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# Anticancer, Bioactive, & Therapeutic Applications of Cannabinoids

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***Abstract***

*Cannabinoids, a complex class of lipophilic compounds found in Cannabis sativa L., are attracting significant clinical interest for their multifaceted therapeutic potential, particularly within oncology. This review provides a comprehensive synthesis of contemporary knowledge detailing the distinct anti-cancer properties of phytocannabinoids (such as δ-tetrahydrocannabinol and cannabidiol), endogenous endocannabinoids, and synthetic analogues. Accumulating evidence from robust in vitro and in vivo oncological models demonstrates that these compounds aggressively suppress tumor progression by inhibiting cancer cell proliferation, migration, invasion, and tumor-induced angiogenesis. The cannabinoids exert their antineoplastic effects by modulating the canonical endocannabinoid system, primarily G-protein-coupled CB1 and CB2 receptors, alongside non-cannabinoid targets. These upstream interactions trigger downstream signaling cascades that downregulate the PI3K/Akt/mTOR survival pathway, stimulate de novo ceramide synthesis, and induce endoplasmic reticulum (ER) stress. Consequently, this triggers intracellular mechanisms such as cell cycle arrest, apoptosis, and autophagic cell death. The recent studies confirm cannabinoids to safely sensitize resilient tumor cells to conventional chemotherapies and mitigate treatment-induced toxicities. However, translating these promising preclinical outcomes into widespread clinical practice remains hindered by a scarcity of large-scale, well-designed human trials, stringent regulatory frameworks. This paper balances these molecular insights and cancer-specific findings against structural challenges, establishing clear directions for future translational research to optimize cannabinoid-based oncological regimens.*

**Keywords:** Angiogenesis, anticancer therapy, apoptosis, bioactive compounds, cannabis, oncology

## INTRODUCTION

*Cannabis sativa* L. has been recognized for its medicinal and commercial properties since ancient times, with documented use spanning several millennia across diverse civilizations for therapeutic, ritualistic, and industrial purposes. The plant produces over 150 active compounds known as phytocannabinoids, which have sparked renewed scientific interest due to their diverse pharmacological activities [1]. Among these, delta-9-tetrahydrocannabinol ($\Delta^9$-THC) and cannabidiol (CBD) are the most extensively studied; however, minor constituents – such as cannabinol (CBN), cannabigerol (CBG), and tetrahydrocannabivarin (THCV) – are increasingly recognized as pharmacologically relevant [2, 3]. These compounds interact with the endocannabinoid system (ECS), a complex cellular communication network essential for maintaining various biological functions and bodily homeostasis, including memory, pain perception, reproduction, bone remodeling, and immunity.

The canonical ECS comprises two primary endogenous ligands, N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), along with the $G_{i/o}$ protein-coupled transmembrane receptors $CB_1$ and $CB_2$. Beyond this core framework,

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an "extended ECS" has been delineated, encompassing endocannabinoid-degrading enzymes such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), additional G protein-coupled receptors including GPR55, members of the transient receptor potential (TRP) channel family, and peroxisome proliferator-activated receptors (PPARs) [2, 4, 5]. These additional components have been identified as possible targets for strategies to combat cancer progression, substantially broadening the therapeutic landscape beyond classical receptor-based pharmacology. Alterations in the ECS have been observed in numerous diseases, including cancer, suggesting its potential as a therapeutic target [6]. In cancer, the endocannabinoid system is altered in numerous types of tumors and can relate to cancer prognosis and disease outcome. Aberrant expression of $CB_1$ and $CB_2$ receptors, as well as dysregulated levels of endocannabinoids and their metabolizing enzymes, has been documented in malignancies ranging from glioblastoma and breast cancer to colorectal and prostate carcinomas. Such findings not only implicate the ECS in tumor pathophysiology but also underscore its potential utility as both a prognostic biomarker and a pharmacological target.

The global burden of cancer remains formidable. According to the GLOBOCAN 2020 database, lung cancer alone accounts for an estimated 2.2 million new cases annually, representing 11.4% of all cancers and 18.0% of all cancer-related deaths worldwide [3, 5]. When considered across all malignancies, the demand for novel, well-tolerated, and mechanistically distinct anticancer agents is acute, particularly given the dose-limiting toxicities and acquired resistance associated with conventional chemotherapy and radiotherapy. While the medical use of cannabis has been approved in several jurisdictions for conditions, such as chemotherapy-induced nausea and vomiting or chronic pain, its direct role as a cytotoxic anticancer agent is still under investigation. Evidence from preclinical research consistently demonstrates that cannabinoids exhibit significant antitumor activity. A substantial body of literature indicates that these compounds influence multiple stages of tumor development through diverse signaling pathways and molecular mechanisms. In particular, experimental studies have shown that cannabinoids suppress cancer cell proliferation, invasion, metastasis, angiogenesis, chemoresistance, and epithelial–mesenchymal transition (EMT). Moreover, they promote apoptosis and autophagic cell death in tumor cells while also regulating immune responses within the tumor microenvironment. Importantly, these antineoplastic effects are not limited to $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC) but also involve non-psychoactive phytocannabinoids, such as cannabidiol (CBD), and agents that inhibit endocannabinoid degradation, highlighting promising therapeutic approaches with potentially improved safety and tolerability profiles. Despite this compelling preclinical evidence, the translation of cannabinoid-based anticancer strategies into clinical practice remains in its early stages. Aspects that are still not fully understood include the precise role of the ECS in carcinogenesis, the impact of cannabinoids on the immune system in the context of cancer development, and the paradoxical stimulation of cancer cell proliferation observed under certain conditions [6]. These complexities highlight the necessity for rigorous, well-designed studies that systematically address mechanistic gaps and establish the conditions under which cannabinoids exert net antitumor effects.

This review aims to provide a comprehensive and detailed account of the current understanding of cannabinoids, their mechanisms of action in cancer, and their specific effects across different cancer types, highlighting both promising preclinical observations and the critical areas requiring further translational and clinical research [7]. By synthesizing existing evidence within a structured framework, this work seeks to inform future experimental design and support the rational development of cannabinoid-based oncological therapeutics.

## RESEARCH PLAN & METHODOLOGY

The international search databases namely Scopus, EMBASE, Googler-Scholar, Academia-Edu, Web of Science and Live-DNA were searched for screening of latest research papers evaluated for this review. The current review has been compiled following the PRISMA matrix explained as follows (Figure 1):

 

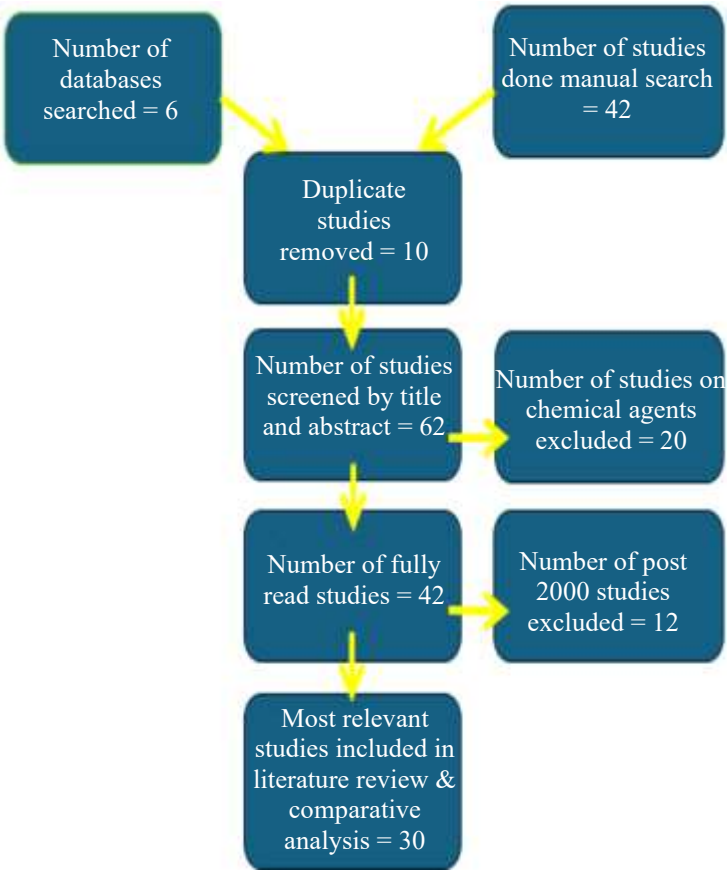


**Figure 1.** PRISMA flowchart outlining the study selection and screening process.

## TYPES OF CANNABINOIDS AND THE ENDOCANNABINOID SYSTEM (ECS)

Cannabinoids are broadly categorized into three main types: phytocannabinoids, endocannabinoids, and synthetic cannabinoids.

### Phytocannabinoids

Phytocannabinoids are naturally occurring chemical compounds derived from the *Cannabis sativa L.* plant. Over 150 distinct phytocannabinoids have been identified. The most extensively studied among them are Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Other notable phytocannabinoids include cannabigerol (CBG), cannabichromene (CBC), cannabinol (CBN), cannabidivarin (CBDV), and their acidic forms (THCA, CBDA, CBGA, CBCA, CBDVA) (Figures 2 and 3). All cannabinoids are biosynthesized from cannabigerolic acid (CBGA), which acts as the precursor to other major cannabinoids, like THCA, CBDA, and CBCA, through specific synthase enzymes [8].

**Figure 2.** The 3D chemical structure cannabigerolic acid (CBGA).

 

**Figure 3.** 3D chemical structure of phytocannabinoids Δ9-tetrahydrocannabinol (left) and cannabinol (right).

**Endocannabinoids**

Endocannabinoids are lipid-derived chemical compounds naturally produced within the human body. The two primary endocannabinoids are anandamide (AEA) and 2-arachidonoylglycerol (2-AG). These endogenous ligands are typically released on demand from membrane lipids and play crucial roles in regulating various physiological functions, including metabolic, cardiovascular, reproductive, inflammatory, immune, and pain pathways. and 2-arachidonoylglycerol (left to right)

Their activity is modulated by enzymes, like fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), which are responsible for their degradation. Modulating the activity of these enzymes is an active area of therapeutic investigation (Figure 4).

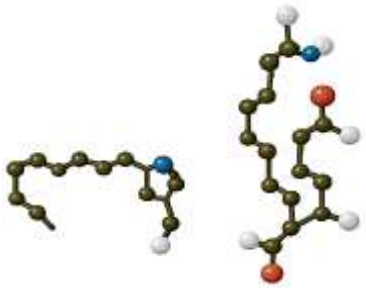

**Figure 4.** The molecular structure of endocannabinoids anandamide.

**Synthetic Cannabinoids**

Synthetic cannabinoids are compounds designed to mimic the effects of natural cannabinoids, often exhibiting high bioactivity. Examples include WIN55-212-2 (a potent CB1 receptor agonist), JWH-018, JWH-073, JWH-133 (CB receptor agonists), and SR141716 or Rimonabant (a CB1 receptor antagonist) (Figure 5). While some synthetic cannabinoids show high anticancer potential, they can also have numerous side effects.

**Figure 5.** 3D chemical structure of WIN55-212-2 a synthetic cannabinoid.

 

### Cannabinoid Receptors and Other Molecular Targets

Cannabinoids exert their effects primarily through interactions with specific receptors, termed cannabinoid receptors (CB-R) [9]. The two main types are:

- *Cannabinoid Receptor Type 1 (CB1):* Predominantly expressed in the central nervous system, but also found on mitochondria, where it regulates energy metabolism of the hippocampus and mitochondrial autophagy.
- *Cannabinoid Receptor Type 2 (CB2):* Primarily expressed in peripheral cells and cells of the immune system, modulating immune cell migration and cytokine release. Both CB1 and CB2 receptors exhibit different expression profiles across various cancer types.
- Beyond the classical CB1 and CB2 receptors, cannabinoids also interact with a range of non-cannabinoid receptors and ion channels, including:
- *G-protein-Coupled Receptor 55 (GPR55):* A "putative" cannabinoid receptor, whose activation has been reported to lead to metastasis in triple-negative breast cancer, while its antagonism by CBD can reduce proliferation of pancreatic tumor cells.
- *Transient Receptor Potential (TRP) channels:* This family includes TRPV1, TRPV2, TRPV4, TRPM8, and TRPA1. For instance, CBD induces mitochondrial dysfunction and mitophagy via TRPV4 activation in glioma cells. Cannabinoids from *C. sativa* (THC, CBD, CBGV, CBG, CBDV, CBN, THCV) induce $Ca^{2+}$ levels in TRPV2-transfected HEK293 cells, with THC and CBD showing higher potency.
- *Peroxisome Proliferator-Activated Receptors (PPARs):* Nuclear receptors – like PPARγ – are involved in the antitumoral action of cannabinoids, particularly on hepatocellular carcinoma.

## ANTICANCER MECHANISMS OF CANNABINOIDS

Cannabinoids exert their anticancer effects through a variety of molecular mechanisms, often involving modulation of cell signaling pathways and induction of cell death processes [1, 9, 10].

### Cell Cycle Arrest and Apoptosis

Many studies demonstrate that cannabinoids induce cell cycle arrest and apoptosis (programmed cell death) in various cancer cell lines.

- CBD has been shown to induce apoptosis in human leukemia cells by regulating the expression of p22phox and Nox4. In human lung cancer cells, CBD-induced apoptosis is conferred by COX-2 and PPAR-γ.
- THC can induce apoptosis in pancreatic cancer cells (MIA PaCa-2, PANC-1) by upregulating the stress-related genes p8, ATF-4, and TRIB3, which are part of the endoplasmic reticulum (ER) stress pathway (Figure 6). The p8 protein, in particular, increases with ceramide treatment and enhances anticancer effects [11].

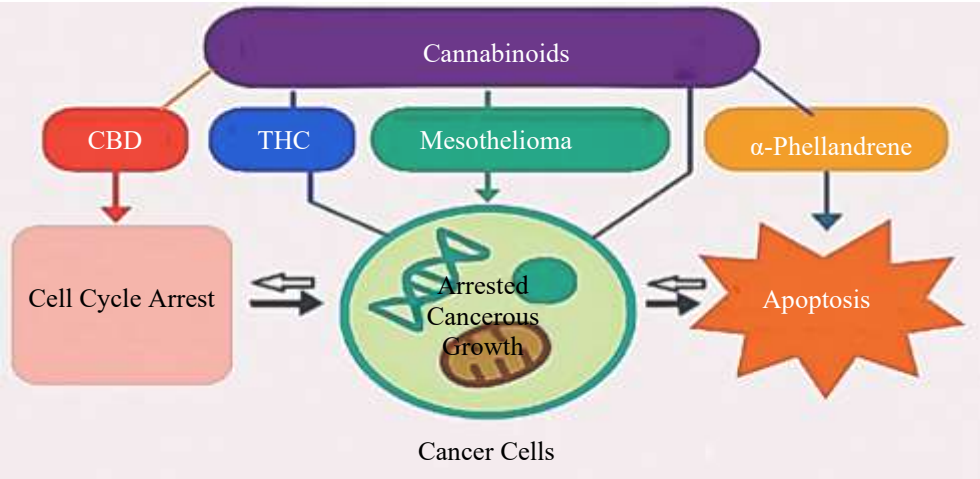


**Figure 6.** Cancer cell interactions with various cannabinoids arresting cancerous growth.

 

In mesothelioma cell lines (rat II-45, human MSTO and H2452), both CBD and CBG potently induce cell cycle arrest and apoptosis. Alpha-phellandrene, a monoterpene found in *Cannabis*, induces G0/G1 cell cycle arrest, increases reactive oxygen species (ROS) and intracellular $Ca^{2+}$, and decreases mitochondrial membrane potential in murine leukemia cells. In human liver tumor cells, it leads to necrosis by increasing nitric oxide and ROS production, and lactate dehydrogenase leakage, ultimately depleting ATP [3, 5, 7, 12].

**Induction of Autophagy and Mitophagy**

Cannabinoids are known to modulate autophagy (cellular self-digestion) and mitophagy (autophagy of mitochondria) in cancer cells. CBD tends to induce autophagy rather than apoptosis in glioma human cell lines, which is linked to mitochondrial dysfunction, mitophagy cell arrest, elevated $Ca^{2+}$ influx, and TRPV4 activation, impacting downstream mediators like the AKT-mTOR axis. In MCF7 cancer cells, CBD causes a dose-dependent increase in mitochondrial ROS production and $Ca^{2+}$ influx, leading to increased mitochondrial cleavage and induction of mitophagy/autophagy. Similar effects are seen in acute lymphoblastic leukemia cells, where CBD increases mitochondrial $Ca^{2+}$ uptake, disrupts mitochondrial membrane potential and ATP production, increases ROS, and ultimately induces mitophagy and cancer cell death [13]. THC has been reported to induce autophagy in human glioma cells (U87MG) by stimulating ER stress, which upregulates p8 and TRB3 and inhibits Akt and mTORC1. Alpha-phellandrene also induces autophagy through the downregulation of PI3K-I, mTOR, Akt, and upregulation of phosphorylated Bcl-2, PI3K-III, LC3-II, and Beclin-1.

**Modulation of Signaling Pathways**

Cannabinoids interfere with various intracellular signaling pathways critical for cancer cell growth and survival.

- *PI3K/Akt/mTOR Pathway:* This pathway is crucial for cell metabolism, growth, and survival. Cannabinoids have been shown to downregulate PI3K/Akt and ERK signaling pathways. Apigenin, a flavonoid in *Cannabis*, frequently induces apoptosis and inhibits cancer progression by downregulating NFkB, PI3K, Akt, and pAkt (Figure 7).

**Figure 7.** Image of apigenin – a flavonoid inhibitor of cancer cell growth.

- *ERK1/2 Signaling:* Activation of CB1 and CB2 receptors can stimulate ERK1/2 signaling, leading to cell cycle arrest by regulating p27, p21, cyclins D and E, cdc2, and cdk2 through an increase in pRb. CBD has also been shown to induce autophagy via ERK1/2 activation in neural cells. Hence the ERK 1/2 pathway is an important signaling unit that controls a wide range of cellular functions and may be implicated in many diseases. Understanding the exact mechanisms of this pathway may provide solution for finding targeted therapies for curing diseases like cancer [2, 6, 9, 14].
- *NF-κB Pathway:* This nuclear factor pathway is associated with various cancer-related characteristics, including immune suppression, inflammation, angiogenesis, and survival. CBD can modulate the tumor microenvironment and inhibit the EGF/EGFR pathway, which is relevant to NF-κB. Alpha-phellandrene also activates the NF-κB pathway (Figures 8 and 9).

 

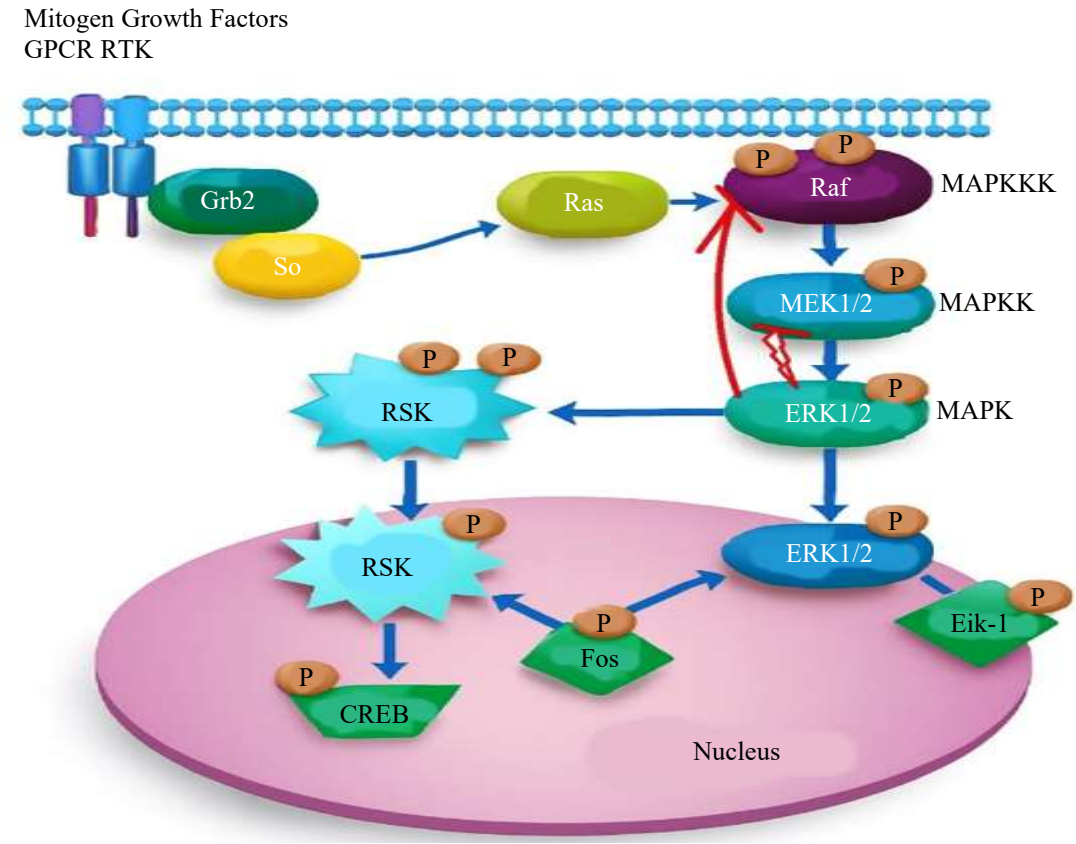


**Figure 8.** Mechanism of initiating ERK1/2 signaling by cannabinoids for arresting cancer cell growth.

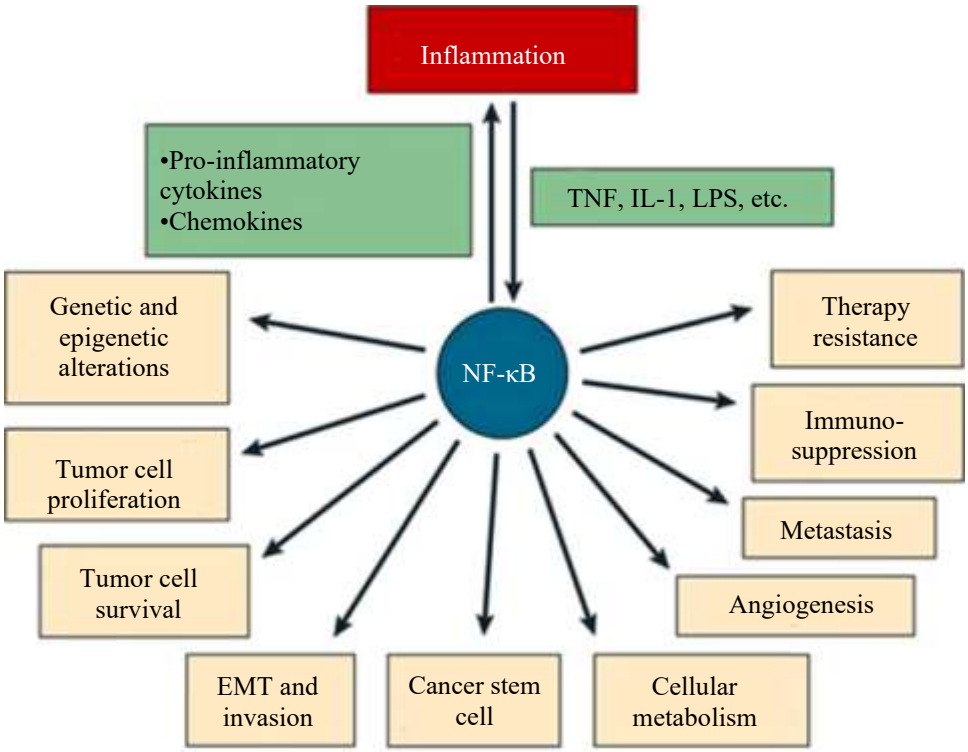


**Figure 9.** Cancer cell inactivation and apoptosis mechanism of nuclear factors initiating by cannabinoids (redrawn from Taniguchi & Karin, 2018).

 

- *ROS Production:* Increased ROS production, often triggered by cannabinoids, can disrupt cellular redox balance and promote carcinogenesis. This mechanism is linked to apoptosis and autophagy induction (Figure 9).

**Synergistic Effects**

Combinations of cannabinoids, or cannabinoids with conventional therapies, often show enhanced anticancer activity.

- *"Entourage Effect":* The various compounds in the cannabis plant (cannabinoids, terpenes, flavonoids) are believed to work synergistically to produce a more potent therapeutic effect than isolated compounds. The entourage effect refers to the idea that compounds found in cannabis – such as cannabinoids, terpenes, and flavonoids – can work synergistically, enhancing the therapeutic effect outcome compared to the effects when they are used individually.

The term entourage effect has highlighted exploring the interaction of endogenous cannabis compounds, where it was found that inactive metabolites, such as fatty acid glycerol esters, could enhance the effects of the endocannabinoid 2-Arachidonoylglycerol (Figure 10), when combined in both in vitro and *in vivo* studies [2, 8, 11, 15]. The enhanced effect observed within specific metabolite concentration ranges was described as the entourage effect and suggests a potential role in the therapeutic application of cannabis-based products. For example, botanical drug preparations were found to be more potent than pure THC in breast cancer models.

- *With Chemotherapy:* Cannabinoids can enhance the efficacy of chemotherapeutic agents. In pancreatic cancer, CB1 and CB2 receptor ligands can synergize with gemcitabine, particularly in gemcitabine-resistant cell lines, by increasing cannabinoid-induced autophagy via a ROS-mediated mechanism. Apigenin acts synergistically with paclitaxel and sorafenib to decrease cell viability and induce apoptosis in liver cancer cells. Studies have shown that apigenin can enhance paclitaxel's ability to induce apoptosis in liver cancer cells. This synergy is thought to be mediated through apigenin's ability to suppress superoxide dismutase (SOD) activity, leading to increased reactive oxygen species (ROS) and ultimately, caspase-2 activation and apoptosis [16, 17]. Apigenin also appears to work synergistically with sorafenib, another anti-cancer drug, in liver cancer cells. This combination has shown enhanced cytotoxic effects and apoptosis induction compared to either drug alone [18].

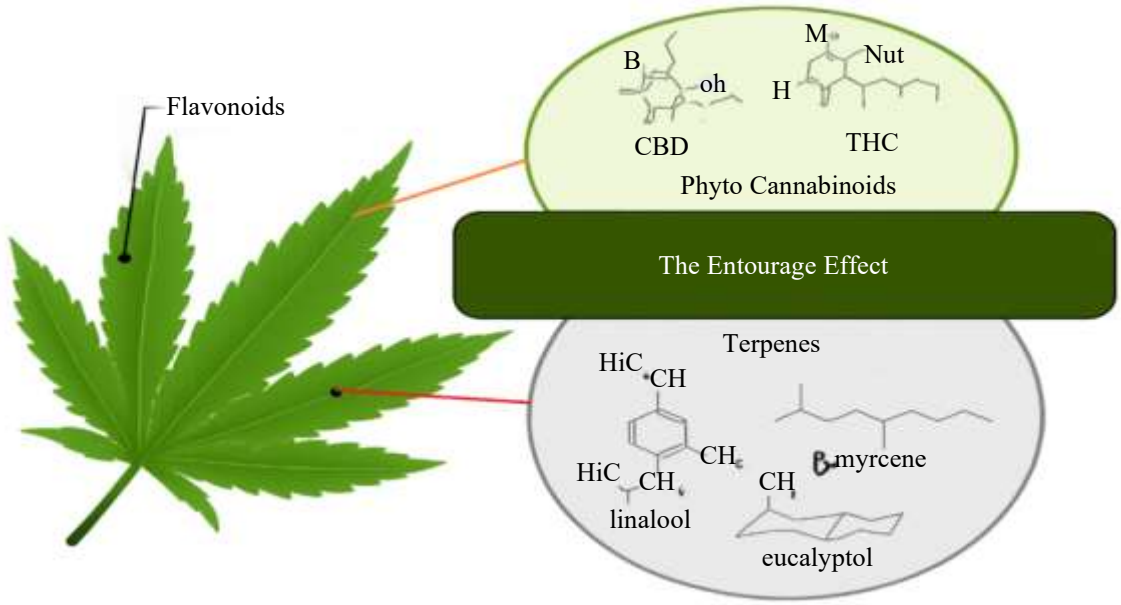


**Figure 10.** The synergistic effect of cannabinoids with flavonoids and terpenes.

 

The synergistic effect is likely due to apigenin's ability to modulate various cellular pathways involved in cancer cell survival and death. It can sensitize cancer cells to chemotherapy drugs by modulating oncogenes, AKT phosphorylation, NFκB, Nrf2, and upregulating p53 and MAPK. Additionally, it can promote apoptosis through the intrinsic and extrinsic pathways by modulating Bax/Bcl-2 ratio and activating caspases. Alpha-pinene and beta-pinene show synergistic antitumor effects with paclitaxel against non-small cell lung carcinoma (NSCLC). Caryophyllane sesquiterpenes can potentiate the cytotoxicity of doxorubicin in HepG2 cells.

## PRECLINICAL AND CLINICAL EVIDENCE BY CANCER TYPE

Preclinical studies, including in vitro cell line experiments and in vivo animal models, have provided substantial evidence for the anticancer potential of cannabinoids across various cancer types [3, 13, 16, 19]. While these findings are promising, clinical data remain limited.

### Brain Cancer (Glioma)

- CB1 receptors are expressed in the human pituitary gland and pituitary adenomas. The endocannabinoid system is altered in human gliomas, with observed changes in cannabinoid receptor expression.
- CBD has been shown to inhibit human glioma cell migration through a cannabinoid receptor-independent mechanism.
- In human glioma cell lines (U87MG, T98G, HG19), a combination of THC and CBD (1:1 ratio) significantly decreased cell viability and enhanced both apoptosis and autophagy.
- THC alone has been observed to increase autophagy and TRB3 expression in U87MG xenografts.
- A pilot clinical study involving THC in patients with recurrent glioblastoma multiforme (GBM) reported tumor regression in some cases. More recently, a clinical study investigated the safety and preliminary efficacy of nabiximols (a 1:1 THC:CBD extract) combined with dose-intense temozolomide (TMZ) in GBM patients [17], showing promising survival rates (83% at 1 year for nabiximols vs. 44% for placebo) although the study had a small sample size.

### Breast Cancer

The ECS plays a role in the body's defense against cancer growth. Preclinical studies on triple-negative breast cancer (TNBC) models highlight the antitumor effects of phytocannabinoids, which regulate cell proliferation and enhance apoptosis and autophagy through actions on cannabinoid receptors [20]. CBD has been identified as the most potent among several plant-based cannabinoids (CBD, CBG, CBC, CBDA, THC) in inhibiting proliferation in human breast cancer cell lines like MDA-MB-231 and MCF-7. Its apoptotic effects are mediated via CB2 and TRPV1 activation, or receptor-independent increases in intracellular $Ca^{2+}$ and ROS generation [21].

Omega-3 endocannabinoids, such as EPEA and DHEA, demonstrate greater antiproliferative effects in MCF-7 and MDA-MB-231 cells compared to their precursor fatty acids, without affecting the growth of non-malignant MCF-10a cells, suggesting a cancer-cell specific action. However, some studies indicate that THC may potentially increase tumor growth in breast cancer models.

### Prostate Cancer

Various phytocannabinoids, including CBD, CBG, CBC, CBN, CBDA, CBGA, CBDV, CBGV, THC, THCA, THCV, and THCVA, have been tested on human prostate cancer cell lines (LNCaP, 22RV1, DU-145, PC-3). 2-AG has been shown to inhibit the invasiveness of androgen-independent prostate cancer cell lines (PC3, DU145) through the activation of the CB1 receptor. A CBD-rich extract (CBD-E) showed tumor inhibition in subcutaneous xenografts in athymic nude mice. Alpha-pinene, a terpene, has been reported to inhibit human prostate cancer growth in a mouse xenograft model [7, 22].

### Lung Cancer

CBD induces apoptosis in human lung cancer cells via COX-2 and PPAR-γ pathways. Inhalant CBD has been shown to impede tumor growth in a human lung cancer model by decreasing tumor stemness

 

and impairing angiogenic switch. Case reports describe striking lung cancer responses to self-administration of CBD [8, 15, 23]. For example, one patient in her 80s with non-metastatic lung cancer experienced progressive shrinking of her tumor from 41 mm to 10 mm over 32 months with oral cannabis oil (20% CBD, 19.5% THC, 24% THCA).

**Hematological Cancers (Leukemia, Lymphoma, Myeloma)**

In a murine lymphoma cell line (EL-4 cells), CBD (25 mg/kg) induced maximal apoptosis mediated through the CB2 receptor. THC (5mg/kg) also showed effects in this model. In acute lymphoblastic leukemia of T lineage cells, CBD treatment leads to an increase in mitochondrial $Ca^{2+}$ uptake, disruption of mitochondrial membrane potential and ATP production, increased ROS production, and ultimately, induction of mitophagy and cancer cell death. A case report of a 14-year-old female with acute lymphoblastic leukemia who used various THC-rich extracts ("Rick Simpson oil") showed reduced blast cells. However, the patient ultimately passed away due to complications from chemotherapy, specifically bowel perforation [16, 21, 24].

**Melanoma**

Cannabinoids have been shown to reduce cell proliferation and induce apoptosis in melanoma cells. In mice with induced BRAF/NRAS wild-type tumors, THC promoted autophagy in melanoma cells [25]. CBD significantly reduced tumorigenicity and tumor size in mice with an induced B16F110 tumor. CB1 receptors are being explored as novel targets for melanoma treatment (Tables 1 and 2).

**Ovarian Cancer**

Preclinical studies have assessed the safety of CBD in ovarian and endometrial carcinoma cell lines. There's a reported case of a dramatic response to Laetrile and CBD oil in a patient with metastatic low-grade serous ovarian carcinoma [23]. Alpha-pinene has been shown to induce apoptotic cell death via caspase activation in human ovarian cancer cells.

**Pancreatic Cancer**

The endocannabinoid 2-AG suppresses pancreatic cancer cell proliferation and tumor growth *in vitro* and *in vivo*; this antiproliferative effect is CB1-receptor dependent. GPR55 is also noted to play a role, with increased expression in human pancreatic ductal adenocarcinoma specimens. THC decreases cell proliferation in MIA PaCa-2 cells via CB2 receptor and ceramide-dependent upregulation of p8, ATF-4, and TRB3 [26]. In MIA PaCa-2 xenografts, THC and JWH-133 decreased tumor growth and increased apoptosis and TRB3 expression.

**Oral Cancer/Head and Neck Squamous Cell Carcinoma (HNSCC)**

Epidemiological data concerning the association between cannabis use and oral cancer development are conflicting, requiring further investigation [27]. *In vitro* studies on oral cancer cells have revealed promising anticancer features for cannabinoids, including induction of apoptosis and inhibition of cell proliferation. The endocannabinoids docosahexaenoyl ethanolamide (DHEA) and N-arachidonoyl-L-alanine (NALA) inhibited HNSCC cell proliferation through 5-LO-mediated ROS production, which also decreased phosphorylated Akt. In contrast, THC may potentially increase tumor growth in HPV+ head and neck carcinoma (Table 1).

**Table 1.** Selected preclinical *In Vitro* and *In Vivo* effects of cannabinoids in cancer.

| Cancer type | Cannabinoid | Model (cell line/animal) | Observed effects | Mechanism/notes | Source |
|---|---|---|---|---|---|
| Giloma | THC, CBD | U87MG, T98G, HG19 cells | Decreased cell viability, enhanced apoptosis & autophagy. | Combination of THC:CBD (1:1). | 3, 14, 21 |
| | CBD | Glioma human cell-lines | Induced autophagy, mitochondrial dysfunction, mitophagy cell arrest. | Associated with Ca2+ influx and TRPV4 activation. | 14 |

 

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|---|---|---|---|---|---|
| | THC | U87MG xenografts | Increased autophagy, increased TRB3 expression. | ER stress pathway involved. | 9 |
| Breast Cancer | CBD | MDA-MB-231, MCF-7 cells | Most potent antiproliferative activity, induced apoptosis. | Via CB2/TRPV1 activation or receptor-independent Ca2+/ROS generation. | 11 |
| | EPEA, DHEA | MCF-7, MDA-MB-231 cells | Greater antiproliferative effects, no effect on non-malignant cells. | Omega-3 endocannabinoids. | |
| Prostate cancer | 2-AG | PC3, DU145 cells | Inhibition of androgen-independent cell invasion. | CB1 receptor-dependent activation. | 8 |
| | CBD-E | s.c. xenografts, mice | Tumor inhibition. | Extract (~65% CBD). | 2 |
| Lung Cancer | CBD | Human lung cancer cells | Induced apoptosis. | Via COX-2 and PPAR-γ. | 11 |
| | CBD | Human lung cancer model | Impeded tumor growth. | Decreased tumor stemness and impaired angiogenic switch. | 2, 16, 24 |
| Hematological Cancers | CBD | Murine lymphoma (EL-4) | Maximal apoptosis. | CB2-mediated. | 8 |
| | CBD | T lineage acute lymph. | Increased mitochondrial Ca2+ uptake, ROS, mitophagy, cell death. | Disruption of mitochondrial membrane potential and ATP. | 11 |
| Melanoma | THC | BRAF/NRAS wild-type mice | Promoted autophagy. | Cytotoxic autophagy. | 11 |
| | CBD | B16F110 tumor mice | Significantly reduced tumorigenicity and tumor size. | Pilot study in murine model. | 2 |
| Ovarian Cancer | CBD | Ovarian/endometrial cell lines | Preclinical safety demonstrated. | Assessed in vitro. | 2 |
| Pancreatic Cancer | THC | MIA PaCa-2, PANC-1 cells | Reduction in cell viability via apoptosis. | Via de novo synthesized ceramide upregulation of p8, ATF-4, TRIB3 ER stress genes. | 2 |
| Oral Cancer/ HNSCC | DHEA, NALA | HNSCC cell lines | Inhibited cell proliferation, decreased phosphorylated Akt. | Via 5-LO-mediated ROS production. | – |
| Mesothelioma | CBD, CBG | Rat II-45, human MSTO, H2452 cells | Most potently reduced cell viability; induced cell cycle arrest and apoptosis; inhibited migration and invasion | Neutral cannabinoids were more potent than acidic forms. Signaling pathways involved in anti-cancer effects | 15 |

**Table 2.** Selected case reports and clinical observations of cannabinoid use in cancer patients.

| Cancer type | Cannabinoid/product | Administration/dosage | Observed outcome | Source(s) |
|---|---|---|---|---|
| Glioblastoma Multiforme (GBM) | Δ9-THC | Pilot clinical study, 9 patients | Tumor regression in 2 out of 9 patients, stabilization in 4. Median survival 24 weeks vs 15 weeks (historical control). | 4 |
| | Nabiximols (THC:CBD 1:1) + TMZ | Oral spray, up to 12 sprays/day | 83% 1-year survival vs 44% for placebo (small study, N=21). | 4 |
| Lung Cancer (non-metastatic) | Cannabis oil (20% CBD, 19.5% THC, 24% THCA) | 0.5 mL PO 2–3x daily | Progressive shrinking of tumor from 41mm to 10mm over 32 months. | 8 |
| Ovarian Carcinoma (metastatic, low-grade serous) | Laetrile + CBD oil | Not specified | Dramatic response. | 7, 11 |

 

| | | | | |
|---|---|---|---|---|
| Hodgkin's Lymphoma | Five different THC-rich extracts ("Rick Simpson oil") | Over 78 days after unsuccessful bone marrow transplantation and chemotherapy | Extracts reduced blast cells, but effects varied. Patient passed away due to bowel perforation from chemotherapy. | 9 |
| Malignant Wound | Topical cannabis (8.02% CBD, 5.24% THC) | Topical treatment | Size of malignant wound decreased by ~5% over 4 weeks; significant pain relief. | 2 |
| Pain & Nausea (Cancer-related) | Dronabinol, Nabilone | Oral administration | FDA-approved for chemotherapy-induced nausea/vomiting and anorexia in AIDS patients. | 28 |
| | THC: CBD extract | Oromucosal spray | Significant pain reduction in intractable cancer-related pain refractory to strong opioids. | |

## CHALLENGES AND FUTURE PERSPECTIVES

Despite the promising preclinical findings, the path to widespread clinical adoption of cannabinoids as anticancer therapies faces significant hurdles.

- *Regulatory Obstacles:* Cannabis's classification as a Schedule I drug in many regions makes it difficult to conduct large-scale, multicenter clinical trials. Regulatory hurdles often delay research and limit access to standardized, research-grade cannabis products [28–30].
- *Lack of Robust Clinical Evidence:* There is an extensive need for more well-designed, high-quality, controlled clinical trials to confirm preclinical results and establish efficacy and safety in human cancer patients. Current clinical observations, primarily from case reports, are limited by their anecdotal nature, heterogeneity of data, lack of head-to-head comparisons, and insufficient long-term follow-up.
- *Product Inconsistency and Variability:* The effectiveness of pure cannabinoid compounds versus cannabis extracts is a subject of ongoing debate. The cytotoxic effects of CBD, THC, and extracts appear to depend not only on the specific cannabinoids and the presence of other phytochemicals but also on the nature of the cancer cell lines and test conditions. This variability makes it challenging to define consistent effective dosages and preparation methods.
- *Tumor Heterogeneity:* Tumors differ considerably in their characteristics and sensitivity to cannabinoids, implying that a "one size fits all" approach for optimal cannabinoid ratios or dosages is unlikely.
- *Pharmacokinetic Limitations:* Challenges include inconsistent drug supply, poor pharmacokinetics, and potential off-target effects of natural product-derived drugs.

## FUTURE PERSPECTIVES

Addressing these challenges requires a multifaceted approach focused on rigorous scientific investigation and interdisciplinary collaboration. Further studies are needed to characterize the precise molecular modes of action of cannabinoids, delineate efficacious dosages and routes of administration, and identify optimal synergistic regimes with conventional treatments. The role of CB receptors and cannabinoid compounds as modulators of autophagy/mitophagy in cancer cells requires more solid evidence. Successful development of natural product-derived anticancer drugs necessitates collaboration among pharmacologists, catalyst chemists, drug delivery experts, rational drug designers, and nanotechnologists. This collaborative effort can help solve problems and bottlenecks, leading to new anticancer drugs from natural products. New developments in drug delivery systems, nanotechnology, and targeted drug delivery can enhance the effectiveness and reduce the harmful effects of natural product-derived anticancer agents.

Synthetic biology and genome mining offer new avenues for natural product discovery from underexplored sources, like marine organisms and endophytic fungi, potentially revealing untapped biosynthetic potential. A better understanding of the circadian rhythmicity of the ECS, including

 

endocannabinoids and receptors, as well as the rhythmicity of cancer cell growth processes, could optimize the timing of cannabinoid administration to enhance therapeutic efficacy, similar to approaches used for canonical chemotherapeutics. Given the continuous and increasing global demand for novel anticancer drugs, natural products will remain a critically important source for discovering new, safe, and effective therapies.

## CONCLUSION

Cannabinoids, derived from *Cannabis sativa L.*, or produced endogenously or synthetically, represent a promising frontier in anticancer therapy. Preclinical evidence strongly supports their ability to inhibit cancer cell growth, induce cell death through apoptosis and autophagy, and modulate crucial signaling pathways across a diverse range of cancer types. Furthermore, their potential for synergistic effects with existing chemotherapies offers an avenue for enhancing treatment efficacy and potentially overcoming drug resistance. However, the journey from promising laboratory findings to established clinical practice is complex and ongoing. Significant gaps remain, particularly the urgent need for large-scale, well-controlled clinical trials to validate preclinical observations in human patients, establish optimal dosing, and ensure long-term safety and efficacy. As researchers continue to unravel the intricate mechanisms of the endocannabinoid system and develop innovative drug delivery strategies, cannabinoids hold the potential to become valuable components of future cancer treatment paradigms.

Consider cannabinoids in cancer treatment like a finely tuned orchestra. Each instrument (different cannabinoids, terpenes, flavonoids, and their target receptors) has its own unique sound and role. While a solo performance can be impactful, the true potential lies in how these instruments play together, creating a harmonious and powerful symphony that can effectively combat cancer while minimizing harm. The challenge now is to write the perfect score and ensure every musician plays their part flawlessly.

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