

Emerging role of cannabinoids and synthetic cannabinoid receptor 1/cannabinoid receptor 2 receptor agonists in cancer treatment and chemotherapy-associated cancer management

ABSTRACT

Cannabis was extensively utilized for its medicinal properties till the 19th century. A steep decline in its medicinal usage was observed later due to its emergence as an illegal recreational drug. Advances in technology and scientific findings led to the discovery of delta-9-tetrahydrocannabinol (THC), the primary psychoactive compound of cannabis, that further led to the discovery of endogenous cannabinoids system consisting of G-protein-coupled receptors – cannabinoid receptor 1 and cannabinoid receptor 2 along with their ligands, mainly anandamide and 2-arachidonoylglycerol. Endocannabinoid (EC) is shown to be a modulator not only for physiological functions but also for the immune system, endocrine network, and central nervous system. Medicinal research and meta-data analysis over the last few decades have shown a significant potential for both THC and cannabidiol (CBD) to exert palliative effects. People suffering from many forms of advanced stages of cancers undergo chemotherapy-induced nausea and vomiting followed by severe and chronic neuropathic pain and weight loss. THC and CBD exhibit effective analgesic, anxiolytic, and appetite-stimulating effect on patients suffering from cancer. Drugs currently available in the market to treat such chemotherapy-induced cancer-related ailments are Sativex (GW Pharmaceutical), Dronabinol (Unimed Pharmaceuticals), and Nabilone (Valeant Pharmaceuticals). Apart from exerting palliative effects, THC also shows promising role in the treatment of cancer growth, neurodegenerative diseases (multiple sclerosis and Alzheimer's disease), and alcohol addiction and hence should be exploited for potential benefits. The current review discusses the nature and role of CB receptors, specific applications of cannabinoids, and major studies that have assessed the role of cannabinoids in cancer management.

KEY WORDS: 2-Arachidonoylglycerol, analgesic, anandamide, cannabidiol, cannabinoid receptor 1, cannabinoid receptor 2, cannabinal, delta-9-tetrahydrocannabinol, endocannabinoid system

INTRODUCTION

The plant *Cannabis*, known to the human civilization since antiquity, has been frequently exploited owing to its medicinal and commercial properties. Majorly used cannabis species are *Cannabis sativa* and *Cannabis indica*. Variations are observed in properties of *Cannabis* which can be attributed to the variation in geographic and climatic factors resulting into modification of pharmacologically active ingredients which

are delta-9-tetrahydrocannabinol (THC), cannabidiol (CBD), and cannabinal (CBN). *Cannabis spp* can be categorized into psychoactive species (drug phenotype) or nonpsychoactive species (fiber phenotype) depending on the (%delta-

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9-THC + %CBN)/ (%CBD) ratio; if the ratio exceeds one then the Cannabis is regarded as psychoactive species (drug phenotype), else it is considered as fiber phenotype.^[1] The nonpsychoactive species of *C. sativa* L, known as industrial hemp (THC content <1%) is extensively cultivated and utilized in the textile, paper, and rope industries after processing. The outer layer of the hemp crop called bast fiber has industrial applications. Hemp seeds are nutritious and rich in protein and are edible.^[2] The psychoactive species of *C. sativa* and *C. indica* are known globally for their medicinal properties that are mainly due to the presence of bioactive compounds called “cannabinoids;” also, it contains active but nonpsychoactive cannabinoids such as CBD and CBN.^[3] The psychoactive cannabinoid is strictly lipid and alcohol soluble.

The cannabinoid receptor 1 (CB1) and cannabinoid receptor 2 (CB2) G-protein-coupled cannabinoid receptors in humans which mediate the prime action of phytocannabinoid have been cloned and studied in the last few decades. Autoradiographic studies, immunohistochemistry techniques, *in situ* histochemistry, and various other mapping techniques have shown abundant expression of CB1 receptors in the regions of the brain such as cortex, hippocampus, nucleus accumbens, basal ganglia, hypothalamus, amygdala, cerebellum, and retina. The highest density is observed in cerebellum, basal ganglia, and cortex and is also observed in the peripheral nervous system and peripheral organs. The CB2 cannabinoid receptor is largely localized to the cells and tissues of the immune system.^[4] Phytocannabinoid THC (a plant-derived cannabinoid) deploys its effect by mimicking the endogenous cannabinoid anandamide and 2-arachidonoylglycerol found in the human system and thereby binding specifically to the receptors of the EC with a very high affinity; also, evidences and studies indicate a possible role of various other receptors such as TRPV1, PPARs, and GPR55 in the activation of EC signaling.^[5] Numerous clinical researches conducted to exploit the therapeutic benefits of cannabinoids over the past few decades have led to an interesting discovery showing the compound to be highly potent in the treatment of alcohol addiction, antimicrobial action, bronchial asthma, depression, dysmenorrhea, glaucoma, hypertension, migraine, neuralgia, postpartum psychoses, senile insomnia, and tetanus.^[6-10] The current review discusses the nature and role of CB receptors, specific applications of cannabinoids, and major studies that have assessed the role of cannabinoids in cancer management.

ENDOCANNABINOID SYSTEM AND ITS ROLE

The chemical structures of phytocannabinoids, such as CBD, were elucidated by 1950s, isolation of THC, the primary psychoactive constituent of cannabis was first reported in 1964^[11] and cannabinoid receptor characterization was carried out in the late 1980s.^[12] A few years later, the CB1 and CB2 receptors were cloned in 1990 and 1993, respectively, leading to further studies and characterization of the EC system.^[13] Most of the endocannabinoids identified are amide,

ester, or ether derivatives of long-chain polyunsaturated fatty acids such as arachidonic acid. The selectivity for EC1 and EC2 may vary. The better-explored endocannabinoids include anandamide (N-arachidonylethanolamine) and 2-arachidonoylglycerol (2-AG). Figure 1 shows the endocannabinoid system, its functions, distribution, and components^[14] (used with permission from Elsevier).

ECs usually inhibit adenylate cyclase activity, stimulate mitogen-activated protein kinases, inhibit voltage-activated Ca²⁺ channels, and stimulate K⁺ channels (in case of CB1). Pharmacological, biochemical, and genetic approaches^[15] have elucidated roles of endocannabinoid signaling under physiological and pathological conditions as a natural tool for modulating release of neurotransmitters.^[16,17] CB1 receptors are shown to mediate neuromodulatory actions of ECs in the sensory and autonomic nervous systems, playing major roles in pain perception,^[18] gastrointestinal,^[19] respiratory,^[20] and cardiovascular^[21] functions, food intake, and reproduction.^[22]

While the presence of CB2 receptors in immune cells has been known from a long time, recent reports suggest that the cells of immune system may express functional CB1 leading to regulation of T and B cells as well as macrophages and dendritic cells.^[23-26] Recently, role of CB receptors was also suggested in case of allergic responses through inhibition of mast cell activation in the airway mucosa and skin, identified through upregulated expression in tonsils and peripheral blood immune cells of allergic patients.^[27] Various signalling pathways associated with CB1 and CB2 receptors is discussed in detail by Di Marzo *et al.*^[28] and is also summarized in Figure 2.

PROPERTIES OF CANNABINOIDS USEFUL IN CANCER MANAGEMENT

Antiemetic

Chemotherapy is often a major treatment module, even as part of combination therapies. However, chemotherapy is associated with side effects such as nausea and vomiting, also referred to as chemotherapy-induced nausea and vomiting (CINV). Antiemetic drugs administered both before and after chemotherapy to ensure minimum CINV remain ineffective. Often, release of serotonin (5-HT) from enterochromaffin cells, distributed throughout the gastrointestinal tract epithelium, provides the initial trigger for emesis. 5-HT then activates 5-HT₃ and/or 5-HT₄ receptors present on vagal primary afferent nerves. Vagal afferents may also be activated by enteric neurotransmitters leading to stimulation of circuits in the dorsal vagal complex of the brainstem. Appropriate motor responses involving activation of neuronal centers of laryngeal, salivatory, gastric, esophageal, and hypoglossal neural centers in the brainstem and spinal cord elicit typical emesis.^[29,30]

Cannabis has been known to limit nausea/vomiting since a long time.^[31] Although direct evidences for enterochromaffin cells with CB1 receptors are yet to be generated, studies

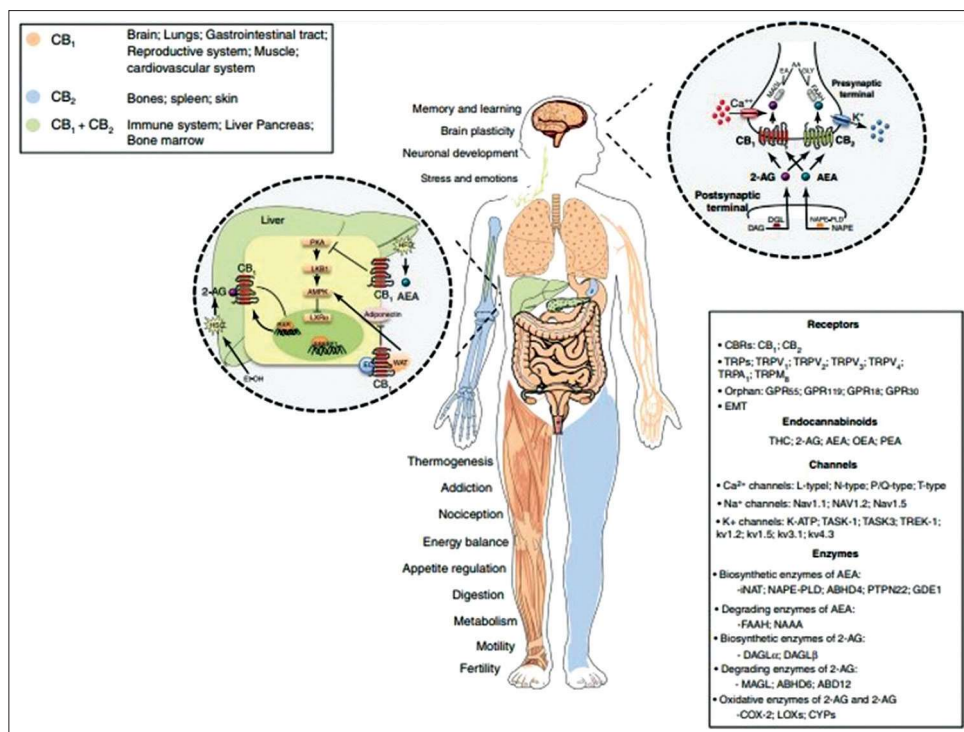


Figure 1: The endocannabinoid system: its functions, distribution, and components (reproduced with permission from Elsevier)^[14]

on house musk shrew model for vomiting have suggested that CB₁ receptor agonists may reduce intestinal release of 5-HT, thus suggesting presence of functional CB₁ receptors.^[32] For extensive details, Sharkey *et al.* and Parker *et al.* can be referred.^[33,34] In summary, the action of cannabinoids on CB₁ receptor localized in the dorsal vagal complex of the brainstem, the region of the brain that brings about the vomiting reflex, is considered responsible for the antiemetic activity of cannabinoid.^[35]

Appetite stimulation

The preparation of bhang is said to be stimulating while the potent preparation of “ganja/charas” inhibits food uptake. Due to lack of scientific knowledge and accessories, a thorough investigation could not be conducted until 1971. In the year 1971, a study conducted to observe the appetite-stimulating effect of marijuana on young volunteers in both the fed and fasting condition did result in more food intake for both types of volunteers. More than half of the patients suffering from various types of cancer and undergoing chemotherapy have expressed lack of appetite and weight loss, resulting in cachexia (wasting syndrome). Studies conducted have provided an insight into the endocannabinoid system and suggested that it might serve as a modulator in the food uptake mechanism; the reason for this could be the presence of CB₁ receptor in the hypothalamus, the region of the brain that controls food intake. Numerous studies have reported the role of THC and some other cannabinoids in appetite stimulation, resulting in weight gain, when administered orally at low or moderate doses, with minimal side effects.^[36] It is worth mentioning that Rimonabant (Acomplia) – a product of Sanofi, the first-ever

drug to act as a selective CB₁ antagonist launched in the European market in 2006 for the treatment of obesity, showed a significant amount of weight loss when used in a clinical trial.^[37] However, later studies have shown association of the drug with psychiatric complications including anxiety and depression. While 26% of the participants displayed adverse psychiatric side effects, 14% of the placebo group reported side effects. Further, patients enrolled in a different study showed the effectiveness of the drug to induce depressive symptoms, which was 2.5 times more compared to placebo.^[38]

Pain suppression

Cannabinoids for centuries have been used as analgesics and surgical anesthesia in ancient China, amelioration of childbirth pain in Israel, and also were widely recognized as potent analgesics in Asia throughout the middle age. In the 1800s, Lilly and Squibb supplied preparations made from cannabis for the treatment of chronic pain.^[39] A large population of people suffering from different types of cancer had made remarks on extreme unbearable chronic and neuropathic pain. Chronic pain mostly experienced in cancer patient originates due to the inflammatory reaction caused at the site of injury, leading to release of nociceptive component.^[35] Interaction of nociceptive component with nociceptors present at the peripheral of primary nerve fiber leads to the nociceptive neurotransmission which is projected from the spinal cord to various regions of brains such as the thalamus and parabrachial nucleus, leading to pain arousal.^[40] Analgesics currently available to treat chronic cancer-associated pain have shown severe side effects with fewer efficacies. Long-term consumption of opiates, as an analgesic, has shown dependency and in worst case scenario

as an addiction. Experimental findings and studies over the years have shown that administration of cannabinoid can lead to suppression of nociceptive stimuli.^[41] The antinociceptive effects of cannabinoid are mediated through its binding at CB1 receptor present at peripheral ends of afferent neurons, leading to suppression of noxious stimuli-induced activity in nociceptive spinal and thalamic regions. Direct application of cannabinoid to spinal nociceptive neurons and thalamic regions of the brain is feasible, resulting in obstruction of nociceptive response.^[42] Studies have suggested reversal of tactile and thermal hypersensitivity on administration of CB2 receptor agonist AM1241, leading to pathways for new research in neuropathic pain.^[43] Sativex, an oral-based phytocannabinoid formulation, is widely prescribed by physicians for its analgesic attributes in certain European countries.^[44]

CANNABINOIDS IN DIFFERENT TYPES OF CANCER

Cannabinoid-based medications currently approved and deployed in markets are synthetic THC (Dronabinol) and LY109514 (Nabilone) which are prescribed to treat nausea and vomiting in response to cancer therapy.^[45] Antineoplastic activity of cannabinoids, first reported by Munson *et al.* in mice, demonstrated inhibition in growth of Lewis lung carcinoma cells when treated orally with cannabinoids such as delta-9-THC, delta-8-THC, and CBN. CBD was also assessed for inhibitory activity but showed negative results.^[46]

ANTITUMOR EFFECT OF CANNABINOID ON GLIOMA

Glioma is the most common malignant brain cancers with a survival rate of less than a year in spite of current therapeutic approaches, i.e., radiation, surgery, and chemotherapy, which indicates current therapeutics to palliative limited, making the treatment quite ineffective and expensive, leading to exploration for a potential therapeutic alternative.^[47] Recent studies have demonstrated that cannabinoids exert potent antiproliferative activity and activate various apoptotic mechanisms eventually leading to cell death in glioma cell lines.^[48] Guzman *et al.* for the first time conducted a phase 1 pilot clinical trial to test effects of THC on patients with recurrent glioblastoma multiforme (GBM). Nine patients with recurrent GBM who had stopped responding displayed clear progression of tumor on sequential magnetic resonance imaging. Among these, two patients survived for 1 year after THC administration.^[49] Human GBM cell line SF126, U87-MG, U251, SF188, and U373-MG were showed decreased survival when exposed to both THC and WIN 55,212-2.^[50] Since some of the cannabinoids are psychoactive in nature, their usage for medicinal purposes is limited. CBD, a nonpsychoactive cannabinoid compound, was found to exert antiproliferative effects for the first time on U87 and U373 human glioma cell lines *in vivo*. Studies further conducted also suggested that the nonpsychoactive CBD does induce apoptosis.^[51] Studies have reported that combinational administration of THC and

temozolomide have shown stronger antitumoral actions on T98G, HG19 tumor xenograft, and U87MG glioma-based cell line that shows resistance toward temozolomide. Studies have also suggested enhanced autophagy.^[52] GW pharmaceuticals which focused on the production of cannabinoid-based therapeutics have been reported to be successful in phase 2 placebo-based clinical study of a proprietary combination of THC and CBD. Patients (83%) with recurrent GBM showed 1-year survival rate when administered with THC and CBD compared to placebo group where 1-year survival rate was only 53%.^[53]

ANTITUMOR EFFECT OF CANNABINOID IN PROSTATE CANCER

Sarfaraz *et al.* explored androgen-sensitive prostate adenocarcinoma cell lines such as LNCaP, CWR22Rr1, DUI45, PC3, and normal human prostate epithelial cells – PZ-HPV-7 and demonstrated higher expression for both CB1 and CB2 in adenocarcinoma prostate cancer cells compared to normal human prostate cells. The study further showed a decrease in cell viability for the LNCaP cells along with no change in cell viability for PrEC cells, when subjected to the agonist WIN-55,212,-2. Apoptosis and necrosis ensued further after cell growth inhibition for the LNCaP cell through CB1 and CB2 receptor-mediated activation by WIN-55,212,-2.^[54] Inhibition of cell growth and induction of apoptosis due to WIN-55,212-2 in LNCaP and PC3 cell were investigated separately in a different study by Sarfaraz *et al.* wherein the mechanistic basis of these phenomena was studied in detail. Treatment of LNCaP and androgenic-independent PC3 cells with WIN-55,212-2 resulted in activation and upregulation of p53 and p27 (tumor suppressors) and downregulation of cyclins D1, D2, E (cell cycle regulation), and transcription factor E2F. Reduced expression was noticed for pRb, DP1, and DP2. Further, inhibition of Akt pathways, upregulation of protein kinases extracellular signal-regulated kinase (ERK) 1/2, dose-dependent increase in Bax/Bcl-2 ratio, and downregulation of caspases 3, 6, 7, and 9 favor and induce apoptosis.^[55] Cannabis extract rich in CBD (20–70 µg/ml CBD, 10–30 µg/ml THC, and 0.4–12 µg/ml CBN) has shown a dose-dependent decrease of cell viability in prostate cancer cells – LNCaP and PC3 cells as compared with normal prostate cells – PrEC cells, along with downregulation in expression of CB1, CB2 receptor, and vascular endothelial growth factor, leading to inhibition in angiogenesis and apoptosis in prostate cancer cells.^[56] Significant cell growth inhibition followed by apoptosis was observed in PC3 cell line as well as primary prostate cancer and benign prostatic hyperplasia culture in a study which was designed to evaluate the *in vitro* effects of endocannabinoids such as 2-arachidonoyl glycerol, anandamide, and its synthetic analog methazolamide. Treatment of PC3 cell line as well as primary prostate cancer and benign prostatic hyperplasia culture with endocannabinoids resulted in an increase in number of activated caspase-3 and a reduction in the level of Bcl-2, leading to decrease in cell viability and confirming the role of apoptotic pathways; furthermore, the study showed an increase in activation of

ERK pathway and a decrease in activation of Akt pathways.^[57] DLD-1 and HT29 when investigated for apoptotic activity by synthetic CB1 and CB2 agonists – ACEA and CB13, respectively, revealed significant protein expression for both CB1 and CB2 on all three cell lines through immunofluorescence and western blot. Apoptosis-based studies have revealed reduced procaspases-3 levels and increased caspase-3 activation in DLD-1 and HT29 in response to CS12 and ACE. Apoptotic studies further revealed reduced procaspase-3 levels along with a significant increase in caspase-3 activation in DLD-1 and HT29 when subjected to CB12 and ACEA, while also mediating activation for TNF-alpha leading to *de novo* ceramide production and eventually resulting in cell death.^[58] CBD treatment of azoxymethane-induced colorectal mice model showed significant chemopreventive effects.^[59]

EFFECT OF CANNABINOID ON BLOOD CANCERS

CB1 and CB2 receptor expressing MCL cell lines – Rec-1, Jeko, and JVM-2 when treated with dose-dependent synthetic endocannabinoid methanandamide and WIN55,212-2 resulted in apoptosis. Inhibitory studies confirmed the synergetic activation of CB1 and CB2 receptor-mediated apoptosis. Mechanism of cell death, when further explored, suggested activation of CB1 and CB2 receptor through methanandamide and WIN5,212-2 led to activation of p38 followed by activation of caspase-3, ultimately leading to apoptosis in cells.^[60] A study conducted on Jurkat Leukemia T cells to determine the effects of THC also showed induction of apoptosis. Data obtained from the study suggested a critical role of Raf-1/MEK/ERK/RSK-mediated bad translocation when induced with THC, resulting into apoptosis.^[61] Treatment of human leukemia cells with CBD showed a reduction in its cell viability and apoptosis, mediated through CB2 receptor activation. Mechanistic basis of such phenomenon was obtained from leukemia cell that when exposed to CBD showed cleavage of poly (ADP-ribose) polymerase, activation of caspase-8, caspase-9, caspase-3, release of cytochrome c from mitochondria, increase in number of reactive oxygen species (ROS) as well as increase in the expression of NAD (P) H oxidases Nox4 and p22^{phox}, ultimately leading to apoptosis.^[62] A study investigating cannabinoid receptor expression in non-Hodgkin lymphoma of B types showed high mRNA expression level for CB1 and CB2 in majority of the lymphoma studied, except MCL which displayed uniform level of receptor expressions for both types such that CB1 and CB2. Furthermore, the study continued to see the effect of endogenous ligand anandamide on MCL, Burkitt lymphoma (BL), chronic lymphatic leukemia, and plasma cell leukemia cell of which except for BL all other showed cell death *in vivo*.^[63]

ANTITUMOR EFFECT OF CANNABINOIDS IN LUNG CANCER

A study conducted on CB1 and CB2 expressing nonsmall cell lung cancer cell lines such as A549 and SW-1573 when exposed to THC showed inhibition in chemotaxis, chemoinvasion, and

EGF-induced growth. Signaling pathways studied during the course suggested THC-inhibited EGF induced phosphorylation of ERK1/2, JNK1/2, AKT, and focal adhesion kinase at tyrosine 397. Additional *in vivo* studies performed on immunodeficient mouse showed a notable reduction of the subcutaneous tumor growth and lung metastasis of A549 cells when THC treated, prompting its significance as a novel therapeutic molecule in lung cancer treatment.^[64] CBD, a nonpsychotropic cannabinoid available in cannabis, when subjected to lung cancer cells – A549 and H460, resulted in upregulation of intracellular adhesion molecule 1 and increased the susceptibility of cancer here toward LAK cells, resulting in LAK-mediated cancer cell lysis.^[65]

ANTITUMOR EFFECT OF CANNABINOIDS IN BREAST CANCER

Antiproliferative and invasive potencies of natural as well as synthetic cannabinoids when tested on CB1 and CB2 receptor expressing breast cancer cell lines – MDA-MB231 and MDA-MB436 showed promising results. Of all the cannabinoids utilized in the experiment – CBD, THC, CBN, WIN55,212-2, CBG, and CP55, 940-CBD was found to be the most potent in terms of antiproliferative effects and invasiveness. Exposure of CBD concentrates to breast cancer cell lines – MDA-MD221 and MDA-MB436 led to effective Id-1 expression inhibition at the mRNA level, which in turn led to inhibition of breast cancer cell invasiveness for the cell lines studied.^[66] Mechanistic basis of phenomenon observed in studies conducted by McAllister *et al.* (2007) revealed modulation of ERK and ROS pathways to play a pivotal role in downregulation of Id-1 gene expression when exposed to CBD, ultimately leading to inhibition of growth and invasiveness in breast cancer cell lines studied.^[67] Breast cancer can be categorized into many subtypes, of which breast tumor expressing epidermal growth factor receptor (EGFR) constitutes one such type. EGFR family further consists of four different members (ErbB1/HER1/EGFR, ErbB2/HER2, ErbB3/HER3, and ErbB/HER4), all of which demonstrate oncogenic processes on their activation.^[68] ErbB2/HER2-positive breast cancer is shown to be aggressive and resistant to existing therapeutic approaches.

A study examining the presence of cannabinoid receptor and effects of cannabinoid THC and JWH-133 on 87 breast cancer tumors showed the presence of CB2 receptor expression in 91% ErbB2-positive breast tumor; furthermore, effects of cannabinoids studied in an ErbB2-driven MMTV-neu mouse model for metastatic breast cancer revealed that cannabinoid induced antitumoral effect brought about by akt pathway regulation. Clinical evidences showed a decrease in metastasis of breast cancer to the lungs.^[69]

ANTITUMOR EFFECTS OF CANNABINOIDS IN ORAL CANCER

A human oral cancer cell line (Tu183), overexpressing bcl-2 and highly resistant to anticancer drugs, was subjected to delta-9-THC and delta-8-THC. Findings suggested cellular respiration inhibition to be more effective by delta-9-THC.

Tu183 when treated with anandamide showed no such effect.^[70]

ANTITUMOR EFFECTS OF CANNABINOIDS IN LIVER CANCER

The exposure of delta-9-THC and JWH-015 on hepatocellular carcinoma cell lines – HepG2 and HuH-7 resulted in autophagy and apoptosis, mediated through activation of the CB2 receptor. Mechanistic basis when studied suggested upregulation of TRB3 and activation of AMPK responsible in bringing about the autophagy.^[71]

CANNABINOID RECEPTOR 1/CANNABINOID RECEPTOR 2 AGONISTS AS POTENTIAL ANTICANCER AGENTS

JWH-133, a selective cannabinoid receptor 2 agonist, as a potent anticancer agent

In 1999, Huffman *et al.* synthesized several 1-deoxy-delta-8-THC analogues, of which a significant affinity for CB2 receptor was displayed by 3-(10, 10-dimethyl butyl)-1-deoxy-D8-THC ($K_i = 677\text{nM}$) as compared to that for

CB1 receptor ($K_i = 3.4\text{nM}$).^[72] In 2001, inhibition of cancer cell growth *in vivo* due to JWH-133 was conducted and reported by Sanchez *et al.* who found a significant regression of C6 glioma cell in mice injected intratumorally with 50 $\mu\text{g}/\text{day}$ of JWH-133 compared to control animals. Proliferation of human astrocytomas *in vivo* by selective CB2 activation was also demonstrated. Later investigation suggested that *de novo* synthesis of ceramide on selective activation of the CB2 receptor triggered apoptosis of C6 glioma cells *in vivo*.^[73] Caffarel *et al.* reported a noticeable reduction in tumor growth and blood vessels in mice model when administered with THC and JWH-133 separately.^[69] Considerable growth inhibition of malignant tumor cell was reported by Casanova *et al.* in nude mice, which was administered with JWH-133 (CB2 selective agonist). Tumor induction in the respective nude mice was made possible after successful inoculation of PDVC.C57 epidermal tumor cells.^[74] JWH-133 at a nontoxic concentration (10^{-5} – 10^{-8} M) showed inhibition of colony formation in A549 cells (nonsmall lung cancer) and human umbilical vein endothelial cells (HUVECs); also, it was successful in inducing DNA fragmentation in A549 cells and in inhibiting steps involved in angiogenesis.^[75]

WIN 55,212-2-A NONSELECTIVE CANNABINOID RECEPTOR 1/ CANNABINOID RECEPTOR 2 AGONIST EXHIBITING ANTICANCER ACTIVITY

WIN55,212-2 is an aminoalkylindole derivative which is a synthetic nonselective agonist for both CB1 and CB2 receptors.^[45] While several roles of WIN 55,212-2 have already been described in previous sections, additional roles and effects are described here. Dose-dependent timely administration of WIN 55,212-2 in rat C6 glioma cells led to the apoptosis of glioma cells and was reported by Ellert-Miklaszewska *et al.*^[76] Combinational effect of WIN55,212-2 and radiation was carried out on human MCF-7 and MDA-MB231 cells and murine 4T1 breast cancer cells by Emery *et al.* who reported effective antiproliferative combinatorial effects in all the cells, compared to effect of only one agent; further studies also suggested that WIN55,212-2 either alone or in combination with radiation promoted growth arrest but not death of tumors in the cell lines.^[77]

While cannabinoids have shown several encouraging properties in various studies, their therapeutic monitoring becomes equally important when being used for cancer management. While several analytical techniques, including thin layer chromatography, gas chromatography, and mass spectrometry, have been used to determine and identify cannabinoid, both natural and synthetic,^[78] not all of them might be suitable for measuring therapeutic response and residual content in body fluids. In the recent decades, spectroscopy-based techniques, especially Raman spectroscopy, have shown immense potential in diagnosis as well as therapeutic monitoring of several biomedical conditions, including cancers.^[79-84] An advancement on Raman spectroscopy, known as surface-enhanced Raman

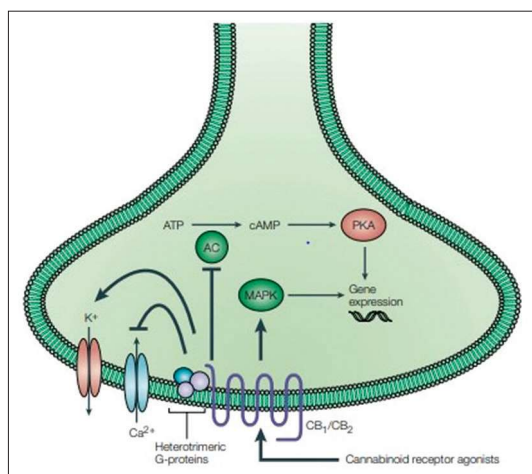


Figure 2: Major signaling pathways associated with cannabinoid receptor activation by agonists. Activation of both cannabinoid CB1 and CB2 receptors and the subsequent stimulation of Gi/o heterotrimeric proteins is well known to be coupled to inhibition of adenylate cyclase with corresponding inactivation of the protein kinase A phosphorylation pathway or to stimulation of mitogen-activated protein kinase. These intracellular events lead to, among other effects, the regulation of expression of several genes. However, more complex protein phosphorylation cascades - specifically, those involving phosphoinositide-3-kinase and protein kinase B - are also proposed to be triggered by CB1 receptors. Furthermore, stimulation, rather than inhibition, of AC by CB1, but not CB2, receptors, through Gs proteins, has also been described occasionally. CB1, but not CB2, receptor stimulation of Gi/o proteins is also directly coupled to inhibition of voltage-activated Ca^{2+} channels and stimulation of inwardly rectifying K^{+} channels in neurons, with subsequent inhibition of neurotransmitter release. The choice between which of these pathways is modulated by cannabinoid receptor activation also depends on the type of agonist under study. Reused with permission from Di Marzo *et al.*^[28] Springer Nature. cAMP = Cyclic AMP, CB1 = Cannabinoid receptor 1, CB2 = Cannabinoid receptor 2

Table 1: Some natural and synthetic cannabinoid-based pharmaceutical drugs

Drugs	Manufacturer	Constituent	Prescribed for	Legality by country	References
Sativex	GW pharmaceuticals	THC and CBD	Analgesic in cancer management multiple sclerosis	European Countries	[17]
Dronabinol/marinol	Unimed pharmaceuticals	Synthetic delta-9-THC	Chemotherapy-induced nausea	USA, Germany, Canada, and Australia	[18]
Nabilone/cesamet	Valeant pharmaceuticals international	Synthetic delta-9-THC	Antiemetic, analgesic, chemotherapy-induced nausea	UK, Europe, and USA	[18]

THC=Delta-9-tetrahydrocannabinol, CBD=Cannabidiol

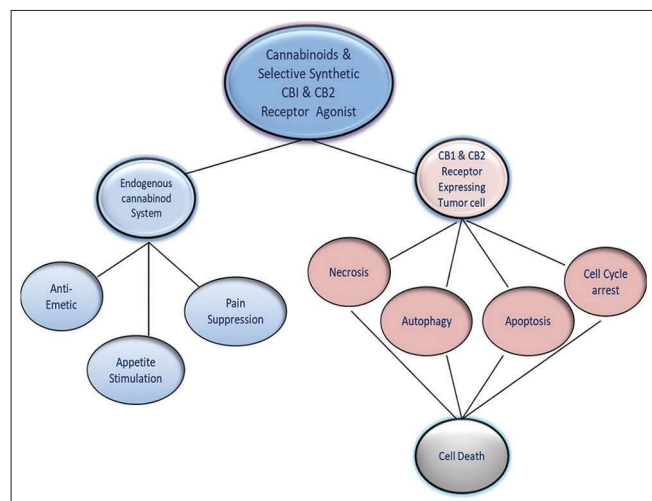


Figure 3: Anticancer and palliative effects of cannabinoids and their synthetic receptor agonists

spectroscopy (SERS) has been shown to detect very small amount of metabolites and molecules. Recent studies have also explored SERS for selection as well as toxicological analysis of cannabinoid derivatives.^[85,86] Table 1 represents some natural and synthetic cannabinoid-based pharmaceutical drugs. Figure 3 represents overall summary of anticancer and palliative effects of cannabinoids and their synthetic receptor agonists.

CONCLUSION

Despite research since decades, treatment for cancers using different classes of compounds such as alkylating agent, alkyl sulfonates, radioisotopes, cytotoxic antibiotics, antimetabolic and miscellaneous agents such as cisplatin and 1-asparaginase,^[87] the utilization of THC and their derivatives is still unexplored pharmacologically owing to their “habit-forming” nature. Specific targeting of cannabinoid receptors can be used to manage severe side effects during chemotherapy, palliative care, and overall cancer management. Furthermore, research evidences on cannabinoids have suggested tumor inhibiting and suppressing properties which warrant reconsidering legality of the substance. Studies on CB1 and CB2 receptors, in case of cancers, have demonstrated the psychoactive constituents of cannabinoids to be potent against tumor growth. Interestingly, studies have also shown that activation of CB1 and CB2 cannabinoid receptors by their respective synthetic agonists tends to limit human cancer cell growth,

suggesting the role of the endocannabinoid system as a novel target for treatment of cancers. Further explorations are required to exploit cannabinoids for an effective cancer management.

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Conflicts of interest

There are no conflicts of interest.

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