et al.* 2014, Mukhopadhyay *et al.* 2015, Park 2012). Increase in expression of CB2, in turn, was observed in breast cancers, gliomas and astrocytoma (Caffarel *et al.* 2006, Sánchez *et al.* 2001). Interestingly, it has been shown that CB receptors at least partially mediate in the development of skin cancer induced by UV irradiation (Zheng *et al.* 2008). Mice devoid of CB receptors showed marked decrease in UV-induced carcinogenesis. Similar results were obtained in hepatocellular cancer model – inactivation of CB1 receptor led to the suppression of hepatocarcinogenesis (Suk *et al.* 2016). Another important observation is that pharmacological blockage of CB1 by its antagonist leads to decrease in carcinogenesis in some models (Marshall *et al.* 2011,

Mukhopadhyay *et al.* 2015, Pisanti *et al.* 2011, Sarnataro *et al.* 2006).

There are studies showing that cannabinoids can stimulate proliferation of cancer cells in some circumstances. In cases of glioblastoma and lung carcinoma cells incubated with nanomolar concentrations of THC, cell proliferation was accelerated. This phenomenon was based on activation of epidermal growth factor receptor (EGFR) and downstream activation of ERK1/2 pathway (Hart *et al.* 2004). Systemic administration of THC has been shown to increase tumor size and number of metastasis in murine model (Mckallip *et al.* 2005). Cannabinoids interacting with CB2 receptor act as immunosuppressants. This probably leads to suppression of antitumor immune response by THC, stimulating development of tumor. FAAH-deficient mice with elevated level of AEA showed increase in hepatocarcinogenesis (Suk *et al.* 2016).

Conclusions

Despite some important gaps in the knowledge of cannabinoids' impact on cancer cells, use of cannabis and cannabinoids-based medicines in anticancer treatment raises big hopes. Especially applying a combination of classical chemotherapy and pharmacological stimulation of endocannabinoids system could be very promising.

However, it is still too early to admit the use of cannabinoid-based medicines as efficient and safe. There is a lack in studies concerning safety on cannabinoids in treatment and their potential interactions with other drugs. Especially, concerns can be raised by studies showing that in some cases activation of CB receptors can promote development of cancer. We still do not

fully understand specific role of particular elements of endocannabinoid system in carcinogenesis. There is a need to ascertain a specific instances in which the use of cannabinoids can be considered as safe. Another important point is that all studies of anticancer

characteristic of cannabinoids were conducted *in vitro* and in animal models. Reliable, well-prepared clinical trials are needed to assess the true efficacy, safety and implications of cannabinoids in cancer treatment.

References

- Andradas, C., Caffarel, M.M., Pérez-Gómez, E., Salazar, M., Lorente, M., Velasco, G., Guzmán, M., & Sánchez, C., 2011. The orphan G protein-coupled receptor GPR55 promotes cancer cell proliferation via ERK. *Oncogene*, 30(2): 245–252.
- Andradas, C., Blasco-Benito, S., Castillo-Lluva, S., Pilla, P. D., Díez-Alarcia, R., Juanes-García, A. Et al. 2016. Activation of the orphan receptor GPR55 by lysophosphatidylinositol promotes metastasis in triple-negative breast cancer. *Oncotarget*. 7(30): 47565–47575.
- Benhar, M., Dalyot, I., Engelberg, D., & Levitzki, A., 2001. Enhanced ROS production in oncogenically transformed cells potentiates c-Jun N-terminal kinase and p38 mitogen-activated protein kinase activation and sensitization to genotoxic stress. *Molecular and Cellular Biology*, 21(20): 6913–6926.
- Benhar, M., Engelberg, D., & Levitzki, A., 2002. ROS, stress-activated kinases and stress signaling in cancer. *EMBO Reports*, 3(5): 420–425.
- Birdsall, S.M., Birdsall, T.C., & Tims, L.A., 2016. The Use of Medical Marijuana in Cancer. *Current Oncology Reports*, 18(7): 40.
- Bisogno, T., Hanus, L., De Petrocellis, L., Tchilibon, S., Ponde, D.E., Brandi, I., Moriello, A.S., Davis, J.B., Mechoulam, R., & Di Marzo, V., 2001. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *British Journal of Pharmacology*, 134(4): 845–852.
- Bisogno, T., Melck, D., De Petrocellis, L., & Di Marzo, V., 1999. Phosphatidic acid as the biosynthetic precursor of the endocannabinoid 2-arachidonoylglycerol in intact mouse neuroblastoma cells stimulated with ionomycin. *Journal of Neurochemistry*, 72(5): 2113–2119.
- Bowles, D.W., O'Bryant, C.L., Camidge, D.R., & Jimeno, A., 2012. The intersection between cannabis and cancer in the United States. *Critical Reviews in Oncology/Hematology*, 83(1): 1–10.
- Cabral, G. A., Raborn, E. S., Griffin, L., Dennis, J., Marciano-Cabral, F., 2008. CB2 receptors in the brain: role in central immune function. *British Journal of Pharmacology*, 153(2): 240–251.
- Caffarel, M.M., Sarrió, D., Palacios, J., Guzmán, M., & Sánchez, C., 2006. Delta9-tetrahydrocannabinol inhibits cell cycle progression in human breast cancer cells through Cdc2 regulation. *Cancer Research*, 66(13), 6615–6621.
- Calvaruso, G., Pellerito, O., Notaro, A., & Giuliano, M., 2012. Cannabinoid-associated cell death mechanisms in tumor models (review). *International Journal of Oncology*, 41(2): 407–413.
- Carracedo, A., Gironella, M., Lorente, M., Garcia, S., Guzmán, M., Velasco, G., & Iovanna, J.L., 2006. Cannabinoids induce apoptosis of pancreatic tumor cells via endoplasmic reticulum stress-related genes. *Cancer Research*, 66(13): 6748–6755.
- Caterina, M.J., Leffler, A., Malmberg, A.B., Martin, W.J., Trafton, J., Petersen-Zeit, K.R., Koltzenburg, M., Basbaum, A.I., & Julius, D., 2000. Impaired nociception and pain sensation in mice lacking the capsaicin receptor. *Science*, 288(5464): 306–313.
- Caterina, M.J., Schumacher, M.A., Tominaga, M., Rosen, T.A., Levine, J.D., & Julius, D., 1997. The capsaicin receptor: a heat-activated ion channel in the pain pathway. *Nature*, 389(6653): 816–824.
- Cianchi, F., Papucci, L., Schiavone, N., Lulli, M., Magnelli, L., Vinci, M.C., Messerini, L., Manera, C., Ronconi, E., Romagnani, P., Donnini, M., Perigli, G., Trallori, G., Tanganelli, E., Capaccioli, S., & Masini, E., 2008. Cannabinoid receptor activation induces apoptosis through tumor necrosis factor alpha-mediated ceramide de novo synthesis in colon cancer cells. *Clinical Cancer Research: an Official Journal of the American Association for Cancer Research*, 14(23): 7691–7700.
- ClinicalTrials.gov, 2016a. A Safety Study of Sativex in Combination With Dose-intensive Temozolomide in Patients With Recurrent Glioblastoma. In *clinicaltrials.gov*. Available at:

- <https://clinicaltrials.gov/show/NCT01812603>
[Accessed July 18, 2016].
- ClinicalTrials.gov, 2016b. Safety and Efficacy of Cannabidiol for Grade I/II Acute Graft Versus Host Disease (GVHD) After Allogeneic Stem Cell Transplantation. In Clinicaltrials.gov. Available at: <https://clinicaltrials.gov/ct2/show/NCT01596075> [Accessed July 18, 2016].
- Contassot, E., Tenan, M., Schnüriger, V., Pelte, M.-F., & Dietrich, P.-Y., 2004. Arachidonyl ethanolamide induces apoptosis of uterine cervix cancer cells via aberrantly expressed vanilloid receptor-1. *Gynecologic Oncology*, 93(1): 182–188.
- Davis, J.B., Gray, J., Gunthorpe, M.J., Hatcher, J.P., Davey, P.T., Overend, P., Harries, M.H., Latcham, J., Clapham, C., Atkinson, K., Hughes, S.A., Rance, K., Grau, E., Harper, A.J., Pugh, P.L., Rogers, D.C., Bingham, S., Randall, A., & Sheardown, S.A., 2000. Vanilloid receptor-1 is essential for inflammatory thermal hyperalgesia. *Nature*, 405(6783): 183–187.
- Davis, M. P., 2014. Cannabinoids in pain management: CB1, CB2 and non-classic receptor ligands. *Expert Opinion on Investigational Drugs*, 23(8): 1123–40.
- Elphick, M.R., 2007. BfCBR: a cannabinoid receptor ortholog in the cephalochordate *Branchiostoma floridae* (Amphioxus). *Gene*, 399(1): 65–71.
- Elphick, M.R., 2002. Evolution of cannabinoid receptors in vertebrates: identification of a CB(2) gene in the puffer fish *Fugu rubripes*. *The Biological Bulletin*, 202(2): 104–107.
- Elphick, M.R. & Egertová, M., 2001. The neurobiology and evolution of cannabinoid signalling. *Philosophical Transactions of the Royal Society of London. Series B, Biological Sciences*, 356(1407): 381–408.
- Elphick, M.R. & Egertová, M., 2005. The phylogenetic distribution and evolutionary origins of endocannabinoid signalling. *Handbook of Experimental Pharmacology*, (168): 283–97.
- Elphick, M.R., Satou, Y., & Satoh, N., 2003. The invertebrate ancestry of endocannabinoid signalling: an orthologue of vertebrate cannabinoid receptors in the urochordate *Ciona intestinalis*. *Gene*, 302(1): 95–101.
- Fernández-Ruiz, J., Romero, J., Velasco, G., Tolón, R.M., Ramos, J.A., & Guzmán, M., 2007. Cannabinoid CB2 receptor: a new target for controlling neural cell survival? *Trends in Pharmacological Sciences*, 28(1): 39–45.
- Fernández-Ruiz, J., Sagredo, O., Pazos, M.R., García, C., Pertwee, R., Mechoulam, R., & Martínez-Orgado, J., 2013. Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid? *British journal of Clinical Pharmacology*, 75(2): 323–33.
- Fredriksson, R., Lagerström, M.C., Lundin, L.-G., & Schiöth, H.B., 2003. The G-protein-coupled receptors in the human genome form five main families. Phylogenetic analysis, paralogon groups, and fingerprints. *Molecular Pharmacology*, 63(6): 1256–1272.
- Galve-Roperh, I., Sánchez, C., Cortés, M.L., Gómez del Pulgar, T., Izquierdo, M., & Guzmán, M., 2000. Anti-tumoral action of cannabinoids: involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. *Nature Medicine*, 6(3): 313–319.
- Gustafsson, K., Christensson, B., Sander, B., & Flygare, J., 2006. Cannabinoid receptor-mediated apoptosis induced by R(+)-methanandamide and Win55,212-2 is associated with ceramide accumulation and p38 activation in mantle cell lymphoma. *Molecular Pharmacology*, 70(5): 1612–1620.
- Guzmán, M., 2003. Cannabinoids: Potential anticancer agents. *Nature Reviews Cancer*, 3(10): 745–755.
- Guzmán, M., Duarte, M.J., Blázquez, C., Ravina, J., Rosa, M.C., Galve-Roperh, I., Sánchez, C., Velasco, G., & González-Feria, L., 2006. A pilot clinical study of Delta9-tetrahydrocannabinol in patients with recurrent glioblastoma multiforme. *British Journal of Cancer*, 95(2): 197–203.
- Hart, S., Fischer, O. M., & Ullrich, A., 2004. Cannabinoids Induce Cancer Cell Proliferation via Tumor Necrosis Factor -Converting Enzyme (TACE/ADAM17)-Mediated Transactivation of the Epidermal Growth Factor Receptor. *Cancer Research*, 64(6): 1943–1950.
- Hegde, V.L., Nagarkatti, P.S., & Nagarkatti, M., 2011. Role of myeloid-derived suppressor cells in amelioration of experimental autoimmune hepatitis following activation of TRPV1 receptors by cannabidiol. *PloS one*, 6(4): e18281.
- Hermanson, D.J. & Marnett, L.J., 2011. Cannabinoids, endocannabinoids, and cancer. *Cancer Metastasis Reviews*, 30(3-4): 599–612.
- Hers, I., Vincent, E.E., & Tavaré, J.M., 2011. Akt signalling in health and disease. *Cellular Signalling*, 23(10): 1515–1527.
- Hu, G., Ren, G., & Shi, Y., 2011. The putative cannabinoid receptor GPR55 promotes cancer cell proliferation. *Oncogene*, 30(2): 139–141.
- Kogan, N., 2005. Cannabinoids and Cancer. *Mini-Reviews in Medicinal Chemistry*, 5(10): 941–952.
- Laurent, A., Nicco, C., Chéreau, C., Goulvestre, C., Alexandre, J., Alves, A., Lévy, E., Goldwasser,

- F., Panis, Y., Soubrane, O., Weill, B., & Batteux, F., 2005. Controlling tumor growth by modulating endogenous production of reactive oxygen species. *Cancer Research*, 65(3): 948–56.
- Ligresti, A., Moriello, A.S., Starowicz, K., Matias, I., Pisanti, S., De Petrocellis, L., Laezza, C., Portella, G., Bifulco, M., & Di Marzo, V., 2006. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *The Journal of Pharmacology and Experimental Therapeutics*, 318(3): 1375–1387.
- Maccarrone, M., Lorenzon, T., Bari, M., Melino, G., & Finazzi-Agro, A., 2000. Anandamide Induces Apoptosis in Human Cells via Vanilloid Receptors: EVIDENCE FOR A PROTECTIVE ROLE OF CANNABINOID RECEPTORS. *Journal of Biological Chemistry*, 275(41): 31938–31945.
- Malhotra, J.D. & Kaufman, R.J., 2007. Endoplasmic reticulum stress and oxidative stress: a vicious cycle or a double-edged sword? *Antioxidants & Redox Signaling*, 9(12): 2277–2293.
- Marshall, A.D., Lagutina, I., Grosveld, G.C. 2011. PAX3-FOXO1 induces cannabinoid receptor 1 to enhance cell invasion and metastasis. *Cancer Research*. 71(24): 7471–7480.
- Massi, P., Massi, P., Vaccani, A., Vaccani, A., Ceruti, S., Ceruti, S., Colombo, A., Colombo, A., Abbracchio, M.P., Abbracchio, M.P., Parolaro, D., & Parolaro, D., 2004. Antitumor Effects of Cannabidiol, a Nonpsychoactive Cannabinoid, on Human Glioma Cell Lines. *Journal of Pharmacology and Experimental Therapeutics*, 308(3): 838–845.
- Massi, P., Vaccani, a., Bianchessi, S., Costa, B., Macchi, P., & Parolaro, D., 2006. The non-psychoactive cannabidiol triggers caspase activation and oxidative stress in human glioma cells. *Cellular and Molecular Life Sciences*, 63(17): 2057–2066.
- Mato, S., Victoria Sánchez-Gómez, M., & Matute, C., 2010. Cannabidiol induces intracellular calcium elevation and cytotoxicity in oligodendrocytes. *Glia*, 58(14): 1739–1747.
- McKallip, R.J., Jia, W., Schlomer, J., Warren, J.W., Nagarkatti, P.S., & Nagarkatti, M., 2006. Cannabidiol-Induced Apoptosis in Human Leukemia Cells: A Novel Role of Cannabidiol in the Regulation of p22 phox and Nox4 Expression. *Molecular Pharmacology*, 70(3): 897–908.
- McKallip, R. J., Nagarkatti, M., & Nagarkatti, P. S. 2005. -9-Tetrahydrocannabinol Enhances Breast Cancer Growth and Metastasis by Suppression of the Antitumor Immune Response. *The Journal of Immunology*, 174(6): 3281–3289.
- McAllister, S.D., Murase, R., Christian, R.T., Lau, D., Zielinski, A.J., Allison, J., Almanza, C., Pakdel, A., Lee, J., Limbad, C., Liu, Y., Debs, R.J., Moore, D.H., & Desprez, P.-Y., 2010. Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis. *Breast Cancer Research and Treatment*, 129(1): 37–47.
- McAllister, S.D., Soroceanu, L., & Desprez, P.-Y., 2015. The Antitumor Activity of Plant-Derived Non-Psychoactive Cannabinoids. *Journal of Neuroimmune Pharmacology*, 10(2): 255–267.
- McKallip, R.J., Jia, W., Schlomer, J., Warren, J.W., Nagarkatti, P.S., & Nagarkatti, M., 2006. Cannabidiol-Induced Apoptosis in Human Leukemia Cells: A Novel Role of Cannabidiol in the Regulation of p22 phox and Nox4 Expression. *Molecular Pharmacology*, 70(3): 897–908.
- Messalli, E. M., Grauso, F., Luise, R., Angelini, A., & Rossiello, R. 2014. Cannabinoid receptor type 1 immunoreactivity and disease severity in human epithelial ovarian tumors. *American Journal of Obstetrics and Gynecology*, 211(3): 234.e1–6.
- Mizushima, N., Levine, B., Cuervo, A.M., & Klionsky, D.J., 2008. Autophagy fights disease through cellular self-digestion. *Nature*, 451(7182): 1069–75.
- Mukhopadhyay, B., Schuebel, K., Mukhopadhyay, P., Cinar, R., Godlewski, G., Xiong, K., Kunos, G. 2015. Cannabinoid receptor 1 promotes hepatocellular carcinoma initiation and progression through multiple mechanisms. *Hepatology*, 61(5): 1615–1626.
- Munson, A.E., Harris, L.S., Friedman, M.A., Dewey, W.L., & Carchman, R.A., 1975. Antineoplastic activity of cannabinoids. *Journal of the National Cancer Institute*, 55(3): 597–602.
- Murataeva, N., Straiker, A., & Mackie, K., 2014. Parsing the players: 2-arachidonoylglycerol synthesis and degradation in the CNS. *British Journal of Pharmacology*, 171(6): 1379–1391.
- National Cancer Institute, 2016. Cannabis and Cannabinoids (PDQ®)–Health Professional Version. Available at: http://www.cancer.gov/about-cancer/treatment/cam/hp/cannabis-pdq#section/_3 [Accessed July 18, 2016].
- Nilius, B., Owsianik, G., Voets, T., & Peters, J.A., 2007. Transient receptor potential cation channels in disease. *Physiological Reviews*, 87(1): 165–217.
- O’Sullivan, S.E. & Kendall, D.A., 2010. Cannabinoid activation of peroxisome proliferator-activated receptors: potential for modulation of inflammatory disease. *Immunobiology*, 215(8): 611–616.

- Office of Diversion Control, 2016. Controlled Substances Act. In 21 USC Charter 13 (1970). Available at: <http://www.deadiversion.usdoj.gov/21cfr/21usc/> [Accessed July 18, 2016].
- Owsianik, G., D'hoedt, D., Voets, T., & Nilius, B., 2006. Structure-function relationship of the TRP channel superfamily. *Reviews of Physiology, Biochemistry and Pharmacology*, 156: 61–90.
- Park, J. 2012. Expression of the cannabinoid type I receptor and prognosis following surgery in colorectal cancer. *Oncology Letters*, 5(3): 870–876.
- Park, J.M., Xian, X.-S., Choi, M.-G., Park, H., Cho, Y.K., Lee, I.S., Kim, S.W., & Chung, I.-S., 2011. Antiproliferative mechanism of a cannabinoid agonist by cell cycle arrest in human gastric cancer cells. *Journal of Cellular Biochemistry*, 112(4): 1192–205.
- Pérez-Gómez, E., Andradás, C., Flores, J.M., Quintanilla, M., Paramio, J.M., Guzmán, M., & Sánchez, C., 2012. The orphan receptor GPR55 drives skin carcinogenesis and is upregulated in human squamous cell carcinomas. *Oncogene*, 32(20): 2534–2542.
- Pertwee, R.G., Howlett, a C., Abood, M.E., Alexander, S.P.H., Marzo, V. Di, Elphick, M.R., Greasley, P.J., Hansen, H.S., & Kunos, G., 2010. International Union of Basic and Clinical Pharmacology. LXXIX. Cannabinoid Receptors and Their Ligands: Beyond CB 1 and CB 2. *Pharmacological Reviews*, 62(4): 588–631.
- Petrocellis De, L., Ligresti, A., Moriello, A.S., Allarà, M., Bisogno, T., Petrosino, S., Stott, C.G., & Di Marzo, V., 2011. Effects of cannabinoids and cannabinoid-enriched Cannabis extracts on TRP channels and endocannabinoid metabolic enzymes. *British Journal of Pharmacology*, 163(7): 1479–94.
- Petrocellis De, L., Ligresti, A., Schiano Moriello, A., Iappelli, M., Verde, R., Stott, C.G., Cristino, L., Orlando, P., & Di Marzo, V., 2013. Non-THC cannabinoids inhibit prostate carcinoma growth in vitro and in vivo: pro-apoptotic effects and underlying mechanisms. *British Journal of Pharmacology*, 168(1): 79–102.
- Piñeiro, R., Maffucci, T., & Falasca, M., 2011. The putative cannabinoid receptor GPR55 defines a novel autocrine loop in cancer cell proliferation. *Oncogene*, 30(2): 142–152.
- Pisanti, S., Picardi, P., D'Alessandro, A., Laezza, C., & Bifulco, M. 2013. The endocannabinoid signaling system in cancer. *Trends in Pharmacological Sciences*, 34(5): 273–282.
- Pisanti, S., Malfitano, A.M., Grimaldi, C., Santoro, A., Gazerro, P., Laezza, C., & Bifulco, M., 2009. Use of cannabinoid receptor agonists in cancer therapy as palliative and curative agents. *Best Practice & Research. Clinical Endocrinology & Metabolism*, 23(1): 117–131.
- Pisanti, S., Picardi, P., Prota, L., Proto, M.C., Laezza, C., McGuire, P.G. 2011. Genetic and pharmacologic inactivation of cannabinoid CB1 receptor inhibits angiogenesis. *Blood*. 117(20): 5541–5550.
- Ramer, R. & Hinz, B., 2008. Inhibition of cancer cell invasion by cannabinoids via increased expression of tissue inhibitor of matrix metalloproteinases-1. *Journal of the National Cancer Institute*, 100(1): 59–69.
- Rimmerman, N., Kozela, E., Juknat, A., Levy, R., Vogel, Z. 2013. Cannabinoid Signaling Through Non-CB1R/Non-CB2R Targets in Microglia. In: Abood, M. E., Sorensen, R. G. Stella, N. (ed.), *endoCANNABINOIDs: Actions at Non-CB1/CB2 Cannabinoid Receptors*, pp. 143–171. NY: Springer New York, New York.
- Rimmerman, N., Ben-Hail, D., Porat, Z., Juknat, A., Kozela, E., Daniels, M.P., Connelly, P.S., Leishman, E., Bradshaw, H.B., Shoshan-Barmatz, V., & Vogel, Z., 2013a. Direct modulation of the outer mitochondrial membrane channel, voltage-dependent anion channel 1 (VDAC1) by cannabidiol: a novel mechanism for cannabinoid-induced cell death. *Cell Death & Disease*, 4: e949.
- Ruhaak, L.R., Felth, J., Karlsson, P.C., Raftar, J.J., Verpoorte, R., & Bohlin, L., 2011. Evaluation of the cyclooxygenase inhibiting effects of six major cannabinoids isolated from Cannabis sativa. *Biological & Pharmaceutical Bulletin*, 34(5): 774–778.
- Ryan, D., Drysdale, A.J., Lafourcade, C., Pertwee, R.G., & Platt, B., 2009. Cannabidiol targets mitochondria to regulate intracellular Ca²⁺ levels. *The Journal of Neuroscience: the Official Journal of the Society for Neuroscience*, 29(7): 2053–2063.
- Salazar, M., Carracedo, A., Salanueva, I.J., Hernández-Tiedra, S., Lorente, M., Egia, A., Vázquez, P., Blázquez, C., Torres, S., García, S., Nowak, J., Fimia, G.M., Piacentini, M., Cecconi, F., Pandolfi, P.P., González-Feria, L., Iovanna, J.L., Guzmán, M., Boya, P., & Velasco, G., 2009. Cannabinoid action induces autophagy-mediated cell death through stimulation of ER stress in human glioma cells. *The Journal of Clinical Investigation*, 119(5): 1359–1372.
- Salazar, M., Lorente, M., García-Taboada, E., Hernández-Tiedra, S., Davila, D., Francis, S.E., Guzmán, M., Kiss-Toth, E., & Velasco, G., 2013. The pseudokinase trilles homologue-3 plays a crucial role in cannabinoid anticancer

- action. *Biochimica et Biophysica Acta*, 1831(10): 1573–1578.
- Sánchez, C., de Ceballos, M.L., Gómez del Pulgar, T., Rueda, D., Corbacho, C., Velasco, G. 2001. Inhibition of glioma growth in vivo by selective activation of the CB2 cannabinoid receptor. *Cancer Research*, 1;61(15): 5784–5789.
- Sarfaraz, S., Adhami, V.M., Syed, D.N., Afaq, F., & Mukhtar, H., 2008. Cannabinoids for cancer treatment: progress and promise. *Cancer Research*, 68(2): 339–342.
- Sarfaraz, S., Afaq, F., Adhami, V.M., Malik, A., & Mukhtar, H., 2006a. Cannabinoid receptor agonist-induced apoptosis of human prostate cancer cells LNCaP proceeds through sustained activation of ERK1/2 leading to G1 cell cycle arrest. *The Journal of Biological Chemistry*, 281(51): 39480–39491.
- Sarnataro, D., Pisanti, S., Santoro, A., Gazerro, P., Malfitano, A.M., Laezza, C. 2006. The cannabinoid CB1 receptor antagonist rimonabant (SR141716) inhibits human breast cancer cell proliferation through a lipid raft-mediated mechanism. *Molecular Pharmacology*. 70(4):1298–1306.
- Schröder, M. & Kaufman, R.J., 2005. The mammalian unfolded protein response. *Annual Review of Biochemistry*, 74(1): 739–789.
- Shrivastava, A., Kuzontkoski, P.M., Groopman, J.E., & Prasad, A., 2011. Cannabidiol Induces Programmed Cell Death in Breast Cancer Cells by Coordinating the Cross-talk between Apoptosis and Autophagy. *Molecular Cancer Therapeutics*, 10(7): 1161–1172.
- Starowicz, K., Nigam, S., & Di Marzo, V., 2007. Biochemistry and pharmacology of endovanilloids. *Pharmacology & Therapeutics*, 114(1): 13–33.
- Stella, N., Schweitzer, P., & Piomelli, D., 1997. A second endogenous cannabinoid that modulates long-term potentiation. *Nature*, 388(6644): 773–778.
- Sui, X., Chen, R., Wang, Z., Huang, Z., Kong, N., Zhang, M., Han, W., Lou, F., Yang, J., Zhang, Q., Wang, X., He, C., & Pan, H., 2013. Autophagy and chemotherapy resistance: a promising therapeutic target for cancer treatment. *Cell Death & Disease*, 4: e838.
- Suk, K., Mederacke, I., Gwak, G., Cho, S. W., Adeyemi, A., Friedman, R., & Schwabe, R. F. 2016. Opposite roles of cannabinoid receptors 1 and 2 in hepatocarcinogenesis. *Gut*, 65(10): 1721–1732.
- Vara, D., Salazar, M., Olea-Herrero, N., Guzmán, M., Velasco, G., & Díaz-Laviada, I., 2011. Anti-tumoral action of cannabinoids on hepatocellular carcinoma: role of AMPK-dependent activation of autophagy. *Cell Death and Differentiation*, 18(7): 1099–1111.
- Velasco, G., Sánchez, C., & Guzmán, M., 2012. Towards the use of cannabinoids as antitumour agents. *Nature Reviews Cancer*, 12(6): 436–444.
- Venkatachalam, K. & Montell, C., 2007. TRP channels. *Annual Review of Biochemistry*, 76: 387–417.
- Verfaillie, T., Salazar, M., Velasco, G., & Agostinis, P., 2010. Linking ER Stress to Autophagy: Potential Implications for Cancer Therapy. *International Journal of Cell Biology*, 2010: 930509–930528.
- Wang, J. & Ueda, N., 2009. Biology of endocannabinoid synthesis system. *Prostaglandins & Other Lipid Mediators*, 89(3): 112–119.
- White, A.C., Munson, J.A., Munson, A.E., & Carchman, R.A., 1976. Effects of delta9-tetrahydrocannabinol in Lewis lung adenocarcinoma cells in tissue culture. *Journal of the National Cancer Institute*, 56(3): 655–658.
- Whiting, P.F., Wolff, R.F., Deshpande, S., Di Nisio, M., Duffy, S., Hernandez, A. V., Keurentjes, J.C., Lang, S., Misso, K., Ryder, S., Schmidtkofer, S., Westwood, M., & Kleijnen, J., 2015. Cannabinoids for Medical Use. *Journal of the American Medical Association*, 313(24): 2456–2473.
- Zheng, D., Bode, A. M., Zhao, Q., Cho, Y., Zhu, F., Ma, W., & Dong, Z. 2008. The Cannabinoid Receptors Are Required for Ultraviolet-Induced Inflammation and Skin Cancer Development. *Cancer Research*, 68(10): 3992–3998.

Streszczenie

Kannabinoidy oddziałują na organizm ludzki wiążąc się z receptorami kannabinoidowymi (CB1 oraz CB2). Dwoma głównymi kannabinoidami roślinnymi są Δ^9 -tetrahydrokannabinol (THC) i kannabidiol (CBD). THC wiąże się z receptorami CB1 obecnymi w obrębie centralnego układu nerwowego, co powoduje psychoaktywne właściwości marihuany. CBD posiada niskie powinowactwo do receptorów CB1, nie posiada właściwości psychoaktywnych, co sprawia, że jego medyczne zastosowanie może być znacznie szersze. Receptory CB są częścią złożonego mechanizmu zaangażowanego w regulację wielu procesów fizjologicznych – układu

endokannabinoidowego. Kannabinoidy znalazły pewne zastosowanie w medycynie paliatywnej, lecz istnieje wiele badań dowodzących ich antynowotworowych właściwości. Agoniści receptorów CB1 powodują akumulację związków z grupy ceramidów w komórkach nowotworowych, stres retikulum endoplazmatycznego i w konsekwencji apoptozę. W efektach wywoływanych przez kannabinoidy posiadając niskie powinowactwo do receptorów CB pośredniczy najprawdopodobniej indukcja produkcji reaktywnych form tlenu. Dotychczasowa wiedza dotycząca przeciwnowotworowych właściwości kannabinoidów opiera się tylko na badaniach przedklinicznych. Istnieje potrzeba przeprowadzania kolejnych badań, które umożliwiłyby oszacowanie rzeczywistego potencjału tych związków.