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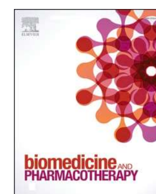

Review

The strengths and limits of cannabinoids and their receptors in cancer: Insights into the role of tumorigenesis-underlying mechanisms and therapeutic aspects

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A B S T R A C T

Cancer, as a mysterious and complex disease, has a multi-stage molecular process that uses the cellular molecular machine and multiple signaling pathways to its advantage. Cannabinoids, as terpenophenolic compounds and their derivatives, showed influences on immune system responses, inflammation, and cell growth that have sparked a growing interest in exploring their effects on cancer cell fate, as well. A large body of evidence in experimental models indicating the involvement of cannabinoids and their related receptors in cancer cell growth, development, and fate. In accordance, the present study provided insights regarding the strengths and limits of cannabinoids and their receptors in critical steps of tumorigenesis and its underlying molecular pathways such as; cancer cell proliferation, type of cell death pathway, angiogenesis, invasion, metastasis and, immune system response. Based on the results of the present study and due to the contribution of cannabinoids in various cancer cell growth control processes, these compounds cancer can be considered worthwhile in finding new alternatives for cancer therapy.

1. Introduction

Cannabinoids are C_{21} terpenophenolic compounds that belong to the group of compounds that are found in Cannabis sativa L. Cannabis sativa (C. sativa) is a member of the Cannabaceae family, and has been cultivated for centuries for industrial and medical purposes due to its psychoactive effects or mental arousal [1]. So far, many chemical compounds called "cannabinoids" have been obtained from the cannabis plant that is mainly divided into three groups; a) Phytocannabinoids, containing various compounds that the most important of which are delta-9 tetrahydrocannabinol (THC), Cannabidiol (CBD), Cannabinol (CBN), Cannabidiolic acid (CBDA), Cannabichromene (CBC), Cannabigerol (CBG), β-caryophyllene, tetrahydrocannabinol acid (THCA) and Δ^9-tetrahydrocannabivarin (THCV) [2]. Among these compounds; THC is the principal active component of C. sativa with psychoactive effects; while CBD accounts as a non-psychoactive chemical representing the chemical marker of this species [3]. b) Endocannabinoids; which were discovered in the human body with similar structure and characteristics to cannabinoids, comprising anandamide (AEA) and 2- arachidonic glycerol (2AG) [4]. c) Synthetic cannabinoids produced and used in the laboratory. Earlier it was assumed that cannabinoids fulfill their action by non-specific binding to cell membrane however later on cannabinoid receptors were discovered which mediate the biological activities of cannabinoids [5]. Cannabinoid receptors (CB) which belong to the G-protein coupled receptor (GPCR) family, are activated by their ligands' (cannabinoids) binding, which activates Gi and subsequently inhibits adenylyl cyclase and link these proteins to the intracellular signaling pathways [6]. The most abundant cannabinoid receptors are CB1 and CB2 which are distributed differently in our body, though each of them carries out certain distinct effects [7]. The CB1 gene which is located in chromosome 6, is primarily present on central nervous system (CNS) neurons as well as in the liver, kidney, and lung and mediates its

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G-protein coupled receptor activities [8]. It has been proved the psychoactive effects of cannabinoids are mediated through CB1 receptors activation, while CB2 receptors, which are nearly absent in CNS and are believed to be mostly found in peripheral nervous system neurons, seem to be not involved in conducting the mental effect of cannabinoids. The CB2 gene is located in chromosome 1 and is mainly expressed on immune cells and immune-derived cells as well as peripheral tissues such as the liver [9]. There have been proofs that show other receptors rather than CB1 and CB2 could also be involved in transferring cannabinoid effects into cells, such as transient receptor potential vanilloid (TRPV) channels and Orphan G-protein-coupled receptor 55(GPR55) [10]. TRPV superfamily is trans-membrane ion channels that are known as "ionotropic cannabinoid receptors" due to mediating cannabinoid activities [11]. Among the TRPV channels, it has been postulated that TRPV1, TRPV2, TRPV3 and TRPV4 mediate cannabinoid activity and can be modulated by cannabinoid agonists [12] GPR55 accounts for a novel cannabinoid receptor that can be modulated by both endogenous and exogenous (synthetic and phytocannabinoids) and is mainly expressed in the brain [13]. The CB1 and CB2 receptors can be activated with both exogenous and endogenous cannabinoids and mediate diverse physiological and pharmacological functions. These receptors also seem to be involved in regulating multiple cellular signaling pathways [14]. In accordance, researches have shown that besides the analgesia and psychoactive functions of cannabinoids, cannabinoid receptors could be involved in diminishing cancer cells by inducing apoptosis and inhibiting cancer-promoting mechanisms, such as angiogenesis, cancer cell viability, and invasion [15]. The controversial shreds of evidence regarding the pro/anti-tumor effect of cannabinoids emphasize the fact that this avenue of research should be continued in more investigations. In the recent decade, various studies on cannabinoids have indicated their probable anti-neoplastic potency. These chemicals seem to be able to impede cancer progression by blocking several tumor-related signaling pathways and mechanisms responsible for it, such as: inhibiting cancer cell angiogenesis [16], migration and invasion [17], and proliferation [18,19]. Cannabinoids also seem to be able of inducing apoptosis in cancer cells by different means and mechanisms [20,21]. On the other hand, cannabinoids are proved to be involved in regulating immunologic responses and alleviating inflammation, which has a critical role in cancer progression [22,23]. Cannabinoid receptors are postulated to modulate the immune response in both cancer and non-cancer diseases [14]. Modulation of immune system responses is mediated by cannabinoid receptors through the production of anti-inflammatory cytokines/chemokines as well as suppression of pro-inflammatory mediators in immune-associated diseases [24,25]. Despite all these promising results which indicate the anti-neoplastic nature of cannabinoids, further studies are required to find a safe and certain way to use these chemicals as a novel therapeutic alternative in cancer therapy. The present study aims to summarize the possible mechanisms of cannabinoids, and their receptors in regulating cancer initiation, progression and development.

1.1. The anti-proliferative effects of cannabinoid and cannabinoid receptors in cancer cells

Cancer progression is dependent on aberrant cell proliferation which is carried out by the altered activity of cell-cycle related proteins. The elevation of cell proliferation alongside suppression of cell death provides the suitable cellular condition for neoplastic progression [26]. Due to the critical role of cell proliferation in the viability of cancer cells, most of the therapeutic strategies are designed based on inhibiting cell proliferation and inducing cell apoptosis in tumor tissues [27]. Recently, it has been shown that cannabinoid derivatives are capable of suppressing proliferation and activating apoptosis-related pathways in various types of cancer cells [28]. This effect is occasionally carried out through cannabinoid receptors and a variety of cannabinoid compounds, including endocannabinoids, phytocannabinoids, C. sativa extracts, and synthetic cannabinoid derivatives, are involved in inducing anti-proliferative features in cancers, that are discussed in this section, respectively and summarized in Fig. 1. In accordance, Anandamide which is an endocannabinoid existing in our body, induced apoptosis in therapy-resistant colorectal cancer cells via cyclooxygenase-2 activation and Reactive Oxygen Species(ROS) elevation. Notably, the observed effect of Anandamide has occurred independently of CB1 and CB2 receptors [21]. Moreover, it was reported that endocannabinoid derivatives, eicosapentaenoyl-ethanolamine (EPEA) and docosahexaenoyl-ethanolamine (DHEA), seem to be able to induce anti-proliferative effects in MCF-7 and MDA-MB-231 breast cancer cell lines but not MCF-10a normal breast cell-line through CB1/CB2 receptors activation and induction of phosphorylation of p38-MAPK, JNK, and ERK proteins [29]. Further investigations showed that treating HEp-2 human laryngeal squamous cell carcinoma (LSCC) cells with endocannabinoids, 2-AG, and Anandamide (AEA) inhibits cell proliferation with the prominent effect of 2-AG in suppressing cell-proliferation in HEp-2 cells. It seems that 2-AG carried out its effect via a CB2-mediated pathway, while AEA seemed to carry out its anti-proliferative effects possibly through a CB1-independent pathway [30]. Regarding the impact of CBD on glioma cells, it has been shown that CBD induced apoptosis through reduction of mitochondrial oxidative metabolism, ceramide elevation, and ROS production in U87 and U373 human glioma cell lines. Furthermore, apoptosis induced by CBD was abrogated following treatment of cells with CB1 antagonist; while CB2 antagonist and pertussis toxin failed to diminish CBD pro-apoptotic effect [31]. A recent study which was carried out on HT-29 human colorectal cancer cell-line revealed that CBD's cytotoxic activity in cell culture media containing 10% of serum, which sustains cell growth factors, is markedly diminished compared to a medium which contains only 0.5% of serum which indicated that the CBD's effect on cancer cells' viability is probably weakened in the actual cell context under the influence of growth factors [32]. Moreover, it was shown that the addition of CBD to THC improves its antitumor potency and the mixture of these derivatives was able to effectively and synergistically inhibit proliferation and induce apoptosis in U251 and SF126 glioblastoma cell lines by restricting cell-cycle, activating caspase, increasing ROS level [33]. Another study that investigated the synergistic effect of a mixture of different cannabinoids, including tetrahydrocannabinol, cannabigerol (CBG), cannabinol (CBN), and CBD on MDA-MB-231 and MCF-7 human breast cancer cell lines revealed that the combination of these chemicals can exert cell-cycle arrest in G2 phase following apoptosis without having any adverse cytotoxic effects on normal cells. Also, nuclear fragmentation besides cytoplasmic vacuolation, lysosome increased size and lipid accumulation was observed following cannabinoid administration [34]. Plus, CBD and Δ9-tetrahydrocannabinol were shown to decrease viability, induce caspase-3 activation, apoptosis and suppress invasion in transitional cell bladder cancer carcinoma. interestingly, these cannabinoids showed a synergistic effect when they were combined with other cannabinoid agents such as cannabichromene or cannabivarin. However, when they were combined with chemotherapeutic agents, they demonstrated a range of responses, from synergistic to antagonistic effects in bladder cancer cells dependent on their concentration [35]. In addition, evidence revealed that CBD or CBD-rich cannabis extract was capable of inhibiting the growth of MDA-MB-231 breast carcinoma xenograft tumors in athymic mice or rat v-K-ras--transformed thyroid epithelial cells models and suppressing cancer cells' migration and metastasis to lungs without affecting normal cells. The observed effect was assumed to be carried out via direct or indirect activation of cannabinoid CB2, vanilloid transient receptor and potential vanilloid type-1 receptors. Meanwhile, CBD was able to induce cell death by direct/indirect activation of CB2/TRPV receptors in breast cancer cells by increasing intracellular Ca and ROS levels in these cells [20]. It was observed that treatment of endometrial cancer cell lines (Ishikawa and Hec50co cells) with CBD, AEA, THC induced reduction of cell viability. Moreover, AEA and CBD induced activation of caspase3/7,

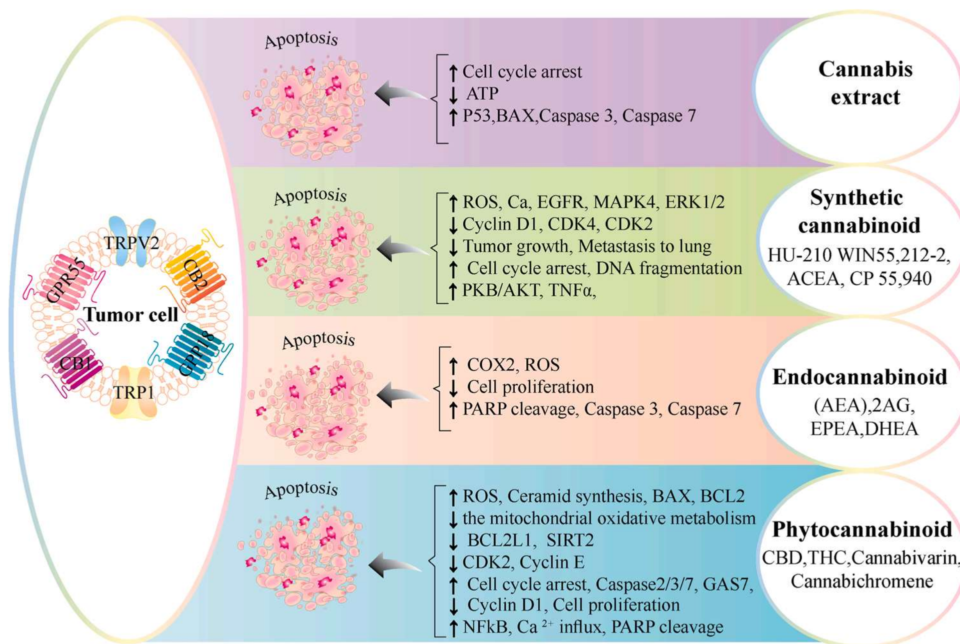

Fig. 1. Anti-proliferative effects of cannabinoids on cancer cells. Different cannabinoids limit cancer cells' multiplication through different means, namely, inducing DNA fragmentation, halting the cell cycle, decreasing metabolism, ATP production, and increasing cancer cells' oxidative stress by increasing ROS production. They are also able to trigger apoptosis in cancer cells by inducing PARP cleavage, increasing intracellular ceramide level, Ca^{2+} influx, NF-κB pathway and COX-2, and decreasing cell-cycle promoting factors such as cyclin D, cyclin E, CDK2, CDK4, RB, and E2F1, which is accompanied by an increase of annexin V on cancer cells' surface. Cannabinoids also suppress cancer cells' migration and invasion by decreasing MMP9. The effects of each of the cannabinoid compound groups are shown separately.

cleavage of PARP, ROS production, Ca elevation and apoptosis in Ishikawa cells through TRPV1 receptors indicating that cannabinoids could be a proper alternative for treating endometrial cancers which are non-responsive to usual treatments [36]. Treating U87MG Glioblastoma cancer cell-line with CBD and an ATM-kinase inhibitor, KU60019 caused an increase in the level of pro-inflammatory cytokines and apoptotic and non-apoptotic inflammation-related cell death in these cells, along with the increase in G2/M arrested cells [37]. Moreover, treating A2780 and A2780/CP70 ovarian cancer cell lines with two cannabinoid derivatives, CBD and CBG, resulted in a dose and time-dependent cell death which was carried out through the GPR55 receptor. Further, in the same study, these derivatives displayed synergistic effects when they were combined with the chemotherapeutic drug, Carboplatin; while did not display any synergic activity with Carboplatin in non-tumorous ARPE19 cells. however, CBD and CBG did not show any synergistic effect with Cisplatin in Cisplatin-sensitive and resistant ovarian tumor cells [38]. Further to this, an *in vitro* research which was carried out on Neuroblastoma (NBL) cancer cell lines, SH SY5Y and IMR-32, revealed that treating these cells with CBD causes downregulation of has-7a miRNA and upregulation of has-miRNA-1972 which lead to overexpression of target caspase-2 and 3 and GAS-7, genes which are involved in cell growth arrest, and decrease in the expression of BCL2L1 and SIRT2, genes that are responsible for cell survival, which is then followed by the induction of apoptosis and limitation of NBL cells' invasion and migration. Interestingly, it was observed that CBD proceeds these actions through binding serotonin and vanilloid receptors [39]. Results from another study revealed that CBD can effectively suppress proliferation of human gastric cancer SGC-7901 cells by inducing upregulation in ATM gene and p53 protein and downregulation of p21 protein which was followed by a decrease in the level of CDK2 and cyclin E and therefore, cell-cycle arrest. CBD was also shown to considerably increase Bax expression and decrease Bcl-2 expression and as a result, enhance caspase-3 and caspase-9 and ROS levels which was followed by an increase of apoptosis in these cells [40]. The involvement of TRPV2, as a member of transient receptor potential (TRP) cation channels in the regulation of tumor cell growth, invasion and angiogenesis has been shown previously [41]. In this regard, TRPV2 gene mutation and/or gain or loss of function have been reported in hematological tumors particularly in leukemia and Multiple myeloma indicates its crucial role in regulating the fate of tumor cells [42]. In support of this, it was shown that TRPV2 over-expression mediated increasing the interaction of myeloma cells and bone marrow stromal cells leading to poor prognosis in MM patients [43]. Also, up-regulation of TRPV2 was found in Triple-negative breast cancer cells [44], Esophageal Cancer [45], Gastric Cancer [46], hepatocellular carcinoma [47], bladder cancer [48], and prostate cancer [49] while its anti-proliferative effects were reported in brain tumors [50]. Therefore, the mechanistic study of TRPV2 receptor agonists could provide new therapeutic goals in the treatment of various cancers. Among the agonists that stimulate the TRPV2 receptor, cannabinoids revealed affinity to TRPV2 receptors and interesting evidence demonstrated the role of cannabinoids in stimulating the TRPV2 receptor and regulating the growth of cancer cells. It has been reported that cannabidiol, by itself and in combination with bortezomib-induced cell death and cell cycle arrest in TRPV2-transfected Multiple myeloma cells through activation of NF-κB pathway, the elevation of reactive oxygen species (ROS), reduction of cyclin D1 and inhibition of ERK activation [51]. Moreover, the activity and expression of the TRPV2 receptor was induced by cannabidiol in glioblastoma cells that was accompanied by increases drug uptake, induced Ca^{2+} influx, and induced apoptosis [52]. A functional study revealed that TRPV2 over-expressed in poorly differentiated urothelial carcinoma cells (T24 cells) and CBD administration induced intracellular calcium level and decreased cell viability and increased apoptosis in such cells [53]. In addition, activation of TRPV2 receptor by CBD sensitized Triple-negative breast cancer cells to doxorubicin uptake and induced apoptosis, cleaved caspase-3, and cleaved PARP. Moreover, it was observed that CBD in synergy with doxorubicin-induced lower tumor volume and higher apoptosis markers in an in-vivo mouse model (mice were injected with CBD (5 mg/kg) peritumoral, once per week and with doxorubicin (5 mg/kg) I.P two hours following CBD injection) [44]. A comprehensive study on the effect of cannabinoids on TRPV receptors showed that THC, CBD, CBGV, CBG, CBDV, CBN, and THCV compounds activate the TRPV2 receptor and increase Ca^{2+} level in TRPV2-transfected -HEK293 cells. It is noteworthy that THC and CBD had the most potency on activation of TRPV2 receptor [54]. Treatment of TRPV2-transfected Ishikawa cells by CBD reduced the rate of viable cells, induced apoptosis and accumulation of cells in the G1 phase, reduced migratory ability, and enhanced the effects of the chemotherapeutic drugs [55]. Moreover, CBD inhibited cell proliferation, reduced clonogenic capacity, and induced differentiation of Glioma stem-like

cells in a TRPV2-dependant manner. A notable piece of evidence in this study was that the Acute myeloid leukemia (Aml-1) transcription factor was upregulated following CBD treatment and activated TRPV2 promotor [56]. Results from another study which was carried out on ovarian cancer showed that both CBD and Cannabis sativa extract can induce cell cycle and apoptosis in HeLa, ME-180 and, SiHa cervical cancer cells by increasing the number of subG0/G1 cells, rate of annexin V positive cells, overexpression of p53, caspase 3/7, Bax and a decrease in the ATP level [57]. Results from another study which investigated the effect of crude C. sativa ethanol extract on My-La and HuT-78 cutaneous T-cell lymphoma (CTCL) cell-lines and peripheral blood lymphocytes from Sézary patients (SPBL) revealed that two particular derivatives from C. sativa extract, S4, and S5, can induce cell cycle arrest as well as apoptosis in these cells in a dose-dependent and synergistic manner [58]. Interestingly, recent studies have shown that C. sativa extract which has been exposed to gamma-radiation, contain more anticancer cannabinoids, particularly delta-9-tetrahydrocannabinol, and can carry out anti-proliferative effects on several cancer cell lines, including BJ-5ta, BT16, HCC1806, and IMR5, more effectively compared to non-radiated cannabis extracts [59]. Numerous studies have also examined the role of various synthetic compounds of cannabinoids in regulating the growth and proliferation of cancer cells that are summarized in Table 2. In accordance, it was declared that Anandamide, THC, and synthetic cannabinoids HU-210 and WIN55,212-2 were able to promote mitogenic kinase signaling pathways in glioblastoma U373-MG and lung carcinoma NCI-H292 cell-lines and speed up metalloprotease and EGFR-dependent cell proliferation which was against the past observations regarding the effect of THC. It was observed that activating the CB receptor triggers a pathway that leads to activation of EGFR and mitogen-activated protein kinases, extracellular signal-regulated kinase 1/2, PKb/AKT, and TNF-alpha converting enzyme which is all involved in cell proliferation [18]. Moreover, treating human gastric adenocarcinoma cell lines (AGS) with different AEA, Met-AEA, and CP55,940 altered DNA synthesis, cell morphology and viability. AEA, and CP had a higher potency for inducing apoptosis, while Met-AEA mostly caused necrosis via transient and rapid apoptosis in AGS cells [60]. Further to this, when A549 lung cancer cell line, testicular cancer (HoTu-10 testicular non-seminomatous germ cell cancer cell-line) and neuroblastoma cell-line (IMR-5) were treated with WIN 55,212-2, synthetic selective CB2 agonist, a dose-dependent reduction in cell viability were observed. The decrease in viability was more visible in testicular and lung cancer cell-lines, which was seemingly due to apoptosis [61]. It was also observed that adding WIN55, 212–2 to BEL7402 hepatocellular carcinoma (HCC) cells culture medium could induce downregulation of phosphorylated-extracellular signal-regulated kinases (ERK)1/2, upregulation of p27, and downregulation of cyclin D1 and cyclin-dependent kinase 4 (CDK4). The inhibition of ERK1/2 resulted in cell cycle arrest at the G0/G1 phase, which subsequently caused cell growth suppression. Additionally, WIN treatment caused a reduction in matrix metalloproteinase-9(MMP-9), retinoblastoma(RB) protein, and E2F1 expression which followed the inhibition of HCC cells migration and invasion [62]. Although the anti-tumor function of WIN55-212 has been shown in numerous researches, its psychoactive side effects have been a serious limitation for taking advantage of this chemical as an anti-cancer alternative. Searching for a solution for this problem, a group of researchers designed Nano-micelles containing WIN55-212 which was conjugated with styrene-maleic acid (SMA) which could effectively lower the triple-negative breast cancer(TNBC) cells' growth with considerably milder psychoactive effects [63]. Results of a study which was performed on MDA-MB-231 and MCF-7 breast cancer cell lines which were not sensitive to chemotherapeutic agents such as Paclitaxel, showed that treating these cells with synthetic isomers of CBD(CBD), abnormal CBD, and a similar compound, O-1602 would effectively decrease their viability by inducing apoptosis and limiting the ability to migrate in a dose-dependent manner. Interestingly, these abnormal CBD derivatives seemed to exert their anticancer effects through binding GRP55 and GRP18. Moreover, results from in vivo studies using a zebrafish xenograft model showed that O-1602 and abnormal CBD were able to suppress tumor growth remarkably [64]. Moreover, the effect of various CB1 and CB2 selective synthetic ligands, ACEA and AM281, JWH133 and AM630, on different human glioblastoma cell lines were evaluated. It was observed that treating these cell lines with cannabinoid ligands didn't seem to affect tumor type-related miRNAs or induce cell death in any of the cell lines. However, these ligands could significantly inhibit invasion in LN229 cells through specific receptors. Regarding the UG-87 cell line, treatment with ACEA could effectively limit their invasion through binding CB1 receptor, whereas treatment with JWH-133 had a contrasting effect, improving cancer cells' invasiveness, which was CB2-receptor-dependent [65]. It was also observed that synthetic cannabinoids, WIN55,212-2 and JWH-133, can effectively induce apoptosis through the mitochondrial pathway, activating caspase cascade, inducing DNA fragmentation and cell-cycle arrest in low and high-grade Glioblastoma biopsies and T98G, LN18, LN229, U251MG, U87MG, T3, T10 GBM cell-lines with p53 and PTEN mutations which are known to cause resistance to chemotherapeutic agents. JWH-133 also was able to decrease the level of the phosphorylated form of Rb, which is involved in inducing cell-cycle arrest in the non-phosphorylated form [66]. Plus, synthetic cannabinoids, AM-1251 and particularly, AM-251 were able to significantly decrease the viability and induce apoptosis in DU-145 and PC3 prostate cancer cell lines. AM-251 induced an increase in the cleavage of caspase-3, caspase-8, and PARP which led to an increase of Sub-G1 phase cell population and apoptotic cell death in DU-145 cells. Post-treatment DNA fragmentation was also observed in DU-145 prostate cancer cells. The cell death observed in PC3 cells, however, was attributed to a caspase-independent mechanism [67]. Moreover, Oleamide(ODA), an agonist of CB1 and CB2 receptors, was able to exert cell-cycle arrest in the G1 phase and apoptosis in rat RG2 glioblastoma cancer cell line, which interestingly, was carried out independent from CB1/CB2 receptors and intracellular calcium transient pathway. It's noteworthy that treating normal cells with ODA didn't cause any damage to these cells [68]. In addition, CP55940, a synthetic cannabinoid that mimics THCs behavior, has been shown to effectively induce apoptosis through the H2O2 pathway, halt cell-cycle, cause DNA fragmentation, distort mitochondrial membrane potential, and induce intracellular stress in T-cell acute lymphoblastic leukemia (T-ALL) Jurkat cells in a dose-dependent manner and without affecting healthy peripheral blood lymphocyte (PBL) cells. interestingly, this effect was carried out independent from the conventional cannabinoid receptors, CB1 and CB2. and was inhibited when antioxidants such as NAC, pifithrin-α, and SP600125 were added to the Jurkat cell culture media. CP55940 was also able to successfully exert cytotoxic effects ex vivo in T-ALL cells which were taken from chemotherapy-resistant pediatric patients [69]. In addition to studies on different human cell lines, some studies have demonstrated the anti-proliferative role of cannabinoid compounds in mice. For instance, it was observed that feeding murine xenograft models of glioma with a mixture of THC/CBD in a form of microencapsulation or solution leads to reduced cancer cell proliferation and induces apoptosis as well as decreased angiogenesis effectively which was associated with the attenuated level of endothelial cell marker CD3. Notably, mice were treated at a dose of 75 mg micro-particles every 5 days and were sacrificed at day 22 following treatment [70]. In addition, CBD also seemed to be able to significantly decrease melanoma tumor size in C57BL/6 mice with murine B16F10 melanoma tumors. It should be mention that mice were treated intraperitoneally twice per week by 5 mg/kg of CBD [71]. Moreover, novel derivatives from tetrahydrocannabinol acid (THCA), ALAM027 and ALAM108, seem to be able to remarkably decrease viability in PANC-1 and AsPC-1 pancreatic cancer cell lines in vitro as well as a 1.6–2-fold reduction in tumor growth and diminishing tumor size and weight in mice pancreatic cancer xenograft models without causing weight loss in mice. In addition, mice were treated by 120 and 40 mg/kg per day of

Table 1
The anti-proliferative effects of cannabinoid compounds (Endocannabinoid/ Cannabinoids from C. sativa/C. sativa extracts).

Type of cannabinoid compound	Cannabinoid category	Type of cannabinoid receptor	Type of Cell line/ Human tissue	Effective dosage	Observations	Ref
AEA	Endocannabinoid	Independent of CB1/CB2 receptors	Chemotherapy-resistant colorectal cancer cells	10–25 µM	• Induced apoptosis via cyclooxygenase-2 activation and Reactive Oxygen Species(ROS) elevation.	[23]
EPEA DHEA	Endocannabinoid	CB1/CB2 receptors	Breast cancer cell-lines MCF-7 MDA-MB-231	EPEA:70 µM DHEA:100 µM	• Induced anti-proliferative effects in malignant but not normal breast cancer cells • Phosphorylation of p38-MAPK, JNK, and ERK proteins triggered by CB compounds	[29]
2-AG AEA	Endocannabinoid	CB1/CB2 receptors	HEp-2 human laryngeal squamous cell carcinoma (LSCC) cell line	30 µM	• HEp-2 LSCC cell line released AEA and 2-AG • 2-AG showed more potency for decreasing cell proliferation compared to AEA possibly through CB2 receptor	[30]
CBD	Cannabinoids from C. sativa	CB1/CB2 receptors	Glioma cancer cells U87 U373	25 µM	• Induced apoptosis by reducing the mitochondrial oxidative metabolism • Elevation of intracellular ROS and ceramide synthesis activity	[31]
CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Colorectal cancer cell-line HT-29	10 µM	• CBD induced anti-proliferative effect • CBD's anti-proliferative effects were diminished in a cell medium with 10% serum which contained growth factors compared to a medium with only 0.5% of serum.	[32]
CBD	Cannabinoids from C. sativa	TRPV2	TRPV2-transfected Multiple myeloma cells	20 µM	• CBD induced cell death and cell cycle arrest in TRPV2-transfected Multiple myeloma cells. • CBD induced activation of the NF-κB pathway, elevation of ROS, reduction of cyclin D1 and inhibition of ERK activation in MM cells. • CBD in synergy with bortezomib inhibited MM cells proliferation.	[51]
CBD	Cannabinoids from C. sativa	TRPV2	glioblastoma cells	10 µM	• CBD induced TRPV2 activity and expression in glioblastoma cells • CBD induced Ca^{2+} influx, drug uptake and synergized with cytotoxic agents in TRPV2-dependant manner.	[52]
CBD	Cannabinoids from C. sativa	TRPV2	urothelial carcinoma (UC) cells	3 and 30 µM	• TRPV2 upregulated in poorly differentiated urothelial carcinoma cells • CBD triggered intracellular calcium level elevation leading to cell apoptosis	[53]
CBD	Cannabinoids from C. sativa	TRPV2	Triple negative breast cancer cells	5 uM	• CBD sensitized breast cancer cells to doxorubicin uptake. • CBD+ doxorubicin induced apoptosis also caspase and PARP cleavage in the cells. • Treatment of mice with CBD+ doxorubicin reduced breast tumor volume and increased tumor cell apoptosis.	[44]
CBD	Cannabinoids from C. sativa	TRPV2	Type I endometrial cancer cells	3.92 µg/mL	• CBD induced cell death and apoptosis in Type I endometrial cancer cells and increased response to chemotherapeutic drugs in TRPV2-transfected cells.	[55]
CBD	Cannabinoids from C. sativa	TRPV2	Glioma stem-like cell	10 µM	• CBD activated TRPV2 function and induced differentiation and reduced proliferation of Glioma stem-like cells • Acute myeloid leukemia (Aml-1) transcription factor mediated CBD-induced differentiation of cells in a TRPV2-dependant manner	[56]
CBD THC	Cannabinoids from C. sativa	No CB receptor was assessed	Glioblastoma cell lines U251 SF126	*CBD:0.6–1.2 µmol/L THC: 2.5–3.3 µmol/L	• synergistically inhibiting cancer cell proliferation induced apoptosis by impeding cell-cycle, increasing intracellular ROS, activating caspase enzymes	[33]
THC CBG CBN CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Breast cancer cell-lines MCF-7 MDA-MB-231	*THC: 30.13, 40.14 µM CBG: 28.40, 31.45 µM CBN: 23.22, 28.19 µM CBD: 13.82, 20.62 µM	• The mixture induced cell-cycle arrest in G2 phase and apoptosis in a synergistic manner. • Induced DNA fragmentation, cytoplasmic vacuolation, lysosome increased size and lipid accumulation	[34]
CBD THC CBC CBDV	Cannabinoids from C. sativa	No CB receptor was assessed	Transitional cell bladder cancer carcinoma T24 TCCSUP	*CBD: 5.5, 10.5 µM THC: 8.5, 13.5 µM CBDV: 5 µM CBC: 6 µM	• CBD and THC reduced viability, induced caspase-3 and apoptosis • A synergistic effect was observed while combining by other cannabinoids. • A synergistic to antagonistic effects for inducing cell-death was observed while combining with chemotherapeutic agents.	[35]

(continued on next page)

Table 1 (*continued*)

Type of cannabinoid compound	Cannabinoid category	Type of cannabinoid receptor	Type of Cell line/ Human tissue	Effective dosage	Observations	Ref
THC CBD CBGV CBG CBDV CBN THCV	Cannabinoids from C. sativa	TRPV2	Rat TRPV2- HEK293 cells	**THC: 0.65 CBD: 1.25 CBGV: 1.41 CBG: 1.72 CBDV: 7.3 CBN: 19.0 THCV: 4.11 μM	• Cannabinoids induced Ca^{2+} level in TRPV2-transfected -HEK293 cells and can activate TRPV2 • THC and CBD seemed to activate TRPV2 with more potency.	[54]
CBD CBG CBC CBDA THC CBD-rich Cannabis extract	Cannabinoids from C. sativa	CB2/TRPV receptor	Breast cancer cell-line MDA-MB-231	CBD: 6.0 and 10.6 μM	• CBD was the most potent cannabinoid compound in suppressing cancer cell growth • CBD-rich extract was as potent as CBD in inhibiting cancer cell growth • Apoptosis was also carried out by direct/indirect activation of CB2/TRPV receptor and by increasing intracellular ROS and Ca	[22]
CBD THC AEA	Cannabinoids from C. sativa, Endocannabinoid	TRPV1 receptor	Endometrial cancer cell lines Ishikawa cells Hec50co cells	≥ 5 μM	• Both cell-lines expressed TRPV1 receptor • AEA and CBD triggered the activation of caspase3/7, cleavage of PARP, increased ROS level and induced apoptosis in Ishikawa cell-line • These effects were TRPV1 receptor-dependent	[36]
CBD	Cannabinoids from C. sativa,	No CB receptor was assessed	Glioblastoma U87MG cell-line	20 μM	• CBD combined with ATM-kinase inhibitor, KU60019, increased the level of pro-inflammatory cytokines which caused an elevation in apoptotic and non-apoptotic inflammation-related cell death. • These alterations led to an increase in G2/M arrested cells	[37]
CBD CBG	Cannabinoids from C. sativa,	GPR55 receptor	Ovarian cancer cell lines A2780 A2780/CP70	1 nM – 100 μM	• Time and dose-dependent cell-death induced via activating GPR55 receptor • Synergistic effects were observed when cannabinoids were combined with chemotherapeutic agent, Carboplatin. • The derivatives did not show synergistic effects when they were used combined with Cisplatin in cisplatin-sensitive and resistant ovarian tumor cells.	[38]
CBD	Cannabinoids from C. sativa,	TRPV receptor	Neuroblastoma cancer cell lines SH SY5Y IMR-32	10 μM	• Cell cycle arrest induced through down-regulation of has-7a miRNA and up-regulation of has-miRNA-1972 leading to over-expression of caspase2/3 and GAS7 genes • BCL2L1 and SIRT2 genes were downregulated and apoptosis was induced and migration and invasion of NBL cells were inhibited. • These effects were mediated by vanilloid and serotonin receptors.	[39]
CBD	Cannabinoids from C. sativa,	No CB receptor was assessed	Gastric cancer SGC-7901 cell-line	*23.4 μg/mL	• Induction of cell cycle arrest following up-regulation of ATM gene and p53 protein and down-regulation of P21/cyclin E and CDK2 • Bax expression level was increased and Bcl-2 expression level was decreased, which lead to increase of caspase3/9 expression and elevation of intracellular ROS and induction of apoptosis.	[40]
C. sativa extract	C. sativa extract	No CB receptor was assessed	Cervical cancer cell-lines HeLa, ME-180, SiHa	CBD: C. sativa: 50–150 μg/mL	• Induced elevation in the rate of cells at subG0/G1 cell cycle distribution and number of annexinV-positive cells • Overexpression of p53, Bax and caspase3/7 • Decrease in the ATP level	[57]
C. sativa extract (ethanol extract)	C. sativa extract	CB1/CB2 receptors	My-La and HuT-78 cutaneous T-cell lymphoma (CTCL) cell-lines Peripheral blood lymphocytes from Sézary patients (SPBL)	*C. sativa extract: 25.35 μg/mL S4: 16.09 μg/mL S5: 9.72 μg/mL	• S4 and S5 derivatives from the extract were able to halt cell-cycle and induce apoptosis. • The observed effects were dose-dependent and synergistic.	[58]
C. sativa extract exposed to gamma-radiation	C. sativa extract	No CB receptor was assessed	BJ-5ta BT16 HCC1806 IMR5 Cell-lines	0.007 0.015 mg/mL	• Radiated C. sativa extract contained more anticancer agents compared to normal cannabis extracts, particularly Δ-9-THC derivative • Radiated cannabis extract had therefore a higher anti-proliferative potency in the different cancer cell-lines.	[59]

*Indicates IC50
**Indicated EC50

Table 2
The anti-proliferative effects of cannabinoid compounds (synthetic compounds of cannabinoids).

Type of cannabinoid compound	Cannabinoid category	Type of cannabinoid receptor	Type of Cell line/ Human tissue	Effective dosage	Observations	Ref
HU-210 WIN55,212-2 AEA THC	Synthetic derivatives	CB1/CB2 receptors	NCI-H292 (lung cancer), SCC-9 (squamous cell carcinoma), 5637 (bladder carcinoma), U373-MG (glioblastoma), 1321N1 (astrocytoma), and A498 (kidney cancer)	Win; 10 μM THC; 1 μM HU210: 50 nM AEA: 10 μM	• Cannabinoid compounds exacerbated cancer cell proliferation by triggering tumor-promoting signaling pathways, namely EGFR and MAP kinases, ERK1/2, PKB/Akt, TNF-alpha • Cell proliferation was occurred associated with metalloprotease and EGFR activity	[20]
CP 55,940 AEA met-AEA	Synthetic derivatives/ Endocannabinoid	No CB receptor was assessed	Gastric adenocarcinoma cell line (AGS)	*5 μM	• Apoptosis was induced following alteration in DNA synthesis, decrease in cell viability and morphological changes • AEA and CP were more effective in apoptosis induction while Met-AEA mostly induced necrosis	[60]
WIN 55,212-2	Synthetic derivatives	No CB receptor was assessed	Lung cancer cell-line (A549) Testicular cancer (HoTu-10) Neuroblastoma cell-line IMR-5	20 μM	• A dose-dependent decrease in cell viability and induction of apoptosis was observed. • The effect was more visible in A549 and IMR-5 cell lines	[61]
WIN55,212-2	Synthetic derivatives	No CB receptor was assessed	Hepatocellular carcinoma cell-line BEL7402	10 μM	• HCC cells growth inhibition occurred via down-regulation of cyclin D1, CDK4 and up-regulation of p27. • Downregulation of ERK1/2 caused cell-cycle arrest at G0/G1 phase • WIN treatment reduced the expression level of matrix metalloproteinase(MMP-9), retino-blastoma(RB) protein and E2F1 which led to suppression of HCC cells' migration and invasion.	[62]
WIN55,212-2 Nano-micelles conjugated with styrene maleic acid (SMA)	Synthetic derivatives	No CB receptor was assessed	Triple-negative breast cancer cells (TNBC)/ Castration-resistant prostate cancer (PC3) cell lines	10 μM	• cancer cells' growth was significantly lowered with less psychoactive effects.	[63]
O-1602 Synthetic isomers of CBD abnormal CBD	Synthetic derivatives	GPR55 GPR18 receptors	Breast cancer cell-lines resistant to chemotherapeutic agents/ zebrafish xenograft model	0–10 μM	• The viability of cells decreased following induction of apoptosis and inhibition of migration in a dose-dependent manner. • The effects were carried out through binding GPR55 and GPR18 receptors. • O-1602 and abnormal CBD suppressed tumor growth in zebrafish xenograft model significantly.	[64]
ACEA JWH133	Synthetic derivatives	CB1/CB2 receptors	Glioblastoma U-87MG, LN229, U138MG	ACEA:10 μM JWH133: 10 μM	• None of the mentioned derivatives altered tumor-related miRNAs nor induced cell death in different glio-blastoma cell-lines. • The mentioned derivatives significantly limited LN229 invasion by binding CB1 receptor. • In contrast, JWH-133 improved inva-sion in U-87 cell-line via CB2 receptor.	[65]
WIN55,212-2 JWH-133	Synthetic derivatives	CB1/CB2 receptors	Glioblastoma biopsies and T98G LN18 LN229 U251MG U87MG T3 T10 cell-lines	**WIN: 7.36–15.70 μM, JWH133: 12.15–143.20 μM	• Both CB1 and CB2 were overexpressed on GBM cell-lines and tissue samples. • WIN55,212-2 and JWH-133 effec-tively induced apoptosis in GMB cell-lines and both low and high grade GBM tumor tissue samples with p53 and PTEN mutations via mitochon-drial pathway and by activating cas-pase cascade, inducing cell-cycle arrest and DNA fragmentation. • JWH-133 decreased the level of phosphorylated Rb.	[66]
AM1251	Synthetic derivatives	No CB receptor was assessed	Prostate cancer cell-lines DU-145 PC3	Not stated	• Reduction of cell viability and induction of apoptosis was occurred in the cells possibly through caspase-independent pathway.	[67]

(continued on next page)

Table 2 (*continued*)

Type of cannabinoid compound	Cannabinoid category	Type of cannabinoid receptor	Type of Cell line/ Human tissue	Effective dosage	Observations	Ref
					• AM251 caused an increase in the cleavage of caspase3/8 and PARP protein which led to DNA fragmentation, increase of Sub-G1 cells and apoptosis induction in DU-145 cells.	
Oleamide(ODA)	Synthetic derivatives	CB1/CB2 receptors	Rat glioblastoma cancer cell-line RG2	*50 μM 100 μM	• Cell-cycle arrest in G1-phase and apoptosis were induced in GBM cancer cells. normal cells were not affected. • The observed effect was carried independent from CB1/CB2 receptors or intracellular calcium transient-independent pathway.	[68]
CP55940	Synthetic derivatives	Independent of CB1/CB2 receptors	T-cell acute lymphoblastic leukemia (T-ALL) Jurkat cells/ T-ALL cells taken from chemotherapy-resistant pediatric patients (ex vivo)	0–20 μM	• Induction of apoptosis via increase in intracellular H2O2, DNA fragmentation, alteration in mitochondrial membrane potential and induction of intracellular oxidative stress • The effects were carried out in a CB1/CB2 receptor independent manner. • By applying antioxidants to the cell-culture, the observed effects were inhibited.	[69]

*Indicated IC50
**Indicated EC50

ALAM023 and ALAM108, respectively. Cannabinoids were given orally every day (5 days a week) [72]. Altogether, in most observed evidence, it seems that cannabinoid derivatives can induce apoptosis via multiple mechanisms, such as caspase activation, and ROS elevation, and mitochondrial involvement. Based on the evidence, CBD might have an inhibitory effect against proteins that are involved in tumor growth, invasion, and angiogenesis, namely HIF1-alpha, ERK, and AKT. Both the anti-proliferative, and pro-apoptotic effects of CBD in cancer cells are beneficial for proposing these compounds as possible anti-cancer therapeutic approaches. The aforementioned data are summarized in Table 1. (Table 3).

1.2. *The anti-angiogenesis effects of cannabinoid and cannabinoid receptors in cancer cells*

Angiogenesis is a crucial process in disposing of wastes and nourishing cancer cells with oxygen and other nutrients, mainly glucose. Tumor cells send signals to stimulate angiogenesis-related proteins' production, such as vascular growth factors, pro-inflammatory cytokines, and adhesion molecules to build this vascular network. Hence, several methods have been developed through the past decades to fight angiogenesis in cancer cells [4]. Lately, it has been shown that cannabinoid derivatives are also able to inhibit angiogenesis by multiple mechanisms (Fig. 2). It was observed that activating CB1 by Anandamide triggers bFGF-dependent angiogenesis which is followed by endothelial proliferation and migration, and capillary-like tube formation, through pro-survival and migratory pathways involving ERK, AKT, FAK, JNK, Rho, and MMP-2. Therefore, inhibiting CB1 could be considered as an efficient anti-angiogenesis strategy in curing cancer [73]. Furthermore, it has been demonstrated that treating rat metastasis-derived thyroid cancer cells in athymic mice with 2-methyl-arachidonyl-2'-fluoro-ethylamide (Met-F-AEA) or Anandamide (AEA), leads to inhibition of VEGF gene expression and its related proteins (flt-1/VEGFR-1), which seem to be upregulated by p21. Met-F-AEA, on the other hand, activated cyclin-dependent kinase inhibitor p27(kip1), a critical mediator of the cell cycle, which is also known to be suppressed by p21. Notably, the p21-RAS oncogene was effectively downregulated by these derivatives which were followed by retardation of metastasis and tumor growth. Met-F-AEA and AEA seemed to carry out these effects via the CB1 receptor. Notably, for this study mice were injected by 0.5 mg/kg/dose of Met-F-AEA on the dorsal right side [74]. Moreover, eicosapentaenoyl-ethanolamine (EPEA) and docosahexaenoyl-ethanolamine (DHEA) are an altered form of omega-3 long-chain polyunsaturated fatty acids seem to be able to limit MCF-7 and MDA-MB-231 breast cancer cell lines migration and invasion by attenuating the expression of VEGF and MMP1 [29]. It has also been demonstrated that CBD induces the downregulation of angiogenesis-related proteins in human umbilical vein endothelial cells (HUVEC), can build a vein network. As when HUVEC was treated with CBD, angiogenesis was significantly suppressed. Moreover, CBD showed inhibitory effects on HUVEC proliferation, migration, and endothelial morphogenesis, which resulted in cell cytostatic, without causing apoptosis or toxicity. Also, it was shown that angiogenesis-related mediators such as MMP9, TIMP1, PAI-1, uPA, CXCL16, ET-1, PDGF-AA, and IL-8 were down-regulated [16]. Recently, it has been shown that THC is capable of impairing angiogenesis in embryo/HUVECs via inhibition of RhoA/MLC signaling pathway, and consequently endothelial cell (EC) proliferation, migration, and tube formation. Decrease of CD31 level, a major marker of EC proliferation has confirmed this effect also, to evaluate placental angiogenesis, C57BL/6 mice were injected every day intraperitoneal with THC (5 mg/kg), and the embryo and placental tissues were applied for the study [75]. Also, it was revealed that Δ9-THC inhibited angiogenesis in rat C6 glioma, the human U373 MG astrocytoma, the mouse PDV.C57 epidermal carcinoma, and human ECV304 bladder cancer epithelium cells via downregulation of VEGF-related genes, VEGF production, and VEGF receptor-2 expression which was carried out through ceramide synthesis and ultimately led to tumor shrinkage [76,77]. In 2003, Blázquez C et al. showed that a range of synthetic cannabinoids including JWH-133, HU-210, WIN-55,212–2 SR141716, and SR144528, and the well-known non-psychoactive cannabis derivative, CBD can induce cancer cells' death by restricting vascular endothelial cell migration and viability as well as down-regulating pro-antigenic factors' expression such as VEGF and angiopoietin2 (Ag2) and matrix metalloproteinase-2 in C6 rat glioma cancer

Table 3
The anti-angiogenic effects of cannabinoid compounds.

Type of cannabinoid compound	Cannabinoid category	Type of cannabinoid receptor	Type of Cell line/ Human tissue	Effective dosage	Observations	Ref
AEA	Endocannabinoid	CB1 receptor	Human umbilical vein endothelial cells HUVECs	0.1–0.0001 μM	• B-FGF-dependent angiogenesis was triggered in HUVECS cells • Endothelial proliferation and migration, and capillary-like tube formation through pro-survival and migratory pathways was induced. • These effects were carried out through CB1 receptor.	[74]
Met-F-AEA AEA	Endocannabinoid	CB1 receptor	Rat thyroid cancer cell-derived tumor in athymic mice Lewis lung carcinoma (3LL)	10 μM	• Down-regulation of VEGF and its receptor (flt-1/VEGFR-1). • Suppression of p21 RAS oncogene that upregulate VEGF, and activation of kip1, which is downregulated by p21 • Metastasis and tumor growth was consequently suppressed. • The observed effects were mediated by CB1 receptor.	[75]
EPEA DHEA	Endocannabinoid	CB1/CB2 receptors	Breast cancer cell-lines MCF-7 MDA-MB-231	EPEA:70 μM DHEA:100 μM	• Migration and invasion of the cancer cells were limited that was carried out through downregulation of VEGF and MMP1	[29]
CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Human umbilical vein endothelial cell HUVEC	*9.89 μM	• Suppression of angiogenesis, proliferation, migration and endothelial morphogenesis • Down-regulation of MMP9, TIMP1, PAI-1, uPA, CXCL16, ET-1, PDGF-AA and IL-8 was observed.	[18]
THC	Cannabinoids from C. sativa	No CB receptor was assessed	embryo/HUVEC cells	10 μM	• Angiogenesis was distorted through inhibition of RhoA/MLC pathway. • Endothelial cell (EC) proliferation, migration and tube formation were consequently disrupted following attenuated CD31 level.	[76]
THC	Cannabinoids from C. sativa	No CB receptor was assessed	Rat C6 glioma, Human U373 MG astrocytoma, Mouse PDV.C57 epidermal carcinoma, Human ECV304 bladder cancer epithelioma	10 μM	• VEGF-related genes were downregulated. • VEGF protein level and VEGF-receptor2 level was decreased. • This effect was carried out through intracellular ceramide synthesis. • Tumor size was decreased	[77, 78]
WIN-55,212–2 JWH-133 HU-210	Synthetic derivatives/ Cannabinoids from C. sativa	CB1/CB2 receptors	C6 rat glioma cancer cells	WIN:25 nM HU-210:25 nM JWH-133: 25 nM	• Vascular endothelial cells' viability and migration was reduced. • The production of pro-antigenic factors such as VEGF, Ag2 and MMP2 was decreased.	[79]

*Indicated IC50

cells *in vivo* [78]. Notably, mice were injected intratumorally with JWH-133 for 8 days or 25 days to be obtained from biopsies of tumors. Conclusively, administration of cannabis derivatives, mainly THC and CBD, seems to be effective in metastasis inhibition and tumor growth retardation by suppressing angiogenesis-related proteins' expression, primarily VEGF, VEGF-receptor. The possible effects of CB on the angiogenic process are summarized in Table 2.

1.3. The effect of cannabinoid and cannabinoid receptors on tumor-promoting signaling pathway

Cannabinoids have also been shown to hinder tumor growth by altering and limiting tumor-enhancing signaling pathways (Fig. 3) Based on pieces of evidence, it was revealed that the level of CB1 expression in the tissue samples from metastatic CRC patients was significantly lower compared to non-metastatic CRC patients as well as normal tissues. The decrease in CB1 expression was accompanied by the inhibition of apoptosis, down-regulation of MAPK-p38, ERK1/2, Bax, and caspase-3 gene and protein as well as up-regulation of p-AKT. These observations confirmed the link between the decrease in CB1-receptor's expression and CRC tumors' invasion and metastasis [79]. Investigations have shown that AEA induced anti-neoplastic effects on lung adenocarcinoma cells by altering some tumor-related signaling pathways and agents. Fatty acid amide hydrolase (FAAH), however, breaks down AEA and impedes AEA's anti-tumor activity. Results have shown that treating NSCLC cell lines with Met-AEA and FAAH inhibitor, URB597, results in suppressed EGFR signaling pathway and its downstream signaling agents, including ERK, AKT, and NF-KB, which subsequently leads to inhibition of tumor cells' proliferation and chemotactic activity. This mixture also inhibited the production of major tumor invasion agents, MMP2/MMP9, and stress fiber and induced G0/G1 cell cycle arrest by downregulating CDK4 and cyclinD1, which was followed by activation of caspase9 and PARP and apoptosis occurrence in these cancer cells [80]. Interestingly, they revealed that the tumor size of the nude mouse that was injected subcutaneously into the left flank with Met-F-AEA (5 mg/kg) in combination with URB597 (1 mg/kg) reduced tumor growth and size. In addition, EPEA and DHEA showed to alter several signaling pathways, including phosphorylation of p38-MAPK, JNK, and ERK proteins leading to a significant decrease in MCF-7 and MDA-MB-231 breast cancer cells invasion and migration [29]. Moreover, treating triple-negative breast cancer cells(TNBC) in mice models with CBD seems to diminish the expression of epidermal growth factor

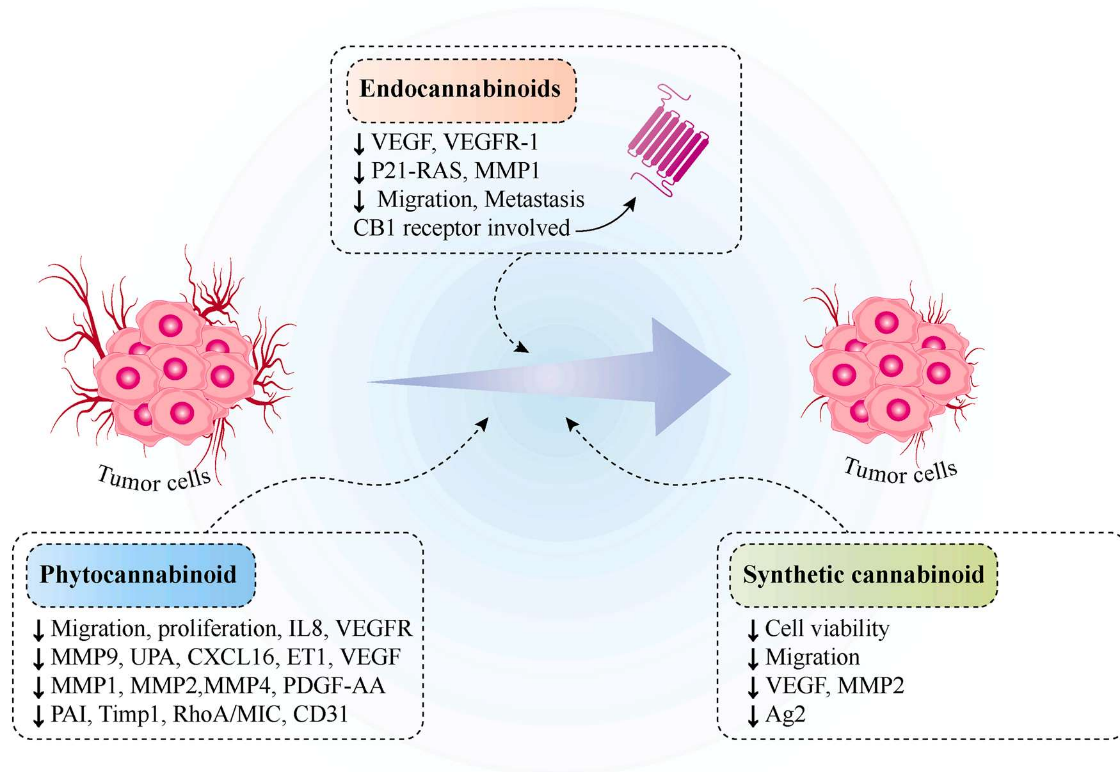

Fig. 2. Anti-angiogenesis effects of cannabinoids. Various types of cannabinoids impede cancer cells' invasion and metastasis by inhibiting angiogenesis by decreasing VEGF, MMP2, and vasculogenesis markers, CD3 and Ag2. The effects of each of the cannabinoid compound groups are shown separately. No data were found regarding the direct effect of C. sativa extracts on the angiogenesis process.

(EGF) and downregulate its related pathways including EGFR, ERK, AKT, and NF-kB pathways, which results in the inhibition of breast cancer cells proliferation, chemotaxis, and decrease in MMP2/9 secretion. The accumulation of tumor-associated macrophages in primary tumor stroma was also suppressed which led to inhibition of secondary lung metastasis [81] Also, they demonstrated that the tumor growth and size were decreased in mice that were injected with CBD (10 mg/kg) peri-tumorally 3 weeks. Moreover, it was revealed that CBD demonstrated an inhibitory effect on proliferation and invasion of U87 and T98G glioma cell lines which was occurred via down-regulation of some critical proteins which are involved in growth, invasion, and angiogenesis including ERK, AKT, and HIF1-alpha proteins. Notably, CBD was able to induce anti-cancer properties without causing any psychoactive side effects [82]. In addition, adding CBD to THC resulted in down-regulation of ERK(MAP-kinase)activity in U251 and SF126 glioblastoma cell lines in a synergistic manner which was followed by inhibition of proliferation and induction of apoptosis in these cancer cells [33]. Furthermore, investigations on the anti-cancer effects of CBD on HCT116 and DLD1 CRC cell lines demonstrated that this cannabinoid derivative implements its actions in these cancer cells by inducing apoptosis using Noxa-ROS signaling pathway also CBD reduced the tumor size of CBD-treated BALB/c nude mice (received 20 mg/ki CBD intraperitoneally injected for every 3 days) [83]. Results from another study revealed that extracellular vehicles(EVs) in GBM cancer cells, which have shown to be involved in pro-oncogenic signaling and cancer invasion pathways, contain less pro-oncogenic miRNA21 and more of anti-oncogenic miRNA126 after treatment with a mixture of CBD and Temozolomide(TMZ) compared to control cells. It's noteworthy that the observed effects were far weaker following treatment GBM cells with TMZ alone. Moreover, following an hour of GBM cells incubation with CBD, the level of Prohibin (PBH), a protein which is assumed to be responsible for chemotherapeutic drug-resistance, was significantly decreased [84]. Furthermore, a study on the effect of S4 and S5, two fractions from C. sativa (Ethanol extract), on My-La and HuT-78 cutaneous T-cell lymphoma (CTCL) cell-lines and peripheral blood lymphocytes from Sézary patients (SPBL) revealed that they can modify the expression of several cancer-related genes and their related signaling pathways in these cell lines, including NFKBIZ, RRM2, SATB1, PIK3R3, AKT1, KCNN4, ATF4, TRIB3 genes and induce apoptosis and cell-cycle arrest effectively and in a synergistic manner [58]. The synthetic CB2 agonist, JWH-015, suppressed epithelial to mesenchymal tissue(EMT) transformation in CALU-1 non-small lung cancer cells by down-regulating EGFR signaling pathway. this synthetic cannabinoid also inhibits lung cancer cells migration and invasion by reducing the expression of FAK, VCAM1, and MMP2 [85]. They also showed that treating an old male FVB mouse with JWH-015 (7.5 mg/kg) thrice for 3 weeks resulted in suppression of the subcutaneous growth of tumor cells and inhibition of tumor growth. Another study revealed that treating T-cell acute lymphoblastic leukemia (T-ALL) Jurkat cells with CP55940, a synthetic cannabinoid with a structure similar to THC, resulted in enhancement of intracellular stress marker, DJ-1 Cys106- sulfonate, stimulated the overexpression of p53 and phosphorylation of transcription factor c-JUN. It also increased the expression level of Bax and PUMA, stimulated mitochondrial proteins PINK1 and Parkin upregulation, and triggered the activation of caspase-3 which ultimately led to the reduction of viability and apoptosis in these cells[69]. Furthermore, treating chemotherapeutic-resistant colon cancer cell lines, HCT116 and SW48 with Rimonabant or SR141716, a CB1 receptor inverse agonist, resulted in inhibition of Wnt/β-Catenin pathway, which is known to regulate cell proliferation, adhesion, and invasion and plays a major role

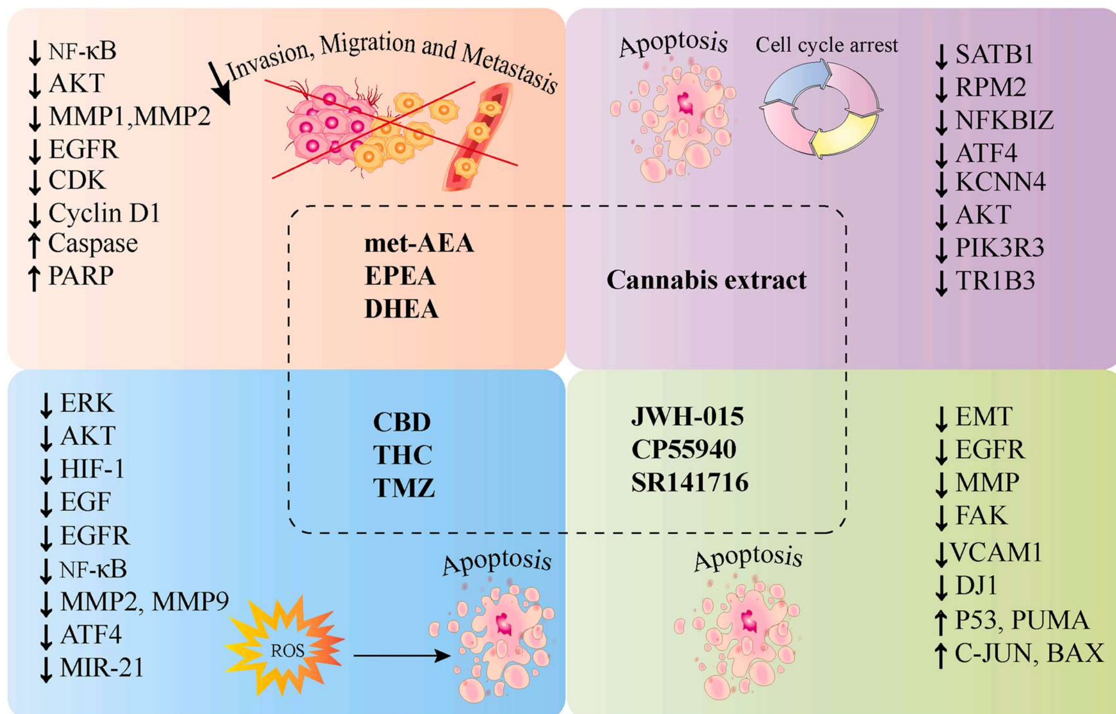

Fig. 3. Effect of CBs on tumor-promoting signaling pathway. Different cannabinoids block tumor cells' growth and invasion by suppressing tumor-related signaling pathways including ERK1/2, EGFR, AKT, NFK-B, and Wnt-β Catenin which lead to the decrease of c-myc and cyclin D, inhibition of proliferation, decrease in TAM, MMP1,2 and 9 and invasion as well as an increase in PINK1 and PARKIN and caspase3 and induction of apoptosis. The effects of each of the cannabinoid compound groups are shown separately.

in initiating colorectal tumors. Rimobanant also silenced the Wnt/β-Catenin pathway downstream target genes via direct inhibition of p300/ KAT3B histone acetyltransferase, which is a coactivator of β-Catenin, and increased β-Catenin phosphorylation and degradation in HCT116 cells, but not in SW48 cells. Rimonabant also activated the Wnt/β-Catenin non-canonical pathway via induction of Wnt5A and activation of CaMKII. This derivative also altered β-Catenin nuclear localization, downregulated cyclin D, and c-Myc and limited tumor growth in HCT116 xenografts significantly[86]. The summary of the effect of cannabinoids on tumor-related signaling pathways is shown in Table 4.

1.4. The effect of cannabinoid and cannabinoid receptors on triggering autophagy and mitophagy in cancer cells

Cannabis derivatives have also been shown to be able to effectively eliminate cancer cells and limiting their viability and invasion by regulating the balance between autophagy and apoptosis [28] (Fig. 4). It was indicated that THC can decrease cell viability by inducing non-canonical autophagy and apoptosis in chemotherapy-resistant BRAF/NRAS wild-type melanoma cancer cells through the Atg7 gene, as a major mediator of autophagy. It seemed that the autophagy induced by THC has occurred independently from Beclin-1 or Ambra1 and caspase activity. In addition, the same study reported that melanoma xenograft mice models under treatment with Sativex (contain equal amounts of THC and CBD) showed better cytotoxic effects compared to THC which was associated with triggered autophagy-dependent apoptosis and reduction in the viability of melanoma cancer cells (mice received 15 mg/kg of THC or 7.5 mg/kg THC/7.5 mg/kg CBD (Sativex) for 20 days by oral gavage) [87]. Furthermore, it was observed that THC can induce autophagy in U87MG cells and glioma cancer cells and biopsies from recurrent glioblastoma multiform patients by triggering ceramide accumulation and eIF2α(eukaryotic translation initiation factor 2α) phosphorylation which leads to increase ER stress, inhibition of Akt/mammalian target of rapamycin complex 1 (mTORC1) by tribbles homolog 3(TRIB3), which eventually led to autophagy and apoptosis. These findings suggested that autophagy is probably a necessary step in cancer cell death induced by cannabinoids *in vivo*. Notably, tumor biopsies were taken from patients who received 6–10 μM THC intra-tumorally for 26 days [88]. In addition, the combination of THC and chemotherapeutic agent, Temozolomide (TMZ), was able to significantly reduce tumor growth and induce autophagy-dependent cell death both *in vitro* and in U87 and T98 glioma xenograft models which were resistant to TMZ alone. Combined administration of THC, and CBD, as well as THC, CBD and TMZ were also remarkably effective in increasing autophagy and reducing cancer cell viability in both TMZ-sensitive and TMZ-non sensitive glioma tumor xenografts. It's noteworthy that inhibiting autophagy prevented this effect which supports the pivotal role of autophagy in cancer cell death induced by cannabinoids. Notably, mice have been injected peritumorally for 14 days by 5 mg/mL of THC and THC-CBD [89]. Interestingly, pseudokinase TRIB3 was identified as a key button for determining cancer cells' fate in response to cannabinoids and the induced ER stress which directs cancer cells from autophagy to apoptosis and ultimately, cell death. The inability of THC to carry out its anticancer effects on TRIB3 deficient mice models confirmed this point. It is noteworthy that mice have been injected for 15 days peritumorally with THC (15 mg/kg per day) which revealed reduced tumor growth [90]. It was also revealed that CBD can induce death by altering the balance between autophagy and apoptosis in MDA-MB-231 breast cancer cells. CBD seems to carry out this effect by inducing the cleavage of Beclin-1, a protein that is involved in regulating autophagy, transferring the cleaved Beclin-1 to mitochondria, causing the release of cytochrome C and triggering apoptosis. CBD was also able to increase ER stress and as a result, suppress AKT/mTOR pathway, reduce the level of phosphorylated mTOR, 4EBP1, and cyclin D, elevate the level of caspase-8 and increase the level of cleaved PARP and LC3-II, markers of apoptosis and autophagy, respectively, which led to activation of intrinsic

Table 4
The effects of cannabinoid compounds on tumor-promoting signaling pathways.

Type of cannabinoid compound	Cannabinoid category	Type of cannabinoid receptor	Type of Cell line/ Human tissue	Effective dosage	Observations	Ref
CB1 receptor gene expression	———	CB1 receptor	Tissue specimens from invasive, non-invasive CRC patients	———	• Decreased expression level of CB1 in tissue specimens from metastatic CRC patients compared to specimens from non-metastatic CRC patients and healthy subjects. • CB1-receptor's lower expression altered the regulation of several tumor-related pathways, including MAPK-p38 and ERK1/2, Akt. The expression level of Bax, caspase3 and apoptosis occurrence was also diminished. • CB1-receptor lower expression in metastatic specimens of CRC patients was attributed to increase of invasion.	[80]
Met-AEA FAAH inhibitor (URB597)	Endocannabinoid	No CB receptor was assessed	Non-small cell lung cancer cell lines A549 H460	Met-F-AEA:10 μM URB597: 0.2 μM	• Down-regulation of EGFR pathway, ERK, AKT and NF-KB. • Inhibition of Cancer cells' proliferation • Reduction of MMP2/MMP9 and stress fiber production • Down-regulation of CDK4 and cyclinD1 followed by activation of caspase9 and PARP and induction of apoptosis	[81]
EPEA DHEA	Endocannabinoid	CB1/CB2 receptors	Breast cancer cell-lines MCF-7 MDA-MB-231	EPEA:70 μM DHEA:100 μM	• Phosphorylation of p38-MAPK, JNK, and ERK proteins were altered. • Suppression of cancer cells' invasion and migration.	[29]
CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Breast cancer triple-negative cells TNBC	6 μM	• Decrease in the expression level of EGF and EGFR, ERK, AKT and NF-kB • Inhibition of cancer cells' proliferation, chemotaxis and MMP2/9 production • Reduced accumulation of tumor-associated macrophages in primary tumor stroma and prevention of secondary lung metastasis	[82]
CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Glioma cell-lines U87 and T98G	*0.94 –11.38 μM	• Reduction in glioma cancer cells' proliferation and invasion in a dose dependent manner • Down-regulation of ERK, AKT and HIF1-alpha which regulate tumor growth, invasion and angiogenesis	[83]
CBD THC	Cannabinoids from C. sativa	No CB receptor was assessed	Glioblastoma cell lines U251 SF126	*CBD:0.6–1.2 μmol/L THC: 2.5–3.3 μmol/L	• Downregulation of ERK(MAP-kinase)activity in U251 and SF126 glioblastoma cell lines in a synergistic manner followed by inhibition of proliferation and induction of apoptosis in these cancer cells.	[33]
CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Colorectal cancer cells HCT116 DLD1 CRC	0–8 μM	• Induction of apoptosis and inhibition of tumor growth through Noxa-ROS signaling pathway. • CBD induced ROS production and reticulum endoplasmic stress and mitochondria dysfunction	[84]
CBD TMZ	Cannabinoids from C. sativa	No CB receptor was assessed	Glioblastoma cell-lines LN18, LN229, CRL-2611	CBD:5 μM TMZ:800 μM	• CBD/TMZ treatment caused increase of anti-oncogenic miR126 and decrease of pro-oncogenic miR21 content in extracellular vehicles(EVs), which are attributed to tumor invasion. • TMZ alone showed less effects • CBD reduced the level of Prohibin(PBH), a factor which is involved in chemotherapeutic resistance in the cells	[85]
C. sativa extract (ethanol extract)	C. sativa extract	CB1/CB2 receptors	My-La and HuT-78 cutaneous T-cell lymphoma (CTCL) cell-lines Peripheral blood lymphocytes from Sézary patients (SPBL)	*C. sativa extract: 25.35 μg/mL S4: 16.09 μg/mL S5: 9.72 μg/mL	• Several oncogenic genes and their related cancer-promoting signaling pathways, namely NFKBIZ, PIK3R3, AKT1, KCNN4, ATF4, TRIB3, RRM2, SATB1 genes were increased. • Cell-cycle arrest and apoptosis was induced by these cells following exposure to C. sativa extracts • The observed effect of S3 and S4 fractions was synergistic.	[58]
JWH-015	Synthetic derivatives	CB2 receptor	Non-small cancer cells A549 Mesenchymal cells CALU-1 Murine cells ED1	5 μM	• Inhibition of epithelial to mesenchymal tissue (EMT) transformation followed by downregulation of EGFR pathway. • The expression of FAK, VCAM1, and MMP2 was decreased leading to prohibition of tumor migration and invasion.	[86]
CP55940	Synthetic derivatives	Independent of CB1/CB2 receptors	T-cell acute lymphoblastic leukemia (T-ALL) Jurkat cells/ T-ALL cells taken from	0–20 μM	• Elevation of intracellular stress marker, DJ-1 Cys106 which stimulated the expression of p53 and phosphorylation of transcription factor c-JUN, BAX and PUMA, upregulation of	[69]

(continued on next page)

Table 4 (*continued*)

Type of cannabinoid compound	Cannabinoid category	Type of cannabinoid receptor	Type of Cell line/ Human tissue	Effective dosage	Observations	Ref
			chemotherapy-resistant pediatric patients (ex vivo)		mitochondrial proteins PINK1 and Parkin and caspase and ultimately induction of apoptosis	
CB1 inverse agonist SR141716	Synthetic derivatives	CB1 receptor	Chemotherapeutic-resistant colon cancer cell-lines HCT116 SW48	10 μM	• Down-regulation of Wnt/β-Catenin pathway and its downstream target genes via direct inhibition of p300/ KAT3B histone acetyltransferase. • Phosphorialtion of β-Catenin in HCT116 cells which led to its degradation. • Wnt/β-Catenin non-canonical pathway was activated via induction of Wnt5A and activation of CaMKII. • In tissue samples taken from xenografts, tumor growth was inhibited and c-Myc and Cyclin D1 were downregulated.	[87]

*Indicated IC50

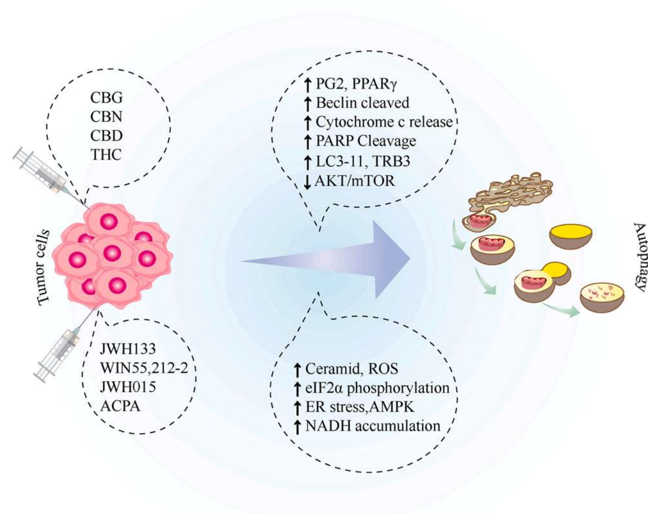

Fig. 4. Effect of cannabinoids on inducing autophagy in cancer cells. Various cannabinoids trigger autophagy-dependent cell death in cancer cells by increasing intracellular ceramide, inducing ER stress, and inhibition of AKT/mTORC1 axis as well as increasing the level of PPAR-gamma. They also elevate autophagy markers, LC3, LC2 and P62. The cannabinoids from C. sativa and synthetic derivatives of cannabinoids and their effects on autophagy are shown separately.

(mitochondrial) apoptosis and autophagy. Moreover, CBD enhanced ROS production, which seems to play an important role in inducing cell death induced by CBD [31,91,92]. In addition, treating MB231 and MCF-7 breast cancer cells with a combination of cannabinoids, including tetrahydrocannabinol, cannabigerol(CBG), cannabinol (CBN), and CBD, altered their morphology by ER-derived vacuoles formation, lysosome enlargement and increase of the endoplasmic reticulum chaperone protein glucose-regulated protein 78 (GRP78), and ultimately, induction of ER stress which could be related to both autophagy and para-apoptosis [34]. Moreover, the synthetic CB1 and CB2 agonist, ACPA and GW induced the production of ROS followed by an increase in AMP/ATP ratio and AMPK activity (main enzymes in regulating autophagy), GADPH relocation in cells' nucleus, and suppression of glycolysis in Panc1 pancreatic cancer cell line. Elevation of ROS resulted in NADH accumulation and blockage of the respiratory chain and Krebs cycle and limited cancer cells' metabolism. Based on data provided by Dando et al., inhibition of AKT/c-Myc pathway, PTEN activation, and attenuated pyruvate kinase isoform M2 (PKM2) activity caused limited glycolysis and glutamine uptake that all together facilitate autophagy induced by CB1 and CB2 agonist [93]. It was also revealed that the viability of HepG2 HCC cells decreased following THC and JWH015 administration which was associated with induction of apoptosis and autophagy through up-regulation of TRIB3, blockage of AKT/mTORC1 pathway, activation of AMPK by CaMKKb, and activation of the CB2 receptor. Moreover, cannabinoids were able to slow down tumor growth and inhibit ascites in HCC xenografts (Athymic nude mice were injected subcutaneously injections by 15 mg/kg THC/ 1.5 mg/kg JWH-015 every day up to 15 days) [94]. It was shown that CBD mediated reduction of Glioma stem-like cell viability in a TRPV2-dependant manner through increased autophagy-related proteins Beclin-1 and cleaved LC3-II [56]. In addition, WIN55,212-2 caused apoptosis via ER-stress induction, also the elevation of LC3-II protein, p62, and LC3, formation of acidic vacuoles to mediate autophagy as a pro-survival behavior against the cytotoxicity induced by WIN55,212-2 in colon cancer cells. It seemed that down-regulation of PPAR- gamma and increase in lysosomal membrane permeabilization (LMP) play a critical role in WIN55,212-2-induced cell death [95]. Moreover, a recent study showed that treating rat C6 glioma cells, tissue samples from patients with low and high-grade Glioblastoma tumor specimens and T98G, LN18(grade IV) and, LN229, U251MG, U87MG (grade II) GBM cell-lines with p53 and PTEN gene defects with synthetic non-selective agonist WIN55,212-2, can cause autophagy followed by apoptosis via an increase in ceramide synthesis, increase in ER stress and inhibiting AKT/mTOR pathway, which was confirmed by the increase of acidic vesicular organelles formation and LC3II marker. It's noteworthy that the observed effect was majorly dependent on the CB1 receptor. Interestingly, suppressing autophagy in LN18 cells led to improvement in caspase 3, 7 activity, PARP degradation, and as a result, apoptosis in these cells which indicates that in this case, autophagy was a cytoprotectivemeasure [66]. Moreover, treating PC3 prostate cancer cell-line by synthetic cannabinoids, AM-251 and AM-1251 caused LC3B-II elevation, a hallmark protein for autophagosome formation, and consequently, autophagy in PC3 cells, which is assumed to be carried out via PI3K pathway / p-AKT / mTOR pathway. PC3 cells then went through late-apoptosis indicated by an increasein PI/AnxV [67]. It is taken for granted that mitochondria are keyc ellular organelles that have a pivotal role in controlling cell metabolism and energy as well as cell fate and homeostasis thus mitochondria dysfunction resulted in many diseases such as cancer [96]. Therefore, the processes of controlling the proper function of mitochondria can play an essential role in controlling cancers. Mitophagy is selective autophagy of mitochondria is considered as crucial quality control of mitochondria function and morphology, and it is postulated that identifying factors that regulate mitophagy might potentially lead us to potent therapeutic approaches [97]. Cannabinoids and their receptors seem to affect normal and cancer cells through modulating mitochondrial morphology and function. Studies have

shown that CB1 is expressed on mitochondria snd is involved in the regulation of energy metabolism of the hippocampus and reduction of Serine 65-phosphorylated ubiquitin (as a hallmark of mitophagy) in CB1-deficient mice indicated the regulatory role of CB1 in mitochondrial autophagy [98]. It was also reported that activating CB1 with its endocannabinoid ligand, AEA, leads to cleavage of mitochondria in renal proximal tubular cells, and deletion of CB1 in HK-2 cells using CRISPR-CAS genome editing technique resulted in alteration in mitochondrial morphology [99]. In addition, it was shown that CBD tended to induce autophagy rather than apoptosis due to the induction of mitochondrial dysfunction and mitophagy cell arrest following CBD administration in glioma human cell-lines which was associated with elevation of Ca2 + influx and TRPV4 activation and its downstream mediators such as AKT-mTOR axis [100]. Another study demonstrated that treating MCF7 cancer cell-line with CBD causes a dose-dependent increase in mitochondrial ROS production and Ca2 + influx and as a result, increases in mitochondrial cleavage and mitophagy/autophagy induction [101]. Another study which was carried out on acute lymphoblastic leukemia of T lineage cells revealed that treating these cells with CBD leads to an increase of mitochondrial Ca2 + uptake, disruption of mitochondrial membrane potential and ATP production, increase of ROS production, and ultimately, induction of mitophagy and cancer cell death [102]. It is apparent that CB receptors and cannabinoid compounds might be considered as promising modulators of autophagy and mitophagy in cancer cells; while required further solid evidence. Table 5 shows the summary of the significance of CBs to the autophagy/mitophagy process.

1.5. The effects of cannabinoid and cannabinoid receptors on the immune system

Investigations have revealed that cannabinoids can participate as a key switch in modulating immune responses and inflammatory agents in cell context which can indeed, play a vital role in determining cancer cells' growth, migration, and invasion [14,28,103]. Evidence is summarized schematically in Fig. 5 and detail in Table 6 In accordance, it was shown that AEA induced down-regulation of inflammasome components' expression and decrease IL-1β production which facilitates tumor cell progression. They provided shreds of evidence regarding the involvement of CB1 and TRPV1 receptors in this regard [104]. It was also reported that endocannabinoids and other compartments of ECS may affect the leukocytes in the tumor microenvironment (TME), which are responsible for regulating tumor progression and therefore have a pivotal role in determining tumor's fate [105]. Results from a study which was carried out on in primary human periodontal ligament fibroblast cells (hPDLFs) revealed that the combination of AEA, SMM-189, and HU-308 can diminish the production of pro-inflammatory cytokines, IL-6 and MCP-1. This effect seems to be carried out through the CB2 receptor, which is known to increase during inflammation. Further investigations showed that these derivatives inhibit the production of several other major inflammatory agents, including PS, TNF-α, and IL-1β IL-6 and MCP-10 [24,106]. Furthermore, it was observed that the level of GM-CSF and CCL3, two major cytokines which trigger macrophage accumulation and activation and therefore, tumor invasion, were lowered in conditioned medium of CBD-treated TNBC cancer cells and the migration of RAW 264.7, a monocyte/macrophage cell-line, to TNBC cancer cells which were treated with CBD, was prohibited [81]. Furthermore, treating GBM cells with CBD caused upregulation of gene and protein of death receptor DR5/TRAIL-R2 via JNK-AP1 and NF-κB activation, which ultimately increased Glioblastoma cells' sensitivity to TRAIL-induced apoptosis. CBD also notably reduced the level of PD-L1, a critical immune checkpoint agent for T-lymphocytes contributing to cancer cells' immune escape, on U87MG GBM cells' surface. This phytocannabinoid also enhanced the secretion of pro-inflammatory cytokines, IL1β, IL6, IL8, and death ligands, FAS-L and TRAIL in U87MG GBM cells [37]. It was also revealed that JWH015 can reduce tumor-associated macrophage (TAM) population and as a result, limit tumor progression and invasion in A549 non-small lung cancer cells [85].

2. Discussion

The Cannabinoid family is comprised of various natural and synthetic terpenophenolic compounds which are known to be able to regulate numerous physiological and pathophysiological procedures in our body [103,107]. These chemicals appear to perform their effects by activating cannabinoid receptors, which belong to a cell-signaling endogenous system known as the endocannabinoid system that endures alterations in several pathological conditions, including cancer [5, 108]. Hence, it was speculated that investigating the cannabinoid system, their ligands, and their contribution to cancer progression and control can be considered worthwhile in finding new alternative therapeutic approaches to cancer. Cannabinoids seem to be capable of affecting cancer cells' viability, growth, migration, and invasion through different mechanisms including limiting tumor cells' proliferation [21] and angiogenesis [74], blocking tumor-related signaling pathways [80], inducing autophagy [80], and manipulating immune responses [85] in cancer cells. One of the major anticancer mechanisms employed by cannabinoids is inhibiting cancer cells' proliferation by promoting various cell-death pathways and limiting several tumor-growth-related processes. The well-known endocannabinoid, AEA, can distort the growth of various types of cancer cells and effectively reduce their viability, namely, colorectal [21], gastric [60], and endometrial [109] cancer cells. AEA seems to be able to inhibit their proliferation and destroy cancer cells by different means, including inhibition of cell proliferation [30], induction of apoptosis [21] increasing the activity of COX-2 and ROS level [21,109], and stimulating of caspase3/7 activity [21], and cleavage of PARP, which has a pivotal role in cell survival [109]. It's s noteworthy that AEA seems to carry out its anti-cancer effects independent from conventional CB1/CB2 receptors and but dependent on TRPV1 receptors [21,109]. However, it has been also observed that AEA has performed its action by binding CB1 receptors in LSCC cells [30]. Another major endocannabinoid, 2-AG, has also been reported to induce cell death in different cancer cells by inhibiting their proliferation and inducing apoptosis. Interestingly, it seems to be more potent than its other endocannabinoid counterpart and carry out this effect by binding CB2 receptor [30]. Among the diverse phytocannabinoids, CBD has always been a favorable antitumor alternative due to its relatively high potency for eliminating cancer cells' proliferation as well as having no common psychoactive side effects of cannabinoids. CBD can induce cell death in a broad range of cancers, including glioma [31, 82], breast [20] cervical [110], and endometrial [109] cancer cell through different ways such as decreasing tumor cells' viability, proliferation, and invasion, suppressing such as ERK, AKT, and HIF1-alpha, which play an essential role in tumor growth [82], inducing apoptosis by decreasing mitochondrial oxidative metabolism and increasing the level of ROS and ceramide production, which was carried out through CB1 and independent from CB2 [31], increasing ROS and intracellular Ca [20] and increase of inflammatory cytokines [37]. Further studies confirmed the effectiveness of CBD in inducing apoptosis, which was indicated by an increase in the number of annexin V-positive tumor cells and subG0/G1 cells, overexpression caspase3/7, and p53 and increase in caspase3 [110]. In the case of xenograft tumors of human MDA-MB-231 breast carcinoma, CBD inhibited its growth and metastasis to the lungs through CB2 or TRPV1 [20]. CBD also seems to alter cell-cycle related genes and proteins such as has7a-miR and has-miR-1972, caspase2/3, GAS7, BCL2L1, SIRT2 genes [39], ATM gene, p53 and p21 protein, cyclin E, CDK2, bax [40]. The involvement of TRPV channels in triggering mechanisms underlying cancer pathogenesis has been well-documented. CBD accounts as agonists of the TRPV2 receptor that have significant effects in controlling the growth and proliferation of various cancer cells. Evidence of several functional studies revealed CBD

Table 5
The effects of cannabinoid compounds on autophagy and mitophagy in cancer cells.

Type of cannabinoid compound	Cannabinoid category	Type of cannabinoid receptor	Type of Cell line/ Human tissue	Effective dosage	Observations	Ref
THC CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Melanoma cell lines CHL-1, A375, SK-MEL- Chemotherapy-resistant BRAF/ NRAS wild-type melanoma xenograft mice models	THC: 1–5 μM THC-CBD: 0.5 μM	• Induction of non-canonical autophagy-dependent apoptosis by THC. • The effect was independent from caspase pathway and Beclin-1 or Ambra1 factors and appeared to be dependent on Atg7 gene • The activator role of THC on autophagy was not observed in Healthy melanocytes • Sativex (THC+CBD) also caused autophagy cell death and halted tumor growth in melanoma xenografts in mice.	[88]
THC	Cannabinoids from C. sativa	No CB receptor was assessed	Glioma cancer cells U87MG biopsies from recurrent glioblastoma multiform patients	5 μM (for cell studies) 6–10 μM (for intra tumorally administration in patient)	• Induction of ceramide accumulation leading to eIF2α phosphorylation • Induction of ER stress, inhibition of Akt/ mTORC axis by TRB3 and stimulation of autophagy and apoptosis.	[91]
THC CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Glioma cells U87 T98	THC:1–3 μM TMZ: 25–200 μM	• The mixture of THC and CBD limited GBM tumor growth and induced autophagy-mediated cell death in TMZ-non responsive GBM cells and xenografts. • The combination of THC, CBD and TMZ also considerably improved autophagy and cell death in GBM cells	[92]
THC	Cannabinoids from C. sativa	No CB receptor was assessed	Mouse embryonic fibroblasts (MEFs) from Trib3+/+94and Trib3−/−mice transformed with oncogenes RasV12and E1A	6 μM	• Treating TRIB-3 deficient mice with THC led to inability of this derivative for inhibiting Akt phosphorylation and its downstream target and inhibition of mTOR pathway and as a result, carrying out its antineoplastic effects.	[93]
CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Breast cancer cells MDA-MB-231	0–10 μmol/L	• CBD induced increase in ER stress, inhibition of mTOR/Akt pathway, elevation of caspase-8, apoptosis and autophagy markers, cleaved PARP and LC3-II • Induction of autophagy and mitochondrial apoptosis • ROS production was increased which facilitate induction of both autophagy and apoptosis. • Beclin-1 was cleaved and transferred to mitochondria, which induced the release of cytochrome C and apoptosis	[90]
CBD	Cannabinoids from C. sativa	TRPV2	Glioma stem-like cells	10 μM	• CBD induced the cleaved LC3-II and Beclin-1 expression in Glioma stem-like cells through TRPV2 activation	[56]
THC CBG CBN CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Breast cancer cell-lines MCF-7 MDA-MB-231	*THC: 30.13, 40.14 μM CBG: 28.40, 31.45 μM CBN: 23.22, 28.19 μM CBD: 13.82, 20.62 μM	• Alterations in cancer cells' morphology was observed, including formation of ER-derived vacuoles, lysosome expansion and increase in GRP78, a marker of ER stress. • These alterations indicated the occurrence of autophagy or para-apoptosis in breast cancer cells.	[34]
ACPA (CB1 agonist) GW (CB2 agonist)	Synthetic derivatives	No CB receptor was assessed	Pancreatic adenocarcinoma cell line Panc1	200 μM	• Increase in the ROS leading to increase in AMP/ATP ratio and AMPK activity. • Cancer cells' nucleus which were transfected with GADP caused suppression of glycolysis, followed by NADH accumulation and blockage of respiratory chain and Krebs cycle. • These alterations stimulated autophagy in Panc1 cancer cells.	[94]
JWH015 THC	Synthetic derivatives/ Cannabinoids from C. sativa	CB2 receptor	HepG2 HCC HuH-7	JWH015: 8 μM THC: 8 μM	• Autophagy was triggered in HCC and followed by apoptosis in HepG2 cells. • Autophagy was induced by TRB3 upregulation and suppression of Akt/ mTORC1 pathway as well as activation of AMPK via CaMKKB. • These effects were carried out through CB2 receptor.	[95]

(continued on next page)

Table 5 (*continued*)

Type of cannabinoid compound	Cannabinoid category	Type of cannabinoid receptor	Type of Cell line/ Human tissue	Effective dosage	Observations	Ref
					• Tumor growth and ascites was also inhibited in HCC xenograft models.	
WIN55,212-2	Synthetic derivatives	No CB receptor was assessed	Human colon cancer HT29, HCT116 and Caco-2 cells	10 lM	• ER stress was increased and as a result, apoptosis was induced. • LC3 protein was over expressed and acidic vacuoles were formed in response to cytotoxic effects of WIN. • Increased lysosomal membrane permeabilization (LMP) suspended autophagosome degradation, which was autophagic degradation markers, p62 and LC3. • PPAR-gama, which is involved in regulating autophagy influx, was downregulated at both mRNA and protein level.	[96]
WIN55,212-2 JWH-133	Synthetic derivatives	CB1/CB2 receptors	Glioblastoma biopsies and T98G LN18 LN229 U251MG U87MG T3 T10 cell-lines	**WIN: 7.36–15.70 μM, JWH133: 12.15–143.20 μM	• Autophagy and apoptosis occurred in parallel in GBM cell-lines through increase in ceramide synthesis, induction of ER stress and inhibition of Akt/ mTORC1 axis by both synthetic agonist, but WIN55,212-2 was more effective. • Autophagy was carried out through CB1 receptor. • Inhibition of autophagy improved apoptosis in GBM cells, suggesting that in this case, autophagy was a cytoprotective response in GBM cell-lines.	[61]
AM1251	Synthetic derivatives	No CB receptor was assessed	Prostate cancer cell-lines DU-145 PC3	Not stated	• Autophagy marker, LC3B-II, was increased after treatment with both agonists, indicating the occurrence of autophagy followed by late-apoptosis in PC3 cells. • The observed apoptosis was carried out in a caspase-independent manner. • Autophagy seems to be carried out via PI3K pathway / p-AKT / mTOR.	[72]
CB1 receptor	________	CB1 receptor	Adult CB1-deficient mice	______	• Down-regulation of Serine 65-phosphorylated ubiquitin as a marker of mitophagy in CB1-deficient mice • Abnormal mitochondria morphology and reduced mitophagy-like events were observed in CB1-deficient mice	[99]
AEA ACEA: JZL195:	Endocannabinoid	CB1 receptor	Renal proximal tubular cells (RPTCs	AEA: 5 μM ACEA: 5 μM JZL195: 250 nM	• CB1 receptor activation resulted in alteration in the phosphorylation of proteins involved in mitochondria fission which resulted in mitochondrial fragmentation manner and dysfunction and attenuated biogenesis in a cAMP dependent	[100]
CBD	Cannabinoids from C. sativa	TRPV4 receptor	Glioma cells	20–30 μM	• Induction of mithochondria dysfunction, mitophagy cell arrest following CBD administration in glioma human cell-lines • mitophagy induction was associated with elevation of Ca2 + influx and TRPV4 activation and its downstream mediators such as AKT-mTOR axis	[101]
CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Breast cancer cells MCF-7	1, 5, 10, 20 μM	• Mitochondria morphology and function was modulated in a dose-dependent manner following exposure to CBD through stress oxidative induction	[102]
CBD	Cannabinoids from C. sativa		Acute lymphoblastic leukemia of T lineage cells	1–100 μM	• CBD induced elevation of mitochondrial Ca2 + uptake, disruption of mitochondrial membrane potential and ATP production and ROS production • Induction of mitophagy and cancer cell death observed by CBD administration	[103]

*Indicated IC50
**Indicated EC50

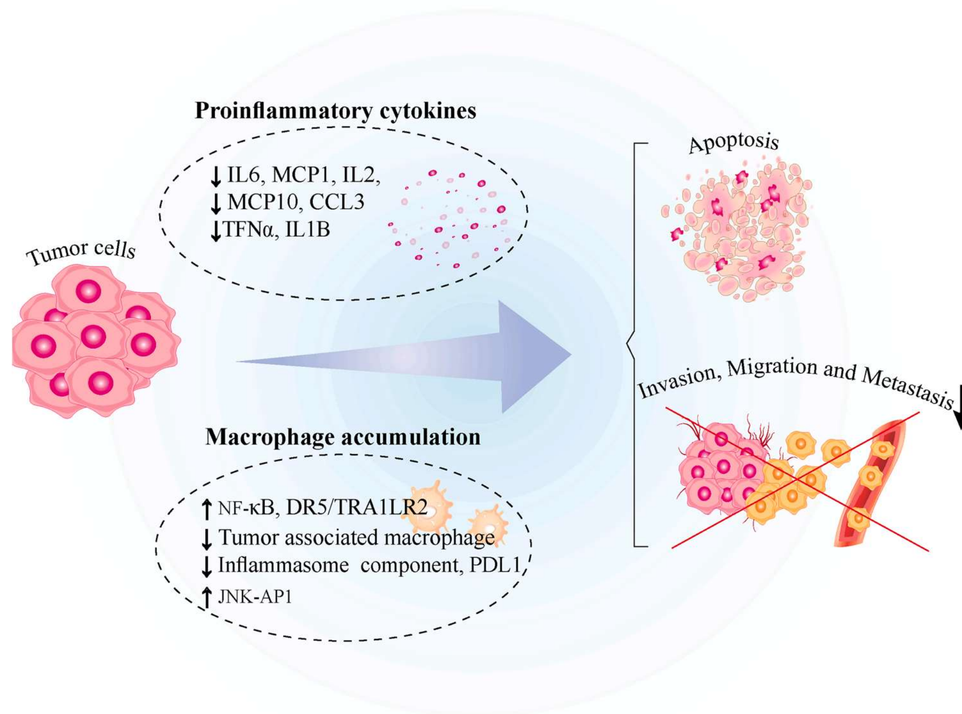

Fig. 5. Effect of cannabinoids on the immunesystem. Different types of cannabinoids alter immune responses which can affect tumor fate. They have been shown to decrease inflammatory factors such as IL-2, IL-6, MCP1, MCP10, PS, TNF-alpha, GM, CSF, CCL3, and PDL1 as well as a decrease in inflammasome formation. They inhibit cancer cells' invasion by decreasing TAM and induce apoptosis by increasing DR5 and TRAIL-R2.

Table 6
The effects of cannabinoid compounds on immune system response to tumor growth.

Type of cannabinoid compound	Cannabinoid category	Type of cannabinoid receptor	Type of Cell line/ Human tissue	Effective dosage	Observations	Ref
AEA	Endocannabinoid	CB2 receptor	Adenocarcinoma gastric cancer cells	10 μM	• Down-regulation of Inflammasome components' expression and its activation was impaired. • As a result of this effect, IL-2, which is responsible for tumor progression, was decreased.	[105]
AEA SMM-189 HU-308	Endocannabinoid/ Synthetic derivatives	CB2 receptor	Human primary periodontal ligament fibroblast cells hPDLFs	AEA:16 μM SMM-189: 13 μM HU-308: 7.3 μM	• Production of pro-inflammatory cytokines, IL-6 and MCP-1 was decreased. • The level of other major inflammatory agents, including PS, TNF-α, and IL-1β IL-6 and MCP-10 was diminished.	[106]
CBD	Cannabinoids from C. sativa	No CB receptor was assessed	Breast cancer triple-negative cells TNBC	6 μM	• GM-CSF and CCL3, two major cytokines were lowered in the medium treated with CBD which was followed by inhibition of macrophage accumulation and tumor invasion inhibition. • The migration of RAW 264.7, a monocyte/ macrophage cell-line to TNBC cells was inhibited.	[82]
CBD	Cannabinoids from C. sativa,	No CB receptor was assessed	Glioblastoma U87MG cell-line	20 μM	• The expression of DR5/TRAIL-R2 was increased via JNK-AP1 and NF-κB activation, which enhanced GBM cells' sensitivity to TRAIL-induced apoptosis. • The level of PD-L1 which contributes to cancer cells' immune escape, on U87MG GBM cells' surface was decreased. • The production level of pro-inflammatory cytokines, IL1β, IL6 and IL8, and death ligands, FAS-L and TRAIL in U87MG GBM cells was elevated.	[37]
JWH-015	Synthetic derivatives	CB2 receptor	Non-small cancer cells A549 Mesenchymal cells CALU-1 Murine cells ED1	5 μM	• The population of tumor associated macrophages were reduced and as a result, lung cancer cells' migration and invasion was suppressed.	[86]

mediated cell death, induced apoptosis and autophagy, elevated Ca^{2+} influx, increased cellular ROS level, and sensitized cancer cells to chemotherapeutic drugs in a TRPV2- dependent manner [52,55,56]. Therefore, the therapeutic potential of cannabinoids on ionotropic channels such as TRPV2 can open up new insights toward cancer pathogenesis and therapeutic approaches. In addition, synthetic cannabinoids such as CP 55,940 [60,69], WIN 55,212-2 [95,111,112], ACEA and AM281, JWH133[65], AM1251, and AM251 [67] also seem

to be capable of disrupting cancer cells' growth through various mechanisms, namely interfering with the expression of cell cycle-related factors such as p53, Bax, PPAR-gamma, ERK1/2, cyclin D1, CDK4, and p27, distorting DNA synthesis and halting cell-cycle, altering mitochondrial membrane potential, increasing the level of H2O2 and ER stress, improving caspase activity and triggering apoptosis, regulating the level of Rb and E2F1 and suppressing cancer cells' migration and invasion [60,64–68,95,112]. Interestingly, different cannabinoids seem to act synergistically and improve each other's anticancer effects on various types of tumors, including glioma [70], lymphoma [58], breast [34], bladder [35] by inhibiting their proliferation, inducing cell-cycle arrest, increasing the level of intracellular ROS, caspase activity and ultimately, apoptosis in cancer cells [33,35,58]. They also seem to act synergistically with some chemotherapeutic agents such as carboplatin [65]. Cannabinoids are also able to limit cancer cells' growth and invasion by cutting off their main source of nourishment, the formationof blood vessels. These chemicals have shown to disrupt the ability of angiogenesis in different types of tumors including glioma [70], bladder [77,113], HUVECs [16,73], thyroid, and lung cancer [74]. Different phyto, endo, or synthetic cannabinoid and their derivatives have been shown to use rather similar pathways for halting angiogenesis in tumor cells, including decreasing the level of VEGF protein, VEGF-receptor2 and related genes' expression [77], a decreaseof endothelial cell marker CD3 [70], reduction of vascular endothelial cells' proliferation, viability, migration, morphogenesis and tube formation [16,75], altering the expression of angiogenesis-related genes and pathways including p21 RAS oncogene, kip1 [74], RhoA/MLC pathway and CD31 [75]. Furthermore, the mixture of CBD and synthetic cannabinoids have also been shownto inhibit the formation of blood vessels by blocking angiogenesis-related antigenic factors such as VEGF, Ag2, and MMP2 and diminish the viability and migration of endothelial cells in tumors [113]. Cannabinoid derivatives have been shown to be capable of eliminating cancer cells and slowing down tumors' growth by suppressing several tumor-promoting signaling pathways in various types of cancers, including lung [80], breast [29,114], colorectal [79,83,115], glioma [33,84], and lymphoma [58,69]. Phytocannabinoids such as THC and CBD, synthetic cannabinoids and fractions from Cannabis *sativa* crude extract seem to be able to limit tumors' growth and invasion by blocking different signaling pathways and their downstream agents including EGFR, ERK, AKT, NF-KB, and Wnt/β-Catenin and altering the expression of various oncogenic and pro-oncogenic genes namely NFKBIZ, RRM2, SATB1, PIK3R3, AKT1, KCNN4, ATF4, and TRIB3. They also seem to be able to regulate the expression of factors controlling the cell cycle and viability including p38-MAPK, JNK, and ERK1/2, HIF-1, caspase3/9, p300/ KAT3B histone acetyltransferase, PARP, CDK and cyclinD1 proteins, c-JUN, BAX and PUMA, PINK1, and Parkin[69] as well as regulatory microRNAs such as miRNA126 and miRNA21. Cannabinoids have been shown to be able to block tumor-progressing signaling agents which are involved in cancer cells' invasion and metastasis such as MMP2/9, VCAM1, FAK, tumor-associated macrophages(TAMs), and extracellular vehicles(EVs), as well as reducing the level of Prohibin which is involved in resistance to chemotherapeutic drugs [29,33,58,79,80,82–85,112,114,115]. Inducing autophagy-de pendent death in cancer cells is another major mechanism utilized by cannabinoids for disrupting tumors' growth and invasion. Although the detailed connection between autophagy, and cancer cell death is not fully understood and is to some extent, dependent on cells' contexts and other factors, cannabinoids seem to make use of this mechanism for triggering apoptosis in various types of tumors including melanoma [87], breast cancer [34,92], glioma [88,89,66], pancreatic [116], hepatocellular [117,118] and prostate cancer [67]. Cannabinoids seems to be inducing autophagy through a mutual molecular mechanism, which is of elevation of increase in ceramide synthesis, induction of ER stress and blockage of AKT/mTOR axis by TRIB3 [66,67,88,92,119,120] which was confirmed by the increase of autophagy hallmarks, LC-II and p62 [67,92,95,118]. In some cases, however, the increase of ROS production [92,116] was also observed which promoted both autophagy and apoptosis. Notably, the autophagy induced by cannabinoids seem to be, at some points, a cytoprotective response in cancer cells which may promote or impede cell death in cancer cells depending on the cell context. It was also mentioned that TRIB3 plays a key role in directing cancer cells' fate from autophagy to apoptosis. In some cases, however, autophagy and apoptosis occur simultaneously [90]. These effects have been carried out via both CB1 and CB2 receptors, depending on the type of cells' environment [66,119]. Various types of cannabinoids can modulate immune responses of the cells as well as cancer cells. Studies have shown that AEA can effectively distort the expression of inflammasome components and decrease the level of IL-2 in gastric cancer cells [104]. Moreover, the combination of AEA, SMM-189, and HU-308 was able to notably diminish the level of pro-inflammatory cytokines, IL-6 and MCP-1 as well as inflammatory agents, including PS, TNF-α, and IL-1β IL-6 and MCP-10 in human fibroblasts [121], while CBD elevated the level of pro-inflammatory cytokines, IL1β, IL6 and IL8, and death ligands, FAS-L and TRAIL in U87MG GBM cells. treating GBM cells with this derivative, however, increased the expression of DR5/TRAIL-R2 which improved the TRAIL-L2 induced apoptosis and decreased PD-L1, a protein on cancer cells' surface that contributesto immune escaping, in U87MG GBM cells [37]. CB2 synthetic agonist, JWH-015 was also able to limit the accumulation of tumor-associated macrophages in A549 lung cancer cells and therefore, prohibit their migration [85]. Despite proofs showing the beneficial contribution of cannabinoids to immune components for inhibiting cancer cells' growth and migration, answering the challenging question of whether the effects of cannabinoids on immune components of cancer cells exclusively cause elimination of cancer cells or may promote their growth needs some additional investigations, since cannabinoids have shown to be able to kill immune cells and modulate pro-inflammatory cytokines from monocytes and, on the other hand, destroy tumor-associated macrophages and prohibit tumor invasion [122]. In addition, other possible mechanisms for the role of cannabinoids in controlling the growth of tumor cells are investigated, which are briefly mentioned here. Studies have shown that cannabinoids also seem to control cancer cell viability and migration through the regulation of exosomes and microvesicles (EMV), which are known to play a pivotal role in the transportation of oncogenic agents, promoting cancer cells' migration, progression, and resistance to chemotherapy. It was reported that treating PC3, HEPG2, and MDA-MB-231 human cancer cell lines with 1–5 μM of CBD leads to significant, dose-dependent, and cancer type-specific decrease in EMV release which seemed to be carried out through modulation of mitochondrial performance including downregulation of STAT3 and Prohibitin[123]. Although data regarding the effect of cannabinoids on EMVs are limited, this promising avenue of research is worth to be continued by future studies. miRNAs are another important regulatory mediators that received considerable attention in cancer pathogenesis and accumulating evidence provided insights regarding the miRNAs dysregulation or activation in various processes of cancer progression [124]. In terms of the association of cannabinoid compounds or receptors and miRNAs in cancer progression, it was shown that betulinic acid-induced down-regulation of miR-27a, Sp1,3, and 4 proteins and consequently reduced the expression of ErbB2 via CB1/CB2 receptors which resulted in induction of apoptosis and tumor growth suppression in breast cancer [125]. accordance, it was shown that ACEA (10 μM), AM281 (1 μM), JWH133 (10 μM), and AM630 (1 μM) cannabinoid compounds were unable to alter the expression level of miRNAs that are involved in tumor progression including miRNA-21, miRNA27a, miRNA34a, miRNA210, and miRNA423-5p in glioma cancer cell line, although glioma cells' migration was inhibited following cannabinoid exposure [65]. It was also revealed that the CB1 receptor is involved in miRNA1273g-3p-induced CRC cancer cell proliferation and invasion that is assumed to occur through activation of ERBB4/PIK3R3/mTOR/S6K2 signaling pathway [126]. In accordance, more efforts should be devoted to clarifying whether miRNAs mediate the regulatory role of

cannabinoid receptors in cancer progression.

3. Conclusion

In conclusion, cannabinoids and cannabinoid receptors contribute to tumorigenesis in different types of cancers. Therefore, cancer pathogenesis can be modulated following the action of the cannabinoid system; through influencing cell proliferation and cell death, regulating cancer cell invasion and angiogenesis also the level of the immune system response to cancer cell growth. Keeping in view the significant role of cannabinoids and cannabinoid receptors in cancer pathogenesis, more mechanistic studies are required to clarify the therapeutic potential of this system.

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CRediT authorship contribution statement

Fatemeh Hosami: Investigation; Methodology; Data curation; Writing – original draft, Maryam Haghparast Ghadimkhah and Seyedeh Sara Ghorbanhosseini: Software; Visualization, Vahid Salimi: Conceptualization; Validation; Writing – review & editing, Masoumeh Tavakoli-Yaraki: Conceptualization; Funding acquisition; Project administration; Writing – review & editing.

Declaration of Competing Interest

The authors declare that there is no conflict of interest.

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