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Mini-review

Cannabinoids in the treatment of cancer

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ABSTRACT

Cannabinoids, the active components of the hemp plant *Cannabis sativa*, along with their endogenous counterparts and synthetic derivatives, have elicited anti-cancer effects in many different *in vitro* and *in vivo* models of cancer. While the various cannabinoids have been examined in a variety of cancer models, recent studies have focused on the role of cannabinoid receptor agonists (both CB_1 and CB_2) in the treatment of estrogen receptor-negative breast cancer. This review will summarize the anti-cancer properties of the cannabinoids, discuss their potential mechanisms of action, as well as explore controversies surrounding the results.

1. Introduction

Extracts from *Cannabis Sativa* have been used for centuries for both medicinal and recreational purposes. However, isolation of the most active component of the plant, (−)-trans-Δ^9-tetrahydrocannabinol (Δ^9-THC) did not occur until the 1960s [1]. Currently, there are approximately 66 unique C terpenophenols derived from *Cannabis Sativa*, termed cannabinoids (the number of carbon atoms varies depending on the length of the side chain, C1–C5) [2]. They have been classified into different categories according to their chemical structures, such as Δ^9-THC, Δ^8-THC, cannabinol, cannabidiol and cannabicyclol. Cannabinoids are further classified into phytocannabinoids, synthetic cannabinoids (i.e., JWH-133, WIN 55,212-2 and SR141716) (Fig. 1), and endocannabinoids (i.e., anandamide and sn-2-arachidonylglycerol (2-AG)), which are produced endogenously.

The first endogenous ligand for the cannabinoid receptor to be identified was anandamide (AEA), which was isolated in 1992 [3]. This was followed by the discovery of 2-AG, 2-arachidonylglycerylether (2-AGE), *O*-arachidonoyl-ethanolamine (virohdamine) and *N*-arachidonoyl-dopamine (NADA). These endocannabinoids are arachidonic acid derivatives and appear to act on the central nervous system as neuromodulators or retrograde messengers, which inhibit the release of classical neurotransmitters [4].

Currently, two cannabinoid receptor subtypes have been identified: cannabinoid receptor type 1 (CB_1) and cannabinoid receptor type 2 (CB_2). Both subtypes are members of the G-protein coupled receptor superfamily [5]. The CB_1 receptor was first cloned in 1990 from a cortical rat brain cDNA library [6], this was followed by the cloning of human and mouse analogues. These encode proteins of 427 (human) and 473 (rat) amino acids and have 97–99% amino acid sequence homology across species [5]. The CB_2 receptor was cloned in 1993 from human promyelocitic HL-60 cells. This gene encodes a protein of 360 amino acids, and is only 48% homologous to CB_1 [7]. CB_1 receptors are found in abundance in the brain where they mediate the psychoactivity of cannabinoids, and are also expressed in various other sites such as spleen, eye, testis and uterus [6–9], while CB_2 receptors are expressed mainly in cells and organs of the immune system [7] as well as tumor cells [10,11]. CB_1 activation stimulates cellular signal transduction via $G_{i/o}$, while CB_2 only couples

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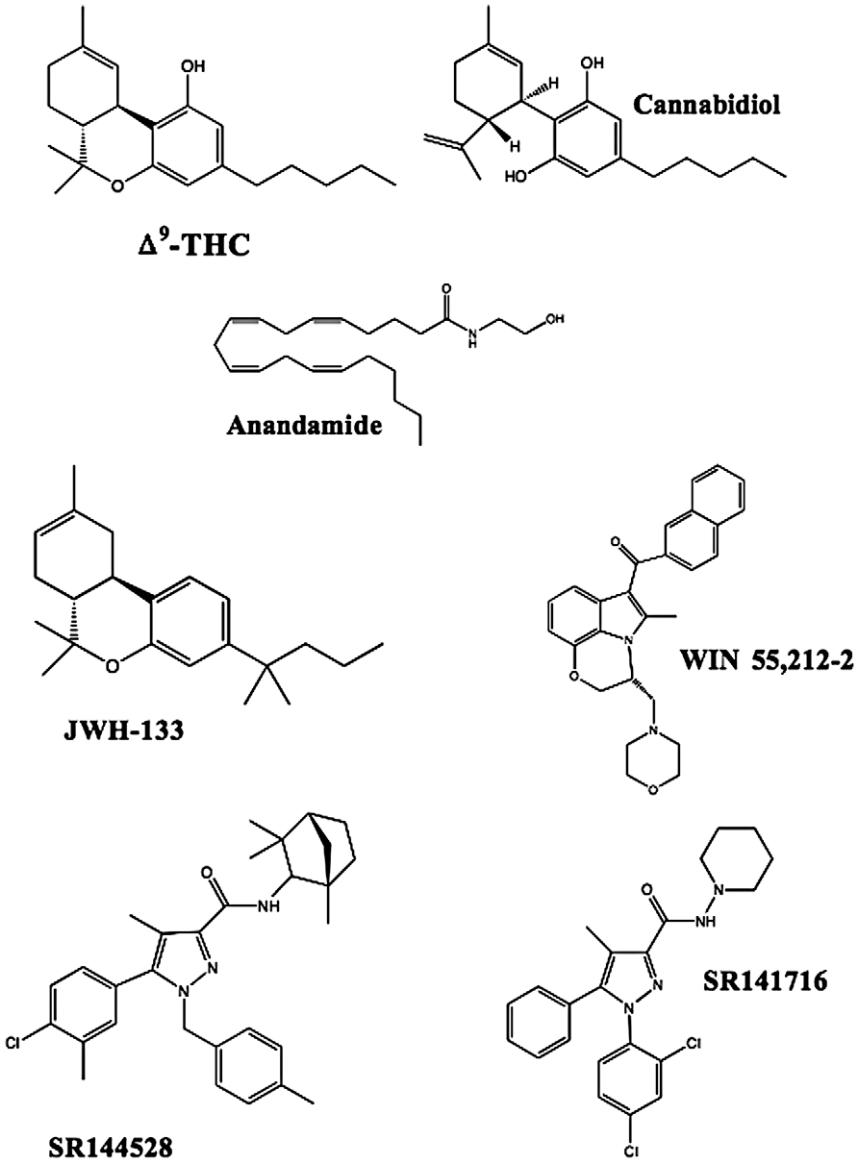

Fig. 1. Structure of cannabinoid receptor agonists and antagonists.

strongly to G_i [12]. Activation of these receptors leads to inhibition of adenylate cyclase, activation of mitogen-activated protein kinase (MAPK) pathways, phosphoinositide 3-kinase (PI3K) pathways, and modulation of ion channels (CB_1 only), which leads to modulation of a plethora of signaling pathways that modulate cell function [13].

2. Cannabinoids in the treatment of cancer

Cannabinoids have been successfully used in the treatment of some of the side effects, such as nausea and vomiting, weight loss, lack of appetite and pain that often accompany cancer. Δ^9-THC (dronabinol) and LY109514 (nabilone) are approved to treat nausea and vomiting associated with cancer chemotherapy [14]. Although cannabinoids are used in the palliative treatment of cancer, they are not yet used as a treatment for tumor progression itself. However, the first study to show that cannabinoids had anti-tumor effects was reported by Munson et al. in 1975 [15]. They demonstrated that administration of Δ^9-THC, Δ^8-THC and cannabinol inhibited the growth of Lewis lung adenocarcinoma cell growth *in vitro*, and *in vivo* after oral administration to mice. Since then, cannabinoids have been shown to have anti-proliferative, anti-metastatic, anti-angiogenic and pro-apoptotic effects in various cancer types (lung, glioma, thyroid, lymphoma, skin, pancreas, uterus, breast and prostate carcinoma) using both *in vitro* and *in vivo* models [16–21]. Recently, more evidence has been obtained that suggests that phyto-, endo- and synthetic cannabinoids could be useful in the treatment of

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cancer due to their ability to regulate cellular signaling pathways critical for cell growth and survival [10,22–25].

3. Cannabinoids regulate cell survival pathways

Growth and survival of tumor cells is often dependent on the increased signaling through pathways that regulate cell survival and proliferation. Two of these include the MAPK signaling pathway (Ras/Raf – MAPK, extracellular-signal regulated kinase (ERK1/2)) and the PI3K/Akt pathway [22]. Both CB_1 and CB_2 cannabinoid receptors are coupled to these pathways via heterotrimeric $G_{i/o}$-proteins. In Chinese hamster ovary (CHO) cells transfected with human CB_1, CP 55940 (a highly potent non-selective CB_1 and CB_2 agonist) increased p42/p44 MAPK activity in a time- and concentration-dependent manner and this was reversed by the CB_1 antagonist/inverse agonist SR141716A [26]. Furthermore, the activation of MAPK was blocked by pertussis toxin, thus suggesting that signal transduction between CB_1 and MAPK involves GTP-binding proteins. Similar results were seen when CHO cells were transfected with CB_2, as CP 55940 increased p42/p44 MAPK activity and the effects were blocked by both SR144528 (a CB_2 selective antagonist) and pertussis toxin [27]. The results from these studies indicate that activation of either CB_1 or CB_2 receptors results in an increase in signaling through the MAPK pathway.

Signaling through PI3K/Akt is also modulated by cannabinoid receptor activation. Gomez Del Pulgar et al. [28] illustrated that Δ^9-THC, anandamide and CP 55940 stimulated Akt activity in a concentration- and time-dependent manner in CHO cells transfected with human CB_1 cDNA. This cannabinoid-mediated stimulation of Akt activity was reversed in the presence of SR141716, pertussis toxin and wortmannin (a selective PI3K inhibitor), thus suggesting that signal transduction between CB_1 and Akt involves GTP-binding proteins and PI3K [28]. In accordance with these results, Sanchez et al. [29] illustrated that Δ^9-THC and methanandamide activated the PI3K/Akt pathway in human prostate PC-3 cells. Cannabinoid-induced activation of this pathway was inhibited by both SR141716 and SR144528, suggesting that the PI3K/Akt pathway is modulated by both CB_1 and CB_2 receptor activation [29]. Furthermore, anandamide (5 μM) inhibited ERK activation in PC12 cells [25].

The molecular mechanisms by which cannabinoid receptors modulate these mitogenic signaling pathways are not yet fully understood. One theory for modulation of the PI3K/Akt pathway by cannabinoids involves the CB_1/CB_2 linked G-protein βγ [30]. Other theories for the modulation of the MAPK pathway by cannabinoids involve tumor necrosis factor (TNF) α-converting enzyme (TACE/ADAM17)-mediated transactivation of EGFR [31] and ceramide synthesis [16,32]. More support for the role of TNF-α has come from a recent report using specific CB_1 and CB_2 agonists in both *in vitro* and *in vivo* models of colon cancer. Specifically, cannabinoid receptor activation stimulated a 4-fold-increase in TNF-α production in DLD-1 and HT29 colon cancer cells and further experiments demonstrated that TNF-α was the main mediator of ceramide *de novo* synthesis [21]. Therefore, in models of *in vitro* and *in vivo* colon cancer, ceramide is an important mediator of the antitumor activity of cannabinoids. Since only the CB_2 receptor is expressed in colon tumors [21], specific ligands for CB_2 may prove to be valuable adjuvants to colon cancer chemotherapy. Therefore, the role of CB_2 specific agonists as anticancer agents is an important aspect of the cannabinoid literature.

4. The role of JWH-133, a CB_2 selective agonist, as an anticancer agent

JWH-133 or 3-(1′, 1′-dimethylbutyl)-1-deoxy-Δ^8-THC), is a synthetic analogue of the phytocannabinoid Δ^8-THC. It is classified as a selective ligand for the CB_2 receptor with 200-fold higher affinity for the CB_2 (K_i = 3.4 nM) over the CB_1 receptor (K_i = 677 nM) (Table 1) [33]. JWH-133 inhibits cancer cell growth *in vitro*. The first study to illustrate this was conducted by Sanchez et al. [17], who demonstrated that rat glioma C6 cell viability was reduced by 50% following JWH-133 (100 nM), compared to vehicle control. Results from further studies suggested that the JWH-133-mediated decrease in cell viability was due to an induction of apoptosis via ceramide synthesis and

Table 1
Binding affinities of various cannabinoids.

Compound	CB_1 (nM)	CB_2 (nM)	Reference
Δ^9-THC			
NON-selective partial agonist	25 ± 6	36 ± 6	[34]
Cannabidiol			
Little to no affinity for CB_1 or CB_2	2210 ± 558	2860	[34]
Anandamide			
Weak non-selective agonist	239 ± 62	439 ± 96	[34]
JWH-133			
Potent CB_2 selective agonist	677 ± 132	3 ± 1	[33]
WIN 55,212-2			
Potent CB_1/CB_2 non-selective agonist	17 ± 2	4 ± 1	[34]
SR141716			
Selective CB_1 antagonist	2	>1000	[35]
SR144528			
Selective CB_2 antagonist	437 ± 33	0.60 ± 0.13	[36]

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ERK1/2 activation [17]. This work was supported by Casanova et al. [18], who demonstrated that JWH-133 (25 nM) decreased the viability of the tumorigenic mouse epidermal cell line PDV.C57 by approximately 40%.

While there is a lack of *in vitro* studies with JWH-133, there have been a number of reports on the effects of JWH-133 using *in vivo* cancer models. For example, Sanchez et al. [17] investigated the effects of JWH-133 in a mouse model of glioma. They administered JWH-133 (50 μg/d intratumorally, 8 d) to Rag-$2^{-/-}$ mice that had been inoculated with rat glioma C6-cells. JWH-133 caused a 71% decrease in tumor growth compared to vehicle control. This anti-tumor effect was reversed when the CB_2 selective antagonist SR144528 (50 μg/d intratumorally) was co-administered, but not following the CB_1 selective antagonist SR141716 (50 μg/d intratumorally). This group also reported that JWH-133 (50 μg/d intratumorally, 25 d) completely inhibited the growth of highly malignant (grade IV) human astrocytomas in the same mouse model. The results from this study suggest that the anti-tumor effect of JWH-133 is mediated via activation of the CB_2 receptor and subsequent induction of apoptosis via ceramide synthesis and ERK1/2 activation [17]. In a similar study by the same group using the same mouse model, JWH-133 treatment (50 μg/d intratumorally) markedly decreased mRNA expression of the proangiogenic factors, vascular endothelial growth factor (VEGF) and angiopoietin 2 (Ang 2), providing another critical feature of JWH-133-mediated tumor suppression [37].

JWH-133 has also shown anti-cancer effects in *in vivo* skin tumor models. Specifically, nude mice bearing epidermal PDV.C57 cell xenografts were treated with JWH-133 (83 μg/d, 11 d via a continuous flow pump). The results showed that JWH-133 reduced tumor volume by 60% [18]. Additionally, mRNA expression of proangiogenic factors VEGF, placental growth factor, and Ang 2 were markedly decreased in the skin tumors following JWH-133 treatment compared to vehicle control. These findings are supported by Blazquez et al. [37], who also demonstrated that JWH-133 (50 μg/d) decreased the expression of VEGF, Ang1, Ang2, MMP-2 and TIMP-2 in both glioma and astrocytoma xenografts. Furthermore, tumor suppression has been reported in B16 melanoma xenografts. Specifically, JWH-133 (50 μg/d, 8 d) decreased tumor volume by ~75% and this correlated with an increase in the number of apoptotic cells, in tumor sections as well as a decrease in tumor vascularization, as shown by CD31 immunostaining, and vascular density [19]. Overall, there is consistent evidence demonstrating that JWH-133 suppresses tumor growth in a variety of *in vivo* tumor models and that an increase in apoptosis and a decrease in angiogenesis play an important role in this effect. However, more mechanisms may be involved as Casanova et al. [18] demonstrated that mRNA of the EGFR and its phosphorylated form were highly expressed in PDV.C57 cell xenografts from control mice, while JWH-133 treatment markedly decreased their expression. Therefore, both CB_2 and the EGFR may be key receptors that initiate a cascade of events that lead to tumor suppression.

5. The role of WIN 55,212-2, a CB_1/CB_2 non-selective agonist, as an anticancer agent

WIN 55,212-2 or (R)-(+)-[2,3-Dihydro-5-methyl-3-[(4-morpholinyl)methyl]pyrrolo[1,2,3,-de]-1,4-benzoxazinyl]-(1-napthalenyl)methanone, is a synthetic non-selective agonist of both CB_1 (K_d = 17 nM) and CB_2 (K_d = 4 nM) receptors (Table 1) [34]. WIN 55,212-2 exhibits anti-cancer effects in a variety of different cancerous cell lines including human prostate cancer [38], human glioblastoma multiforme [39], rat glioma [40] and B16 melanoma cells [19]. For example, WIN 55,212-2 dose-dependently decreased the cell viability of LNCaP prostate cancer cells, with an IC_{50} of 6 μM [38]. Co-treatment with either SR141716 (2 μM) or SR144528 (2 μM) reversed the WIN 55,212-2-mediated decrease in cell viability, implicating an important role for the CB_1 receptor. Furthermore, cell death was due to the induction of apoptosis, as treatment for 24 h with 7.5 μM and 10 μM resulted in an 18% and 26% increase in apoptotic cells, respectively, compared to only 0.3% apoptotic cells in the vehicle control [38]. In a follow up study, this group investigated the mechanisms responsible for WIN 55,212-2-mediated apoptosis in LNCaP cells. The results showed that treatment with WIN 55,212-2 down-regulated ERK1/2 which led to cell cycle arrest in the G_0/G_1 phase of the cell cycle, an induction of p53 and p27, a down regulation of cyclins D and E, a decreased expression of Cdk-2 and a subsequent decrease in the expression of p-Rb [41]. Similar effects were also seen when PC-3 prostate cancer cells were treated with WIN 55,212-2.

WIN 55,212-2 also has growth inhibitory actions in both human glioblastoma multiforme cells (SF126, U87-MG, U251, U373-MG and SF188) (McAllister et al., 2005) as well as rat glioma cells [40] with IC_{50s} of 1 and 15 μM, respectively. The mechanism for the decrease in cell growth in rat glioma cells was suggested to be via an induction of apoptosis as a consequence of a down-regulation of the Akt and ERK signaling pathways [40].

WIN 55,212-2 also has anti-proliferative effects in various *in vivo* cancer models. For example, Sanchez et al. [17] found that treatment with WIN 55,212-2 suppressed glioma tumor growth. Specifically, WIN 55,212-2 (50 μg/d, 8 d, intratumorally) decreased the growth of rat C6 gliomas in Rag-$2^{-/-}$ mice by 71% compared to vehicle treated animals. In accordance with these results, Blazquez et al. [19] found that WIN 55,212-2 (50 μg/d, 8 d, peritumorally) suppressed tumor growth in a mouse xenograft model of melanoma. Specifically, WIN 55,212-2 caused a 56% decrease in tumor volume compared to vehicle treated animals and this correlated with cell cycle arrest at the G_1–S phase transition via inhibition of Akt, and a subsequent decrease in the phosphorylation of Rb [19]. Additionally, WIN 55,212-2 (50 μg/d, ip) inhibited the number of liver and lung metastatic nodules in both nude and C57BL/6 mice injected intraplantarly with B16 melanoma cells [19]. WIN 55,212-2 (83 μg/d, 11 d) has also inhibited the tumor growth of mouse tumorigenic epidermal PDV.C57 cells inoculated in nude (NMRI nu) mice by approximately 80% compared to vehicle treated animals. They also

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illustrated that mRNA expression of proangiogenic factors (VEGF and PlGF) and growth factors (EGFR and p-EGFR) were markedly reduced in the tumor samples from WIN 55,212-2 treated animals. Overall, the results from studies with WIN 55,212-2 demonstrate that this synthetic cannabinoid can suppress the growth of tumors derived from gliomas, melanomas and tumorigeneic epidermal cells. Possible mechanisms of action for these actions appear to involve induction of cell cycle arrest [19] and/or downregulation of pro-angiogenic factors and growth factors [18].

6. Cannabinoids in the treatment of ER-negative breast cancer

CB_2 receptors are not widely detected in normal breast tissue, but are over-expressed in estrogen receptor (ER)-negative breast tumors compared to ER-positive breast tumors [42]. Additionally, CB_2 receptor expression positively correlates with the histological grade of breast cancer, as grade 3 tumors express higher amounts of CB_2 than grade 1–2 tumors [42]. Due to this, there has been a cluster of research papers which have focused on the anti-cancer effects of cannabinoids (agonists for both CB_1 and CB_2 receptors) toward ER-negative breast cancer. For example Grimaldi et al., [43] demonstrated that a stable analogue of anandamide (MET-F-AEA) reduced the proliferation of MDA-MB-231 cells in a concentration-dependent manner. Specifically, 10 μM reduced cell number ~33%, while 20 μM reduced cell number ~50%, compared to control [43]. Further studies by the same group demonstrated that 10 μM of MET-F-AEA resulted in a 4.5-fold increase in the percent of cells in S-phase [44]. This was accompanied by a corresponding decrease in G2/M phase cells. Furthermore, co-treatment with the CB_1 selective antagonist SR141716 (0.1 μM) reversed the effects of MET-F-AEA, suggesting a CB_1 receptor mediated effect. Following mechanistic experiments, the authors concluded that the MET-F-AEA-mediated S-phase arrest was a consequence of the loss of Cdk2 activity, an upregulation of p21waf and a reduced formation of the active CyclinE/Cdk2 complex [44]. It is likely that these events lead to a reduced formation of phosphorylated retinoblastoma protein and thus inhibition of the release of transcription factors essential for cell cycle progression. However, it is important to note that the reported mRNA levels of CB_1 in MDA-MB-231 cells varies within the literature [42,45] Further work in MDA-MB-231 cells by Ligresti et al. [45] found that Δ^9-THC and cannabidiol inhibited MDA-MB-231 cell proliferation with IC_{50s} of 24 and 11 μM, respectively. In contrast, Caffarel et al. [42] reported an IC_{50} of 5 μM for Δ^9-THC in MDA-MB-231 cells. This discrepancy may be due to different culture conditions for the MDA-MB-231 cells or different purities of Δ^9-THC. However, it is surprising that Ligresti et al. [45] found cannabidiol to be more potent than Δ^9-THC, as cannabidiol has little to no affinity for the CB_1 and CB_2 receptors, whereas Δ^9-THC acts as a partial agonist at these receptors (Table 1) [34]. However, the mechanism for the anti-proliferative effect of cannabidiol was via the induction of apoptosis. Specifically, after 48 h of cannabidiol (10 μM) treatment, 15% of cells had undergone apoptosis. Furthermore, they demonstrated cleavage of procaspase-3 into caspase-3 following cannabidiol treatment by Western immunoblotting and inhibition of caspase-3 activity by *N*-acetyl-Asp-Glu-Val-Asp-aldehyde (10 μM) significantly blocked the effect of cannabidiol [45]. Caffarel et al. [42] also demonstrated that cannabinoids induce apoptosis in ER-negative breast cancer cells. Using the EVSA-T cell line, they demonstrated that Δ^9-THC (5 μM, 24 h) caused a significant increase in apoptotic cells, from 3% in vehicle treated cells to 16% following Δ^9-THC treatment. However, Caffarel et al. [42] also illustrated that Δ^9-THC blocked cell cycle progression in the G2/M phase via down regulation of Cdc2, which was not shown by Ligresti et al. [45]. However, Ligresti et al. [45] also examined the tumor suppressive actions of cannabidiol *in vivo*, using an MDA-MB-231 xenograft tumor model in male athymic mice. They demonstrated that treatment with cannabidiol (5 mg/kg intratumorally twice a week for 16 d), inhibited tumor growth by 2.5-fold compared to vehicle control.

Another component to the anti-proliferative effects of phytocannabinoids is likely to be via CB_2 activation, as SR144528 (a selective CB_2 antagonist) but not SR141716 (a selective CB_1 antagonist) partially reversed the anti-proliferative effects of the phytocannabinoids [42,45]. However, results by Laezza et al. [44] did not support these findings, as they demonstrated that the anti-proliferative effect of anandamide was CB_1-mediated. Overall, the proposed mechanism by which cannabinoids regulate the proliferation of ER-negative breast cancer cells varies across the literature, depending on the type of cannabinoid used and the particular model used. Therefore, much more work is needed in order to fully elucidate the role of cannabinoid receptors in the anti-proliferative action of various cannabinoids toward ER-negative breast cancer cells.

7. Controversy regarding the anti-cancer actions of cannabinoids

Although the general consensus in the current literature indicates that cannabinoids have anti-cancer effects, there are a few studies that have shown that Δ^9-THC has a biphasic effect in cancer cells, where lower concentrations result in an increase in proliferation of cancer cells and higher concentrations cause a decrease in cell proliferation. For example, Δ^9-THC at 100–300 nM elicited a 1.2 and 2-fold increase in the proliferation rate of NCl-H292 (lung cancer) and U373-MG (glioblastoma) cells, respectively [31]. In contrast, higher concentrations of Δ^9-THC (4–10 μM) were cytotoxic and increased the number of apoptotic cells (30–80%) [31]. Similarly, Sanchez et al. [29] demonstrated that Δ^9-THC (50–100 nM) increased the proliferation and viability of androgen-independent prostate cancer cells (PC3), while Ligresti et al. [45] demonstrated that higher concentrations of Δ^9-THC inhibited the proliferation of MDA-MB-231 breast cancer cells. This increase in cell proliferation *in vitro* has also been supported by *in vivo* studies. However, the increase in tumor growth was elicited by higher doses of Δ^9-THC. Specifically, McKallip et al. [46] demonstrated that Δ^9-THC (25 mg/kg and 50 mg/kg i.p. every other d, 21 d) caused a

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1.6- to 2-fold increase in tumor volume compared to vehicle control in female BALB/c mice bearing murine mammary 4T1 tumors. However, when they repeated the study in SCID-NOD mice, which are devoid of an immune response, Δ^9-THC (25 mg/kg i.p. every other d, 19 d) did not alter tumor volume compared to vehicle treated animals. They hypothesized that these effects were probably due to a Δ^9-THC-mediated inhibition of a specific anti-tumor immune response. It is well known that cannabinoids may cause suppression of the immune system via CB_2 activation [47] and Xu et al. [48] found that JWH-133 caused a strong suppressive effect of the immune system in an *in vivo* mouse model via CB_2 activation. Although immunosuppressive action may have been the mechanism by which Δ^9-THC caused an increase in tumor growth in the study by McKallip et al. [46], it is unlikely that their results are a true indication of the relevant effects that cannabinoids have on cancer, as the doses used were 5–10-fold greater than doses that have anti-proliferative effects in other *in vivo* models of cancer. For example, Preet et al. [49] demonstrated that Δ^9-THC (5 mg/kg/d, 21 d, peritumorally) reduced non-small cell lung cancer tumor weight and volume in SCID mice compared to vehicle control. Therefore, this contrasting *in vivo* and *in vitro* biphasic effect of Δ^9-THC is very interesting and further emphasizes the need for comprehensive dose–response studies in future anti-cancer studies with the various cannabinoids.

8. Clinical trial data

To date, there has been only one clinical trial published on the effects of a cannabinoid receptor agonist on tumor growth, and this was a Phase I pilot study. Guzman et al. [50] studied the effects of intratumoral administration of Δ^9-THC on nine patients with glioblastoma multiforme, who had failed surgical therapy and radiotherapy and exhibited clear evidence of tumor progression. Different patients received Δ^9-THC treatment for a total of 10–64 d and the total dose range was from 0.80 to 3.29 mg. A major result of the study was that intracranial Δ^9-THC administration was found to be safe and did not result in obvious psychoactive effects. However, Δ^9-THC was also reported to inhibit the proliferation of the tumors in vitro and reduce Ki-67 immunolabelling in tumors from two patients, suggesting that further clinical trials are worthwhile. In other studies of patients with hepatocellular carcinoma, high CB_1 and CB_2 receptor expression has been correlated with a better prognosis [51].

9. Conclusions

The majority of the literature demonstrates that various cannabinoids inhibit cancer cell growth *in vitro* and tumor growth *in vivo* and that the induction of apoptosis plays a major role in the mechanism for this effect. The potency of this effect varies with each cannabinoid. Therefore, the differences in binding properties at the cannabinoid receptors may result in different downstream effects. For example, partial agonism at the cannabinoid receptors by Δ^9-THC or AEA compared to potent full agonism at the cannabinoid receptors by the synthetic cannabinoids JWH-133 or WIN 55,212-2, could lead to a divergence of downstream signaling that could produce altered responses in cell growth. The full potential of these synthetic cannabinoids has yet to be determined and there is a need for much more extensive research into the dose-response relationships as well as the mechanisms elicited by the specific cannabinoids if cannabinoids are going to be further developed into potential cancer treatments.

10. Conflict of interest

The authors have no conflicts of interest.

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