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REVIEW ARTICLE

Insights into the effects of the endocannabinoid system in cancer: a review

Correspondence Ana Isabel Torres-Suárez, Department of Pharmaceutical Technology, Faculty of Pharmacy, Complutense University of Madrid, Madrid 28040, Spain. E-mail: galaaaa@ucm.es

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Ana Isabel Fraguas-Sánchez[1], Cristina Martín-Sabroso[1] and Ana Isabel Torres-Suárez[1,2]

[1]Department of Pharmaceutical Technology, Faculty of Pharmacy, Complutense University of Madrid, Madrid 28040, Spain, and [2]Institute of Industrial Pharmacy, Complutense University of Madrid, Madrid 28040, Spain

In the last few decades, the endocannabinoid system has attracted a great deal of interest in terms of its applications to clinical medicine. In particular, its applications in cancer probably represent one of the therapeutic areas with most promise. On the one hand, expression of the endocannabinoid system is altered in numerous types of tumours, compared to healthy tissue, and this aberrant expression has been related to cancer prognosis and disease outcome, suggesting a role of this system in tumour growth and progression that depends on cancer type. On the other hand, cannabinoids exert an anticancer activity by inhibiting the proliferation, migration and/or invasion of cancer cells and also tumour angiogenesis. However, some cannabinoids, at lower concentrations, may increase tumour proliferation, inducing cancer growth. Enough data has been provided to consider the endocannabinoid system as a new therapeutic target in cancer, although further studies to fully establish the effect of cannabinoids on tumour progression are still needed.

Abbreviations

2-AG, 2-arachidonoylglycerol; ABCP, breast cancer resistance protein; AM-356, methanandamide; CBD, cannabidiol; ECS, endocannabinoid system; HER-2, human epidermal growth factor receptor; MDR1, multidrug resistance protein 1; THC, Δ^9-tetrahydrocannabinol

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Introduction

Nowadays, the term "endocannabinoid system" (ECS) comprises cannabinoid (CB) receptors, endogenous cannabinoids, also called endocannabinoids, and the enzymes involved in their biosynthesis, transport and degradation. The most important endocannabinoids are **N-arachidonoylethanolamine (AEA)**, also called anandamide, and **2-arachidonoylglycerol (2-AG)**, which are derived from arachidonic acid and synthesized on demand. The main synthesis and degradation pathways are shown in Figure 1 (Fraguas-Sanchez *et al.,* 2016; Schurman and Lichtman, 2017). Other minor endocannabinoids have also been identified, such as **oleamide**, **virodhamine** and **2-arachidonyl glyceryl ether**, also known as noladin-ether.

The **CB** receptors belong to the superfamily of GPCRs and two distinct receptors have been identified and characterized to date, **CB_1** and **CB_2**, exhibiting around 44% homology. The CB_1 receptor (first cloned from a rat brain in 1990) has an extended distribution, and although it is mostly expressed in the CNS, it is also found in peripheral nerve terminals and extra-neuronal tissues, including the vascular endothelium, adipose tissue, lungs, liver, spleen, kidneys, uterus, prostate, testis and stomach. The CB_2 receptor (isolated for the first time in 1993 from human promyelocytic HL-60 cells) has a more localized distribution, being found predominantly in the immune system (tissues and cells). Nonetheless, it is also detected in the CNS, primarily after certain circumstances such as inflammation (Console-Bram *et al.,* 2012; Kendall and Yudowski, 2016). Finally, some endocannabinoid effects are mediated by non-CB receptors, particularly the orphan receptors **GPR55** and **GPR18**, which have also been postulated to be members of the ECS (Okuno and Yokomizo, 2011; Pyszniak *et al.,* 2016; Morales and Reggio, 2017).

Since the discovery of the ECS, it has attracted a great deal of interest in therapeutics due to its involvement in several physiopathological processes including energy balance, appetite stimulation, nociception, embryogenesis, immune response and control of nausea and vomiting (Cunha *et al.,* 2011; Katchan *et al.,* 2016; Laprairie *et al.,* 2017). Alterations of ECS expression have been found in many different disease conditions including cancer and neurological disorders such as Parkinson's disease, Huntington's disease and multiple sclerosis (Hasenoehrl *et al.,* 2016; Ligresti *et al.,* 2016; Bridgeman and Abazia, 2017). This review focuses on the role of the ECS in cancer disease progression and as a novel therapeutic target for anticancer treatments.

Endocannabinoid system expression in cancer

Cannabinoid receptors

The expression of both CB_1 and CB_2 receptors is altered in numerous types of tumours (summarized in Figure 2) and has been related to cancer prognosis. The altered expression

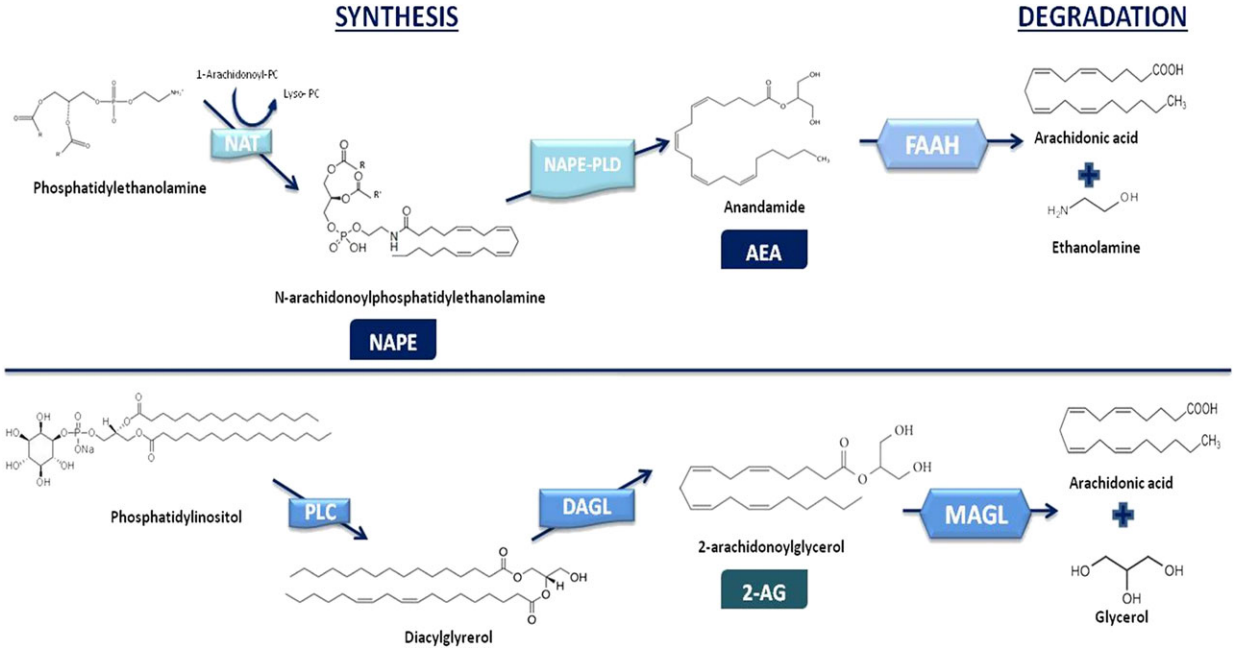

Figure 1

Diagram showing the main biosynthetic and degradation pathways of both AEA and 2-AG. Anandamide is synthesized *via* a phospholipase-D (NAPE-PLD), which converts N-arachidonoylphosphatidylethanolamine (NAPE), formed by the transfer of an arachidonoyl group to phosphatidylethanolamine by the action of N-acetyltransferase (NAT), to AEA. 2-AG is formed from diacylglycerol, *via* diacylglycerol lipase (DGL). Diacylglycerol is synthesized from phosphatidylinositol by the action of a PLC. In terms of degradation pathways, FAAH and MAGL are the most important enzymes responsible for inactivation of AEA and 2-AG respectively. However, other pathways also participate in their degradation including lipoxygenases, cytochrome P450, COX-2 and the domains 6 and 12 of serine lipases a/ß hydrolases.

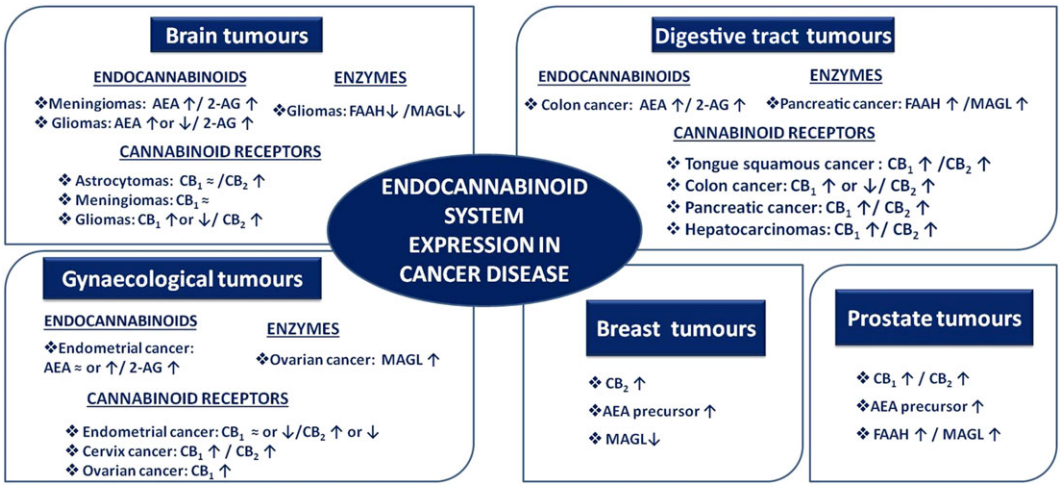

Figure 2

Altered expression of endocannabinoid system in brain, breast, digestive tract, gynaecological and prostate carcinomas.

is correlated with positive and negative survival indicators, depending on the origin of the cancer.

In brain carcinomas, both CB_1 and CB_2 receptor expression is different from that in healthy tissue. Although, in astrocytomas and meningiomas, no differences in the expression of CB_1 receptors have been detected, some studies have reported that in glioblastoma multiforme, their expression is lower (De Jesus *et al.,* 2010). However, recent studies have demonstrated opposite results, showing CB_1 receptors to be highly expressed in high-grade gliomas compared to low-grade tumours and healthy brain samples (Wu *et al.,* 2012). Interestingly, these results have also been found in samples of low-grade paediatric glioma, where overexpression has been associated with tumour regression, due to the apoptosis and cell cycle arrest induced by activation of CB_1 receptors by endocannabinoids (Sredni *et al.,* 2016). Concerning CB_2 receptors, Schley *et al.* (2009) revealed an up-regulation of these receptors in the endothelial cells of blood vessels of glioblastoma tissues. Finally, Wu *et al.* reported an overexpression of both CB_1 and CB_2 receptors in gliomas compared to the healthy brain. Whereas up-regulation of CB_1 receptors was associated with low-grade tumours, over-expression of CB_2 receptors was related to high-grade gliomas (Wu *et al.,* 2012).

In breast tumours, which are mainly grouped into three categories depending on the molecular profile, hormone-receptor positive, **human epidermal growth factor receptor 2 (HER-2)** and triple negative, an increased expression of CB_2 receptors has been detected. More than 90% of HER-2-positive tumours overexpressed this receptor (Caffarel *et al.,* 2010) and this finding was related to a poor prognosis, probably due to the activation of HER-2 pro-oncogenic pathways (Perez-Gomez *et al.,* 2015). However, Elbaz *et al.* (2016) reported that the expression of these receptors in oestrogen-receptor-positive and oestrogen-receptor-negative mammary tumours was related to a better prognosis. In fact, they suggested CB_2 receptors as a potential therapeutic target for treating breast cancer metastases. They demonstrated *in vitro* and *in vivo* (using mice orthotopic models) that the activation of CB_2 receptors decreased the migration and invasion of oestrogen-positive and -negative breast cancer cells, suppressing epidermal growth factor and insulin-like growth factor tumourigenic pathways. Similar results were also found by Murase *et al.* (2014) who reported in mice models of breast cancer that the activation of CB_2 receptors by O-1665, a resorcinol compound analogue of **cannabidiol (CBD)**, reduced gene expression of the Id-1 protein, associated with breast cancer metastases, and also increased the survival rate in advanced stages of carcinoma.

In prostate carcinomas, expressions of both CB_1 and CB_2 receptors were increased compared to the normal prostatic tissue (Orellana-Serradell *et al.,* 2015), and the overexpression of CB_1 receptors has been associated with a higher Gleason score and metastasis incidence, being a negative marker of disease outcome. (Chung *et al.,* 2009; Cipriano *et al.,* 2013).

With respect to cancers of the digestive tract, the overexpression of CB receptors has also been related to cancer prognosis. In this sense, in tongue squamous tumour cells, both CB_1 and CB_2 receptors were overexpressed and this up-regulation has been postulated to be an indicator of cancer outcome, with high levels of CB_1 receptors being a better marker of disease survival than the overexpression of CB_2, or of both CB receptors (Theocharis *et al.,* 2016). Similarly, in colon tumours, both CB receptors were detected. While some studies reveal that CB_1 receptors were down-regulated in colon cancer compared to normal mucosa (Cianchi *et al.,* 2008), others indicate that some tumours had high levels of this CB receptor, and it was an indicator of a poor disease outcome in patients with stage II microsatellite-stable (Gustafsson *et al.,* 2011) or stage IV (Jung *et al.,* 2013) tumours. Targeting the CB_1 receptors could be a good strategy to increase the efficacy of anticancer treatments. Thus their inactivation with **rimonabant**, an inverse agonist at CB_1 receptors. decreased the growth of colon cancer tumours *in vivo* by inhibiting the canonical Wnt/**β catenin**-pathway through the inhibition of **p300-histone**

acetyltransferase activity (Proto *et al.,* 2017). In fact, a recent paper has reported, using 3D cultures of colon cancer cells that this compound acted specifically in tumour cells. Whereas in HTC_{116} cells, it demonstrated a strong synergism with **5-fluorouracil** in overcoming tumour resistances, in GTG7 cells, it slightly increased 5-fluorouracil efficacy and showed an antagonism with **oxaliplatin**, with further studies being necessary (Fiore *et al.,* 2017). As for CB_2 receptors, an up-regulated expression has also been associated with lower survival (Martinez-Martinez *et al.,* 2015). In pancreatic cancer, expression of both CB_1 and CB_2 receptors was increased compared to the normal pancreas (Carracedo *et al.,* 2006), and CB_1 up-regulation has been related to a worse cancer prognosis (Michalski *et al.,* 2008). In contrast, in hepatocarcinoma, where CB_1 and CB_2 receptors were also over-expressed comparing to normal liver (307- and 5.44-fold respectively) (Suk *et al.,* 2016), high levels of both receptors have been associated with better disease-free survival rates (Xu *et al.,* 2006).

In several gynaecological tumours, the expression of CB receptors was also altered. In this context, studies performed in biopsies of patients with endometrial cancer showed that CB_2 receptors, which are barely expressed in the healthy endometrial tissue, were up-regulated, but no significant differences in CB_1 receptor expression were detected (Guida *et al.,* 2010). However, other researchers found low levels of both CB_1 and CB_2 receptors in endometrial carcinoma (Ayakannu *et al.,* 2014). On the other hand, in cervix cancer, high levels of both CB were detected (Contassot *et al.,* 2004a). In invasive ovarian tumours, only higher levels of CB_1 were found and this up-regulation was related to the invasiveness of ovarian cancer (Messalli *et al.,* 2014).

Finally, in melanoma cells (Blazquez *et al.,* 2006) and lung carcinomas, CB_1 and CB_2 receptors are present in 24% and 55% of patients with non-small cell lung cancer respectively (Preet *et al.,* 2011). In leukaemia and lymphomas, the opposite results have been reported. While some murine leukaemia cell lines expressed both CB_1 and CB_2 receptors, human leukaemia cells only expressed CB_2 receptors (high levels) (McKallip *et al.,* 2002). A high CB_1 receptor expression has also been found in Hodgkin lymphoma cells (Benz *et al.,* 2013).

Table 1 summarizes the alterations in expression of CB_1 and CB_2 receptors in several types of tumours.

Endocannabinoid levels

The levels of endocannabinoids, especially AEA and 2-AG, are also abnormal in some tumours, compared with normal tissues. Regarding brain tumours, conflicting information has been documented. While some authors have reported that AEA levels were lower in gliomas compared to non-tumour tissues (Maccarrone *et al.,* 2001; Wu *et al.,* 2012), others have detected higher levels of this endocannabinoid in gliomas and also in meningiomas (Petersen *et al.,* 2005). With respect to 2-AG levels, they were up-regulated in both kinds of brain tumours (Petersen *et al.,* 2005; Wu *et al.,* 2012). In prostate tumours, increased levels of AEA have also been reported (Schmid *et al.,* 2002). However, in breast carcinoma, AEA levels were not increased. Nevertheless, high levels of the AEA precursor, *N*-acylphosphatidylethanolamine, have been detected. In colon cancer, several authors have also reported that levels of both AEA and 2-AG were increased, threefold and twofold respectively (Ligresti *et al.,* 2003). Interestingly, especially AEA levels were increased in lymphatic metastasis (Chen *et al.,* 2015). In patients with endometrial carcinoma, elevated levels of 2-AG have also been shown compared to healthy tissues, but with respect to AEA levels, the opposite results were detected. While some authors showed no significant differences in AEA levels (Guida *et al.,* 2010), in other studies, high levels have been reported (Schmid *et al.,* 2002). Finally, elevated levels of both AEA and 2-AG have been found in pituitary adenomas, correlated with the presence of CB_1 receptors. While in CB_1 receptor-positive samples, higher endocannabinoid levels have been detected, in samples with a low expression of CB_1, endocannabinoid levels were lower (Pagotto *et al.,* 2001).

Endocannabinoid degrading enzymes

Taking into account that, in some tumours, endocannabinoid levels were increased compared to normal tissues, an inhibition of the main enzymes responsible for their degradation could be expected. This happens in gliomas, where the expression and the activity of **fatty acid amide hydrolase (FAAH)** and **monoacylglycerol lipase (MAGL)** enzymes were reduced, compared with normal brain tissue (Wu *et al.,* 2012). However, in some studies, an increase of these enzymes has been reported. For example, in breast ductal carcinomas, MAGL expression was increased (Gjerstorff *et al.,* 2006), and in prostate tumours, high levels of AEA and its major degradative enzyme were detected compared to normal prostate tissue (Endsley *et al.,* 2008). FAAH overexpression has been associated with cancer invasion and disease outcome (Thors *et al.,* 2010). In androgen-independent prostate tumours, elevated levels of MAGL have also been found (Nithipatikom *et al.,* 2005). The expression and the activity of the MAGL enzyme were also increased in invasive ovarian and melanoma tumours, and interestingly, the up-regulation of MAGL in ovarian, melanoma and non-aggressive prostate cancer was associated with higher tumour cell migration and invasion (Van Dross *et al.,* 2013; Qin and Ruan, 2014). Nevertheless, the opposite results were found in pancreatic ductal adenocarcinomas, where both FAAH and MAGL enzymes were overexpressed and related to a good prognosis (Michalski *et al.,* 2008).

Table 2 summarizes the levels of endocannabinoids and expression of endocannabinoid degradative enzymes in several cancer types.

Non-cannabinoid receptors: GPR55

Levels of the orphan GPR55 were associated with high proliferation rates of tumour cells. In this context, *in vitro* and *in vivo* studies undertaken in several tumour models, including pancreas, breast, brain (Andradas *et al.,* 2011; Andradas *et al.,* 2016), prostate, ovary (Pineiro *et al.,* 2011) and skin carcinomas (Perez-Gomez *et al.,* 2013) reported that GPR55 receptors were implicated in the proliferation and progression of cancer. This may be attributed to GPR55 activation by the agonist **L-α-lysophosphatidylinositol (LPI)** (Ford *et al.,* 2010; Hofmann *et al.,* 2015) and, in patients with ovarian cancer, elevated levels of LPI were detected in plasma (Xiao *et al.,* 2001; Sutphen *et al.,* 2004).

Table 1

Expression of CB_1 and CB_2 receptors in several carcinomas, compared with that in normal tissue.

	Cancer type	CB_1	CB_2	Relation to disease outcome	Reference
Brain tumours	Astrocytomas	≈	↑	–	(De Jesus *et al.*, 2010)
	Meningiomas	≈	–	–	
	Gliomas	↑	↑	• CB_1 receptor overexpression is associated with tumour regression in glioblastoma and paediatric-low-gliomas • CB_2 receptors; higher levels are related to tumour grade	(Schley *et al.*, 2009, Wu *et al.*, 2012, Sredni *et al.*, 2016)
–	Breast	–	↑	• CB_2 receptors overexpression in more than 90% of HER-2 positive tumours; is a negative prognosis marker. • CB_2 receptor overexpression is a good prognosis marker in oestrogen negative and positive tumours.	(Caffarel *et al.*, 2010, Perez-Gomez *et al.*, 2015)
	Prostate	↑	↑	• CB_1 receptor overexpression is a good prognosis marker	(Chung *et al.*, 2009, Cipriano *et al.*, 2013, Orellana-Serradell *et al.*, 2015)
Digestive tract tumours	Tongue squamous	↑	↑	• CB_1 receptor overexpression is a positive marker of disease outcome	(Theocharis *et al.*, 2016)
	Colon	↑ or ↓	↑	• $CB_1$and CB_2 receptor overexpression is related to a poor disease outcome.	(Cianchi *et al.*, 2008, Gustafsson *et al.*, 2011, Jung *et al.*, 2013, Martinez-Martinez *et al.*, 2015)
	Pancreas	↑	↑	• CB_1 receptor overexpression is a negative marker of disease outcome	(Carracedo *et al.*, 2006, Michalski *et al.*, 2008)
	Hepatocarcinoma	↑	↑	• CB_1 and CB_2 receptor overexpression is a good indicator of survival	(Xu *et al.*, 2006, Suk *et al.*, 2016)
Gynaecological tumours	Endometrial	≈ or ↓	↑ or ↓	–	(Guida *et al.*, 2010, Ayakannu *et al.*)
	Cervix	↑	↑	–	(Contassot *et al.*, 2004a)
	Ovary	↑	–	• CB_1 receptor up-regulation is associated with a higher tumour aggressiveness	(Messalli *et al.*, 2014)
–	Hodgkin lymphoma	↑	–	–	(Benz *et al.*, 2013)

In the Table, ≈ denotes a similar expression, ↑ higher levels and ↓ lower levels of expression compared with normal tissues

The overexpression of these receptors has also been related to cancer disease aggressiveness and a poor prognosis. For example, in glioblastoma, increased levels of GPR55 were correlated with higher tumour grades and a lower survival rate, and provided a marker of a negative cancer prognosis. This relationship has also been shown in breast and pancreatic tumours (Andradas *et al.*, 2011). Hasenoehrl *et al*. (2018) reported a pro-tumour activity of these receptors in a recent study undertaken in mouse models of colon carcinoma. Although no effect on cell proliferation was detected with an agonist or antagonist of GPR55 receptors, they interfered with the composition of the leukocyte population during carcinogenesis, triggering a tumour-promoting micro-environment with the increase of tumourigenic factors (**COX-2**, STAT3 and NF-κB). Knockout mice exhibited reduced levels. In samples obtained from colon cancer patients, a correlation between high levels of GPR55 and a decrease in relapse-free survival has been also reported, supporting the implication of GPR55 in carcinogenesis (Hasenoehrl *et al.*, 2018).

Interestingly, some studies have reported that the heterodimerization between GPR55 and CB_2 receptors (Balenga *et al.*, 2014) may modulate, in breast and brain tumours, the antitumour activity of some cannabinoids.

Table 2

Expression of the major endocannabinoids and their major degradative enzymes in several carcinomas, compared with normal tissue.

	Cancer type	AEA	2-AG	FAAH	MAGL	Observations	References
Brain cancer	Meningioma	↑	↑	–	–	–	(Maccarrone *et al.*, 2001, Petersen *et al.*, 2005, Wu *et al.*, 2012)
	Glioma	↑ or ↓	↑	↓	↓	–	
–	Pituitary adenomas	↑	↑	–	–	Correlation with CB_1 receptor expression	(Pagotto *et al.*, 2001)
	Breast	Precursor ↑	–	–	↑	Higher levels of AEA precursor have been detected	(Gjerstorff *et al.*, 2006)
	Prostate	↑	–	↑	↑	FAAH and MAGL overexpression related to cancer invasion and disease outcome	(Schmid *et al.*, 2002, Nithipatikom *et al.*, 2005, Endsley *et al.*, 2008, Thors *et al.*, 2010)
Digestive tract tumours	Colon	↑	↑	–	–	High levels of AEA in lymphatic metastases	(Ligresti *et al.*, 2003, Chen *et al.*, 2015)
	Pancreas	–	–	↑	↑	FAAH and MAGL overexpression is a good cancer prognosis	(Michalski *et al.*, 2008)
Gynaecological tumours	Endometrial	≈ or ↑	↑	–	–	–	(Schmid *et al.*, 2002, Guida *et al.*, 2010)
	Ovarian	–	–	–	↑	MAGL up-regulation associate with cancer invasiveness.	(Van Dross *et al.*, 2013, Qin and Ruan, 2014)
–	Melanoma	–	–	–	↑		

In the Table, ≈ denotes a similar expression, ↑ higher levels and ↓ lower levels of expression compared with normal tissues

Endocannabinoid antitumour activity

A large number of studies have been undertaken to evaluate the anticancer activity of plant and synthetic cannabinoids (Guzman, 2003; Fraguas-Sanchez *et al.*, 2016; Velasco *et al.*, 2016; Bogdanovic *et al.*, 2017). Regarding endocannabinoids, their exogenous administration has also been reported to reduce the proliferation, migration and invasion of tumours. Finally, inhibition of the MAGL and FAAH enzymes has also shown anticancer activity.

Several authors have demonstrated that endocannabinoids exert an anticancer activity in brain tumours. Thus, AEA inhibited the proliferation of C6 glioma cells in a mechanism that involves both **TRPV-1 channels** and CB receptors (Fowler *et al.*, 2003). Contassot *et al.* (2004b) reported that this compound also inhibited the proliferation of U87, U251, C6 and H4 glioma cells. However, these authors found that the blockade of both CB_1 and CB_2 receptors did not protect from this activity; on the contrary, blocking these receptors seemed to exacerbate proliferation of these cells. The use of TRPV-1 channel antagonists significantly decreased the antiproliferative effect, suggesting that this was responsible for AEA action. The involvement of these receptors was also demonstrated by Bari *et al.* (2005), who found that the pretreatment of C6 glioma cells with the lipid raft disruptor, methyl-β-cyclodextrin, decreased the apoptosis induced by AEA. While co-incubation with the TRPV-1 channel antagonist significantly reduced the apoptotic effect, CB_1 antagonists almost doubled it, also preventing methyl-β-cyclodextrin activity. All these data support the participation of TRPV-1 channels in AEA apoptotic activity. Finally, the involvement of the COX-2 enzyme in cell death induced by this endocannabinoid has also been suggested in H4 cells (Hinz *et al.*, 2004). Ma *et al.* (2016) also found *in vitro* that AEA decreased not only the proliferation but also the migration and invasion of U251 glioma cancer cells, showing, in agreement with earlier results, that the inhibition of cell growth was due to induction of apoptosis and even a cell cycle arrest at the G_0/G_1 phase. They also demonstrated the antiproliferative effect of this cannabinoid in mice, reporting a significant tumour growth inhibition compared to the control.

In addition to AEA, other endocannabinoids have been investigated. 2-AG also decreased the proliferation of C6 glioma cells, showing a similar IC_{50} value to AEA (1.8 and 1.6 μM respectively) (Fowler *et al.*, 2003). Jacobsson *et al.* (2001) also reported that 1-AG and 2-AG inhibited the proliferation of C6 glioma cells. Interestingly, both endocannabinoids showed practically the same inhibitory profile and sensitivity as TRPV-1 and CB receptor antagonists; blocking completely their activity. All these data suggest that the action of 2-AG may be secondary to its conversion to 1-AG (Jacobsson *et al.*, 2001).

With respect to breast cancer, both the major endogenous cannabinoids, AEA and 2-AG, and also minor compounds such as oleamide, inhibited the proliferation of breast cancer cells (EFM-19, MCF-7 T-47D and BT4744–6) *in vitro* by cell cycle arrest and/or the induction of apoptosis. The involvement

of CB_1 receptors has also been reported (Bisogno *et al.*, 1998; Melck *et al.*, 2000). The nerve growth factor (NGF) induced proliferation was also inhibited by both AEA and 2-AG suppressing **NGF/Trk receptor** levels, and the co-administration of several endocannabinoids, such as the combination of AEA with oleamide, potentiated this antiproliferative effect (De Petrocellis *et al.*, 1998).

Concerning prostate carcinomas, various studies have reported the anti-proliferative activity of endocannabinoids. In a CB_1 receptor-dependent manner, AEA has been shown to inhibit the proliferation of PC-3, DU-145 and LNCaP cells, including the proliferation induced by **epidermal growth factor**, by decreasing the expression of its **receptors** and blocking the cell cycle at the G1 phase (Mimeault *et al.*, 2003; Nithipatikom *et al.*, 2011). The growth of primary cultures of prostate tumours was also inhibited by AEA, triggering apoptosis (Orellana-Serradell *et al.*, 2015). It has been reported that AEA and also 2-AG decreased the **prolactin**-induced growth of DU-145 prostate cancer cells. All these effects seem to involve CB_1 receptors. On the other hand, noladin ether, a minor endogenous cannabinoid, also reduced the proliferation of prostate tumour cells, but this action was not mediated by CB receptors (Nithipatikom *et al.*, 2011).

The effect of endocannabinoids on prostate tumour invasion has also been investigated. The increase in endogenous 2-AG levels *via* **diacylglycerol lipase** inhibition enhanced the invasion of PC-3 and DU-145 cells (androgen-independent) (4.2- and 2.0-fold increase respectively). However, in LNCaP (androgen-dependent), the opposite results were found, suggesting that this endocannabinoid may be a potential inhibitor of androgen-dependent prostate tumours. This anti-invasive effect was related to inhibition of **adenyl cyclase** and a reduction of **PKA** activity in a mechanism that seems to involve CB_1 receptors (Nithipatikom *et al.*, 2004). Interestingly, Endsley *et al*. (2007) showed endogenous 2-AG to be an anti-invasive compound in PC-3 cells, while its exogenous administration had the opposite effect, stimulating the invasion capacity of these cells. The administration of exogenous **arachidonic acid** also showed this effect, suggesting that the rapid hydrolysis of 2-AG may be responsible for the increase in the invasion rate. In fact, Nomura *et al*. (2011) reported that MAGL inhibitors decreased the invasion capacity of prostate carcinomas and that this effect was partially reversed by blocking CB_1 receptors. The disruption of MAGL activity also interfered with the expression of the epidermal growth factor receptor, decreasing the proliferation induced by epidermal growth factor (Cipriano *et al.*, 2014). Finally, noladin ether has also been reported to inhibit the invasion of androgen-independent prostate tumours, inhibiting PKA activity *via* the CB_1 receptors (Nithipatikom *et al.*, 2004).

Regarding tumours of the digestive tract, AEA and 2-AG have been demonstrated to reduce the proliferation of several lines of colon cancer cells (DLD-1, HT-29, SW620 and CaCo-2). The involvement of CB receptors in this antiproliferative effect is disputed and may depend on cell type. While some researchers reported that these effects were mediated by CB_1 receptors and CB_2 receptors in the case of DLD-1 cells (Ligresti *et al.*, 2003; Linsalata *et al.*, 2010), others showed that CB were not involved (Gustafsson *et al.*, 2009b; Patsos *et al.*, 2010). Interestingly, Gustafsson *et al*. (2009b) demonstrated the involvement of oxidative stress due to the use of α-tocopherol, and a **NO synthase** inhibitor attenuated the AEA antiproliferative activity. Linsalata *et al*. (2010) postulated that the antiproliferative activity of AEA may be due to the reduction of polyamine levels that play a critical role in cell proliferation. Finally, the inhibition of FAAH also reduced the viability, migration and invasion of Colo-205 cells *in vitro* (Wasilewski *et al.*, 2017).

In gastric carcinomas, some researchers have reported that AEA diminished the proliferation of cancer cells, inducing cell cycle arrest at the G_0/G_1 phase (Park *et al.*, 2011; Ortega *et al.*, 2016). It also enhanced the pro-apoptotic effect of **paclitaxel**, being a promising combination drug in chemotherapy (Miyato *et al.*, 2009). In hepatocarcinomas, the opposite results were found. While anandamide showed an *in vitro* antiproliferative activity in cholangiocarcinoma cells, 2-AG stimulated cell growth. Both effects were not mediated by CB receptors and involved lipid rafts. AEA seemed to exert its action by stabilizing lipid rafts and recruiting Fas and FasL. 2-AG disrupted the lipid raft structure (DeMorrow *et al.*, 2007). *In vivo* studies undertaken in mice supported the antiproliferative activity of AEA and reported the activation of non-canonical Wnt signalling pathway as one of the mechanisms responsible for its action, increasing the expression of **Wnt5a**. The increase of this protein induced the triggering of calcium-independent pathways that involved the orphan receptor **Ror2** (DeMorrow *et al.*, 2008).

With regard to gynaecological cancers, AEA has been reported to inhibit the proliferation of several cervical cell lines (CC299, CasKi and HeLa) by the induction of apoptosis (activating the cleavage of **caspase-7**). Interestingly, CB receptors were not involved in this induction of apoptosis, although they were expressed by these cells. By contrast, the blockade of both CB_1 and CB_2 receptors with selective agonists did not prevent the induction of apoptosis but potentiated it, suggesting that these receptors may have a protective role in death of cervical cancer cells and the apoptotic effect was attributed, at least in part, to TRPV-1 receptors (Contassot *et al.*, 2004a). Nevertheless, CB receptors were involved in the reduction of the migration and invasion of cervical cancer cells triggered by some cannabinoid compounds. For example, Rudolph *et al*. (2008) reported that CB_1 receptors mediated the anti-migratory effect of 2-AG in SW 756 cancer cells.

The synthetic analogue of anandamide, **methanandamide (AM-356)**, has been reported to inhibit the growth of established thyroid cancer *in vivo* and also to decrease the expression of **VEGF**, producing anti-angiogenic effects. All these actions were attenuated by CB_1 receptor antagonists, so CB_1 receptors are involved in the anti-tumour activity of AM-356. The same authors also demonstrated that AM-356 inhibited the *in vitro* proliferation of metastasis-derived thyroid cancer cells, especially lung metastasis cells (Portella *et al.*, 2003). Interestingly, *in vivo* studies in thyroid tumour xenografts induced in mice reported that arachidonyl-5-HT, an FAAH inhibitor, and VDM-11, an inhibitor of endocannabinoid re-uptake, decreased tumour growth, involving both non-cannabinoid and CB_1 receptors (Bifulco *et al.*, 2004).

In lymphomas, some murine cell lines that express both CB_1 and CB_2 receptors were sensitive to the action of AEA and also to other CB receptor agonists which induce apoptosis (McKallip *et al.,* 2002). AM-356 also decreased the proliferation of mantle cell lymphoma, normally a very aggressive carcinoma, *via* the activation of the novo ceramide synthesis pathway in a CB_1 receptor-dependent manner (Gustafsson *et al.,* 2009a).

Finally, AEA has been shown to reduce the proliferation of human leukaemia cells, such as Jurkat, Mol-4 and Sup-1 cells, inducing apoptosis with the involvement of CB_2 receptors (McKallip *et al.,* 2002).

The anti-tumour activities of endocannabinoids are summarized in Table 3.

Involvement of the endocannabinoid system in tumour progression

Effect on tumour neovascularization

The ECS has also been postulated as a modulator of tumour angiogenesis, being implicated in anti-angiogenic action by decreasing the survival and migration of endothelial cells and/or reducing the expression of pro-angiogenic factors. In fact, several cannabinoids, including AEA and CBD, have been shown to have anti-angiogenic properties (Rajesh *et al.,* 2010; Thapa *et al.,* 2011; Solinas *et al.,* 2012). This effect is involved in the inhibition of the growth of numerous kinds of tumours such as lung, breast, skin and brain carcinomas. For example, *in vitro* and *in ovo* (in the chick chorioallantoic neovascularization model), AM-356 exerted an anti-angiogenic effect, decreasing the proliferation and inducing apoptosis of endothelial cells, with the diminution of **metalloproteinase-2** activity. The mechanisms responsible for these effects involved CB_1 receptors and were also involved in the anti-tumour activity of cannabinoids in thyroid cancer (Pisanti *et al.,* 2007). Similar results were previously reported by Portella *et al*. (2003), showing that the inhibition of angiogenesis in thyroid tumours by AM-356 involved a reduction of the expression of VEGF, a pro-angiogenic factor, also showing the participation of CB_1 receptors. This effect was attributed to inhibition of p21ras activity (necessary for VEGF action). AEA was also reported to reduce pro-angiogenic pathways in breast cancer cells. In an *in vitro* model of angiogenesis, AEA decreased the MDA-MB-231-induced proliferation of endothelial cells and reduced the levels of a significant number of pro-angiogenic factors, especially those of **IFNγ**, **leptin**, **TGFβ1**, **TIMP1**, **TIMP2**, **thrombopoietin** and VEGF (Picardi *et al.,* 2014).

CB receptors are also implicated in the anti-angiogenic activity of other synthetic cannabinoids such as WIN-55212–2 and **JWH-133**, in brain tumours (gliomas and astrocytomas). Blazquez *et al*. (2003) reported that these compounds impaired tumour neovascularization by inhibiting cell survival with the induction of apoptosis and the migration of vascular endothelial cells. They also reduced the expression of several angiogenesis stimulation factors, specifically VEGF and angiotensin II.

The inhibition of the MAGL enzyme with the consequent increase of 2-AG levels was also reported to decrease tumour growth, exerting an anti-angiogenic activity. *In vivo* studies reported that MAGL inhibitors down-regulated pro-angiogenic factors, particularly VEGF and **FGF-2**, and also reduced the number of vessels (Pagano *et al.,* 2017).

In spite of this anti-angiogenic effect of cannabinoids, minor endocannabinoid compounds have been postulated as pro-angiogenic factors, stimulating angiogenesis in a GPR55 receptor-dependent manner (Zhang *et al.,* 2010). Indeed, this effect has also been reported for AEA. In the nanomolar range, this cannabinoid induced the angiogenesis stimulated by FGF-2, in a pathway that involved CB_1 receptors, which were found to be overexpressed during the angiogenesis process. Their involvement in the angiogenesis process has been corroborated *in vivo*. On the one hand, studies in CB_1 receptor knockdown mice reported an inactivation of the proliferation, migration and capillary-like tube formation induced by pro-angiogenic factors (particularly FGF-2). On the other hand, CB_1 blockage also reduced the FGF-2-induced neovascular proliferation in the rabbit cornea assay (Pisanti *et al.,* 2011). The implication of these receptors in carcinogenesis has also been reported by other authors. Malfitano *et al*. (2012) demonstrated using an ascitic tumour model (Meth-A cells specifically injected into mice) that CB_1 receptor blockade reduced tumour growth. Ciaglia *et al*. (2015) found similar results in an *in vivo* model of glioma, also involving the participation of STAT3 pathway. Additionally, in glioma samples from patients, they related low levels of active STAT3 to a lower expression of CB_1 receptors. Nevertheless, Wang *et al*. (2008) found in mice models of colon cancer that the loss or inhibition of CB_1 receptors induced tumour growth. So the involvement of these receptors in cancer probably depends on the origin of the tumour.

Stimulation of tumour growth by cannabinoids

In spite of the establishment of anticancer activity of cannabinoids and the involvement of the ECS, the implication of the ECS in cancer progression has also been reported in some tumours. This biphasic effect seems to depend on the cannabinoid concentration and involves CB receptors, specifically CB_2.

Thus, AEA at concentrations of 1 μM stimulated the proliferation of gastric cancer cells (Miyato *et al.,* 2009), and its analogue, AM-356, at lower concentrations also exerted a mitogenic activity in prostate carcinomas. While, in the micromolar range, AM-356 inhibited the proliferation of LNCap prostate cancer cells, at nanomolar concentrations (100–200 nM), it stimulated cell growth. Similarly, **Δ^9-tetrahydrocannabinol (THC)** and JWH-133 exerted pro-proliferative effects in prostate cancer (Sanchez *et al.,* 2003).

The proliferation induced by THC has also been reported in lung, breast and even in brain tumours. This phytocannabinoid, in concentrations of 100–300 nM, stimulated the proliferation of lung tumours and gliomas *in vitro* (Hart *et al.,* 2004). *In vivo*, in mice models, Δ^9-THC also improved the growth and metastases formation of breast tumours (McKallip *et al.,* 2005). Interestingly, this pro-cancer activity has been related to the immune response against the tumour and involves CB_2 receptors. By the activation of

Table 3

Anti-tumour actions of endocannabinoids

Cancer type	Cannabinoid	Cancer cells	Anti-tumour effect	Mechanism	References
Glioma	AEA	U87, U251, C6, H4	Inhibition of cell proliferation	• Apoptosis induction • Involvement of TRPV-1 channels	(Hinz *et al.*, 2004, Contassot *et al.*, 2004b, Bari *et al.*, 2005)
		U251	Inhibition of cell proliferation, migration and invasion	• Induction of apoptosis and cell cycle arrest at G_0/G_1 phase	(Ma *et al.*, 2016)
	2-AG 1-AG	C6	Inhibition of cell proliferation	• Involvement of CB receptors and TRPV-1 channels. • The action of 2-AG seems to be secondary to its conversion to 1-AG	(Jacobsson *et al.*, 2001, Fowler *et al.*, 2003)
Breast cancer	AEA, 2-AG	EFM-19, MCF-7, T47-D, BT-47446	Inhibition of cell proliferation	• Induction of apoptosis and cell cycle arrest at G_1/S phase *via* CB_1 receptors • Suppression of NGF induced proliferation probably due to a reduction of NGF/TrK receptor levels • Oleamide potentiates the antiproliferative activity of AEA.	(Bisogno *et al.*, 1998, De Petrocellis *et al.*, 1998, Melck *et al.*, 2000)
Prostate cancer	AEA	PC-3, DU-145 and LNCaP	Inhibition of cell proliferation.	• Apoptosis induction	(Mimeault *et al.*, 2003, Nithipatikom *et al.*, 2011, Orellana-Serradell *et al.*, 2015)
	AEA, 2-AG	DU-145	Reduction of prolactin induced proliferation	–	(Nithipatikom *et al.*, 2011)
	Noladin-Ether	DU-145	Inhibition of cell proliferation	• In a CB receptor independent manner	
	2-AG	Androgen-independent tumour cells	Inhibition of cell invasion	• Involvement of CB_1 receptors	(Endsley *et al.*, 2007)
Colon cancer	AEA, 2-AG	–	Inhibition of cell proliferation	• Opposite results have been reported in the participation of CB receptors.	(Ligresti *et al.*, 2003, Gustafsson *et al.*, 2009b, Linsalata *et al.*, 2010, Patsos *et al.*, 2010)
Gastric cancer	AEA	AGS	Inhibition of cell proliferation	• Cell cycle arrest at $G_0/G_1$and apoptosis induction.	(Ortega *et al.*, 2016)
Hepatocarcinoma	AEA	–	Inhibition of cell proliferation. Reduction of tumour growth *in vivo*	• CB receptor independent mechanism	(DeMorrow *et al.*, 2007, DeMorrow *et al.*, 2008)
Cervical cancer	AEA	CC299, CasKi, HELA	Inhibition of cell proliferation	• Cell cycle arrest at G_0/G_1 phase and apoptosis induction.	(Contassot *et al.*, 2004a)

continues

these receptors, THC increased the production of **IL-4** and **IL-10**, stimulating a Th-2-type immune response and inhibiting the Th-1 response (Zhu *et al.,* 2000; McKallip *et al.,* 2005).

ECS and drug resistance

Multidrug resistance is probably one of the major problems in chemotherapy of cancer. Tumours become resistant to a great number of different drugs without structural or functional similarities, including anthracyclines, taxanes and *Vinca* alkaloids, and this hampers cancer treatments (An *et al.,* 2017). Much of such resistance to cancer chemotherapy involves the **multidrug resistance protein 1 (MDR1**), an efflux pump that belongs to the family of ATP-binding cassette transporters (ABC) (Lopes-Rodrigues *et al.,* 2016) and other proteins of the ABC superfamily such as the **breast cancer resistance protein (ABCP or ABCG2)** (Chen *et al.,* 2010). Several studies have reported the involvement of the ECS in the mediation of resistance to anticancer drugs.

In T-lymphoblastic leukaemia cells (CEM/VLB100), the two major plant cannabinoids, THC and CBD, modulate the expression of MDR1. While, at shorter incubation times (4 h), they increased its expression and consequently the activity of MDR1, at longer times (72 h), they decreased MDR1 action. The ECS is involved in these actions, although differences in the mechanisms of both cannabinoids have been reported. Although the THC effect was only mediated by CB_2 receptors, the activity of CBD was mediated by both CB_2 and non-CB receptors, specifically TRPV-1 channels (Arnold *et al.,* 2012). Holland *et al*. also reported that both cannabinoids and also **cannabinol** reduced the expression of MDR1 protein in these leukaemia cells, without inhibiting its efflux activity. In breast cancer (MCF-7 cells), CBD also inhibited the expression of MDR1, but it increased expression of ABCP (Feinshtein *et al.,* 2013).

By contrast, other authors have shown that several plant cannabinoids, including CBD, THC and cannabinol, inhibited ABCP (Holland *et al.,* 2007; Tournier *et al.,* 2010) and also MDR1, with CBD being the most potent inhibitor (Holland *et al.,* 2008).

Concluding remarks

In tumours, the abnormal expression of the different components of the ECS, especially CB_1 and CB_2 receptors, compared with that healthy tissues reveals its involvement in cancer. However, this aberrant expression is not consistent and varies with cancer type. Although in some tumours these receptors are up-regulated, in others, their expression is lower. Therefore, it is important to consider the participation of CB_2 receptors, whose levels seem to be up-regulated after certain pathological conditions. The correlation of the aberrant expression in the ECS with cancer outcome reinforces its involvement in tumourigenesis. The ECS either participates in disease progression or exerts a protective role and becomes a potential therapeutic target. In general, for example, in prostate, colon and pancreatic carcinomas, an altered ECS is a negative marker for cancer, being related to a more invasive

Table 3
(Continued)

Cancer type	Cannabinoid	Cancer cells	Anti-tumour effect	Mechanism	References
				• Involvement of non-CB receptors in the generation of apoptosis	
	2-AG	SW-756	Inhibition of cell migration and invasion	• Involvement of CB_1 receptors	(Rudolph *et al.,* 2008)
Thyroid cancer	AM-356	–	*In vivo* inhibition of tumour growth	• Inhibition of tumour angiogenesis due to the reduction of VEGF expression *via* CB_1 receptors	(Portella *et al.,* 2003)
Lymphomas	AEA	Murine cells	Inhibition of cell proliferation	–	(McKallip *et al.,* 2002)
Leukaemia	AEA	Jurkat, Mol-4 and Sup-1	Inhibition of cell proliferation	• Induction of apoptosis *via* CB_2 receptors	

tumour and a lower survival rate, except in hepatocarcinoma where it is an indicator of good prognosis.

CB receptors also mediate anticancer activity, at least in part, of other cannabinoid compounds, including phytocannabinoids such as THC, CBD and cannabinol, and even synthetic cannabinoids, including AM-356. The efficacy of CBD alone and in combination with THC is being extensively evaluated for the treatment of different solid tumours (Ramer and Hinz, 2016).

Besides CB receptors, endocannabinoid levels are also altered in some carcinomas. In this context, it is important to emphasize that the two major endogenous cannabinoids (AEA and 2-AG) administered exogenously inhibit the growth of several kinds of tumours, demonstrating an anti-proliferative, anti-invasive and anti-angiogenic activity. The increase in endocannabinoid levels as a result of inhibiting their degradation pathways, especially the FAAH and MAGL enzymes, has also been useful in reducing cancer proliferation.

In spite of the promising activity of cannabinoids as anticancer treatments, it has to be taken into account that some cannabinoids have also been shown to increase tumour growth, exerting pro-angiogenic and pro-proliferative effects. This biphasic activity has been related to cannabinoid concentration. It seems that while cannabinoids stimulated cancer growth at low concentrations (in the nanomolar range), they inhibited it at higher concentrations (micromolar range). While both CB_1 and CB_2 receptors are involved in cannabinoid anticancer activity, the stimulation of cancer proliferation appears to be mainly attributable to CB_2 receptors.

Finally, cannabinoids have also been associated with resistance to anticancer drugs, interfering in the expression of several ABC drug transporter proteins, especially MDR1, implying that these proteins could provide a good target for cannabinoids to overcome cancer resistance. In fact, some cannabinoids at non-toxic concentrations increase the sensitivity of cancer cells to chemotherapy. For example, THC and CBD potentiate the cytotoxicity of **vinblastine** (Holland *et al.*, 2006) and **temozolomide** in leukaemia and glioma respectively. Consequently, cannabinoids could be a good strategy as co-adjuvant treatments. In fact, a clinical study is currently being performed to evaluate the efficacy and safety of a cannabinoid-based spray containing the two major natural cannabinoids present in *Cannabis sativa*, THC and CBD, in combination with temozolomide for the treatment of glioma (NCT01812603) (Holland *et al.*, 2006; Zogopoulos *et al.*, 2015).

Nomenclature of targets and ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY (Harding *et al.*, 2018), and are permanently archived in the Concise Guide to PHARMACOLOGY 2017/18 (Alexander *et al.*, 2017a,b,c,d,e,f).

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Conflict of interest

The authors declare no conflicts of interest.

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