CBD: Chemo-induced neuropathy and myopathy

Mol Med. 2015 Jan 6;21:38-45. doi: 10.2119/molmed.2014.00261.

Cannabidiol Protects against Doxorubicin-Induced Cardiomyopathy by Modulating Mitochondrial Function and Biogenesis.

Hao E1,2, Mukhopadhyay P1, Cao Z1, Erdélyi K1, Holovac E1, Liaudet L3, Lee WS1,4, Haskó G5, Mechoulam R6, Pacher P1.

Abstract
Doxorubicin (DOX) is a widely used, potent chemotherapeutic agent; however, its clinical application is limited because of its dose-dependent cardiotoxicity. DOX's cardiotoxicity involves increased oxidative/nitrative stress, impaired mitochondrial function in cardiomyocytes/endothelial cells and cell death. Cannabidiol (CBD) is a nonpsychotropic constituent of marijuana, which is well tolerated in humans, with antioxidant, antiinflammatory and recently discovered antitumor properties. We aimed to explore the effects of CBD in a well-established mouse model of DOX-induced cardiomyopathy. DOX-induced cardiomyopathy was characterized by increased myocardial injury (elevated serum creatine kinase and lactate dehydrogenase levels), myocardial oxidative and nitrative stress (decreased total glutathione content and glutathione peroxidase 1 activity, increased lipid peroxidation, 3-nitrotyrosine formation and expression of inducible nitric oxide synthase mRNA), myocardial cell death (apoptotic and poly[ADP]-ribose polymerase 1 [PARP]-dependent) and cardiac dysfunction (decline in ejection fraction and left ventricular fractional shortening). DOX also impaired myocardial mitochondrial biogenesis (decreased mitochondrial copy number, mRNA expression of peroxisome proliferator-activated receptor γ coactivator 1-alpha, peroxisome proliferator-activated receptor alpha, estrogen-related receptor alpha), reduced mitochondrial function (attenuated complex I and II activities) and decreased myocardial expression of uncoupling protein 2 and 3 and medium-chain acyl-CoA dehydrogenase mRNA. Treatment with CBD markedly improved DOX-induced cardiac dysfunction, oxidative/nitrative stress and cell death. CBD also enhanced the DOX-induced impaired cardiac mitochondrial function and biogenesis. These data suggest that CBD may represent a novel cardioprotective strategy against DOX-induced cardiotoxicity, and the above-described effects on mitochondrial function and biogenesis may contribute to its beneficial properties described in numerous other models of tissue injury.
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Cymene: a terpene found in PoP hemp extract tablets, acts on tumors

Biol Pharm Bull. 2016;39(8):1247-53. doi: 10.1248/bpb.b15-00827.

Novel Antitumor Invasive Actions of p-Cymene by Decreasing MMP-9/TIMP-1 Expression Ratio in Human Fibrosarcoma HT-1080 Cells.

Li J1, Liu C, Sato T.
Author information

Abstract
p-Cymene (4-isopropyltoluene) has been reported to have beneficial actions such as anti-inflammatory and antinociceptive activities. To evaluate whether p-cymene exhibits antitumor invasive actions, we examined the effects of p-cymene on the production of matrix metalloproteinase 9 (MMP-9)/gelatinase B and tissue inhibitor of metalloproteinases-1 (TIMP-1) in human fibrosarcoma HT-1080 cells. p-Cymene was found to dose-dependently inhibit the 12-O-tetradecanoylphorbol 13-acetate (TPA)-augmented production and gene expression of MMP-9 in HT-1080 cells. In contrast, p-cymene enhanced the TPA-augmented production and gene expression of TIMP-1 in HT-1080 cells. However, there was no change in the constitutive level of MMP-9 and TIMP-1 mRNAs and TIMP-1 protein in p-cymene-treated cells. In addition, we found that the in-vitro TPA-augmented invasiveness of HT-1080 cells was inhibited by p-cymene in a dose-dependent manner. Furthermore, p-cymene was found to suppress the constitutive and/or TPA-augmented phosphorylation of extracellular signal-regulated kinase (ERK)1/2 and p38 mitogen-activated protein kinase (MAPK) in HT-1080 cells. Thus, these results provide novel evidence that p-cymene is an effective candidate for the prevention of tumor invasion and metastasis through mechanisms that include the inhibition of MMP-9 expression and the augmentation of TIMP-1 production along with the suppression of ERK1/2 and p38 MAPK signal pathways in tumor cells.

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Caryophyllene: a terpene prevalent in PoP tablets, and cancer

Antiinflamm Antiallergy Agents Med Chem. 2014 Mar;13(1):45-55.

Beta caryophyllene and caryophyllene oxide, isolated from Aegle marmelos, as the potent anti-inflammatory agents against lymphoma and neuroblastoma cells.

Sain S, Naoghare PK, Devi SS, Daiwile A, Krishnamurthi K, Arrigo P, Chakrabarti T1.
Author information

Abstract
Aegle marmelos (Indian Bael) is a tree which belongs to the family of Rutaceae. It holds a prominent position in both Indian medicine and Indian culture. We have screened various fractions of Aegle marmelos extracts for their anticancer properties using in vitro cell models. Gas chromatography-Mass spectrometry (GC-MS) was employed to analyze the biomolecules present in the Aegle marmelos extract. Jurkat and human neuroblastoma (IMR-32) cells were treated with different concentrations of the fractionated Aegle marmelos extracts. Flow cytometric analysis revealed that optimal concentration (50 µg/ml) of beta caryophyllene and caryophyllene oxide fractions of Aegle marmelos extract can induce apoptosis in Jurkat cell line. cDNA expression profiling of pro-apoptotic and anti-apoptotic genes was carried out using real time PCR (RT-PCR). Down-regulation of anti-apoptotic genes (bcl-2, mdm2, cox2 and cmyb) and up-regulation of pro-apoptotic genes (bax, bak1, caspase-8, caspase-9 and ATM) in Jurkat and IMR-32 cells treated with the beta caryophyllene and caryophyllene oxide fractions of Aegle marmelos extract revealed the insights of the downstream apoptotic mechanism. Furthermore, in-silico approach was employed to understand the upstream target involved in the induction of apoptosis by the beta caryophyllene and caryophyllene oxide fractions of Aegle marmelos extract. Herein, we report that beta caryophyllene and caryophyllene oxide isolated from Aegle marmelos can act as potent anti-inflammatory agents and modulators of a newly established therapeutic target, 15-lipoxygenase (15-LOX). Beta caryophyllene and caryophyllene oxide can induce apoptosis in lymphoma and neuroblastoma cells via modulation of 15-LOX (up-stream target) followed by the down-regulation of anti-apoptotic and up-regulation of pro-apoptotic genes.

CBD: Lung cancer and COX-2 (inflammation)

Mol Cancer Ther. 2013 Jan;12(1):69-82. doi: 10.1158/1535-7163.MCT-12-0335. Epub 2012 Dec 7.

COX-2 and PPAR-γ confer cannabidiol-induced apoptosis of human lung cancer cells.

Ramer R1, Heinemann K, Merkord J, Rohde H, Salamon A, Linnebacher M, Hinz B.
Author information

Abstract
The antitumorigenic mechanism of cannabidiol is still controversial. This study investigates the role of COX-2 and PPAR-γ in cannabidiol's proapoptotic and tumor-regressive action. In lung cancer cell lines (A549, H460) and primary cells from a patient with lung cancer, cannabidiol elicited decreased viability associated with apoptosis. Apoptotic cell death by cannabidiol was suppressed by NS-398 (COX-2 inhibitor), GW9662 (PPAR-γ antagonist), and siRNA targeting COX-2 and PPAR-γ. Cannabidiol-induced apoptosis was paralleled by upregulation of COX-2 and PPAR-γ mRNA and protein expression with a maximum induction of COX-2 mRNA after 8 hours and continuous increases of PPAR-γ mRNA when compared with vehicle. In response to cannabidiol, tumor cell lines exhibited increased levels of COX-2-dependent prostaglandins (PG) among which PGD(2) and 15-deoxy-Δ(12,14)-PGJ(2) (15d-PGJ(2)) caused a translocation of PPAR-γ to the nucleus and induced a PPAR-γ-dependent apoptotic cell death. Moreover, in A549-xenografted nude mice, cannabidiol caused upregulation of COX-2 and PPAR-γ in tumor tissue and tumor regression that was reversible by GW9662. Together, our data show a novel proapoptotic mechanism of cannabidiol involving initial upregulation of COX-2 and PPAR-γ and a subsequent nuclear translocation of PPAR-γ by COX-2-dependent PGs.

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CBD: Cancer

Cell Death Dis. 2013 Dec 5;4:e949. doi: 10.1038/cddis.2013.471.

Direct modulation of the outer mitochondrial membrane channel, voltage-dependent anion channel 1 (VDAC1) by cannabidiol: a novel mechanism for cannabinoid-induced cell death.

Rimmerman N1, Ben-Hail D, Porat Z, Juknat A, Kozela E, Daniels MP, Connelly PS, Leishman E, Bradshaw HB, Shoshan-Barmatz V, Vogel Z.
Author information

Abstract
Cannabidiol (CBD) is a non-psychoactive plant cannabinoid that inhibits cell proliferation and induces cell death of cancer cells and activated immune cells. It is not an agonist of the classical CB1/CB2 cannabinoid receptors and the mechanism by which it functions is unknown. Here, we studied the effects of CBD on various mitochondrial functions in BV-2 microglial cells. Our findings indicate that CBD treatment leads to a biphasic increase in intracellular calcium levels and to changes in mitochondrial function and morphology leading to cell death. Density gradient fractionation analysis by mass spectrometry and western blotting showed colocalization of CBD with protein markers of mitochondria. Single-channel recordings of the outer-mitochondrial membrane protein, the voltage-dependent anion channel 1 (VDAC1) functioning in cell energy, metabolic homeostasis and apoptosis revealed that CBD markedly decreases channel conductance. Finally, using microscale thermophoresis, we showed a direct interaction between purified fluorescently labeled VDAC1 and CBD. Thus, VDAC1 seems to serve as a novel mitochondrial target for CBD. The inhibition of VDAC1 by CBD may be responsible for the immunosuppressive and anticancer effects of CBD.

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10.1038/cddis.2013.471

CBD: chemo-pain

J Pain Symptom Manage. 2014 Jan;47(1):166-73. doi: 10.1016/j.jpainsymman.2013.02.018. Epub 2013 Jun 4.

A double-blind, placebo-controlled, crossover pilot trial with extension using an oral mucosal cannabinoid extract for treatment of chemotherapy-induced neuropathic pain.

Lynch ME1, Cesar-Rittenberg P2, Hohmann AG3.
Author information

Abstract
CONTEXT:
Neuropathic pain caused by chemotherapy limits dosing and duration of potentially life-saving anti-cancer treatment and impairs quality of life. Chemotherapeutic neuropathy responds poorly to conventional treatments, and there is an urgent medical need for new treatments. Recent preclinical studies demonstrate that cannabinoid agonists suppress established chemotherapy-evoked neuropathy.
OBJECTIVES:
This was a pilot trial to begin to investigate a currently available cannabinoid agent, nabiximols (oral mucosal spray containing cannabinoids), in the treatment of chemotherapy-induced neuropathic pain.
METHODS:
A randomized, placebo-controlled crossover pilot study was done in 16 patients with established chemotherapy-induced neuropathic pain. A 0-10 point numeric rating scale for pain intensity (NRS-PI) was used as the primary outcome measure.
RESULTS:
When examining the whole group, there was no statistically significant difference between the treatment and the placebo groups on the NRS-PI. A responder analysis demonstrated that there were five participants who reported a two-point or greater reduction in pain that trended toward statistical significance and the number needed to treat was five.
CONCLUSION:
Chemotherapy-induced neuropathic pain is particularly resistant to currently available treatments. This pilot trial found a number needed to treat of five and an average decrease of 2.6 on an 11-point NRS-PI in five "responders" (as compared with a decrease of 0.6 with placebo) and supports that it is worthwhile to study nabiximols in a full randomized, placebo-controlled trial of chemotherapy-induced neuropathic pain.

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KEYWORDS:
Neuropathic pain; cannabinoids; chemotherapy; randomized controlled trial
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Anandamide - pain relief

Anandamide suppresses pain initiation through a peripheral endocannabinoid mechanism.

Nat Neurosci. 2010 Oct;13(10):1265-70. doi: 10.1038/nn.2632. Epub 2010 Sep 19. **Author information**

Abstract

Peripheral cannabinoid receptors exert a powerful inhibitory control over pain initiation, but the endocannabinoid signal that normally engages this intrinsic analgesic mechanism is unknown. To address this question, we developed a peripherally restricted inhibitor (URB937) of fatty acid amide hydrolase (FAAH), the enzyme responsible for the degradation of the endocannabinoid anandamide. URB937 suppressed FAAH activity and increased anandamide levels outside the rodent CNS. Despite its inability to access brain and spinal cord, URB937 attenuated behavioral responses indicative of persistent pain in rodent models of peripheral nerve injury and inflammation and prevented noxious stimulus-evoked neuronal activation in spinal cord regions implicated in nociceptive processing. CB_1 cannabinoid receptor blockade prevented these effects. These results suggest that anandamide-mediated signaling at peripheral CB_1 receptors controls the access of pain-related inputs to the CNS. Brain-impenetrant FAAH inhibitors, which strengthen this gating mechanism, might offer a new approach to pain therapy.

Cervical Cancer: CBD > THC

“Cannabidiol rather than *Cannabis sativa* extracts inhibit cell growth and induce apoptosis in cervical cancer cells”

North-west University, South Africa, 2016 (https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5009497/)

ABSTRACT: Background: Cervical cancer remains a global health related issue among females of Sub-Saharan Africa, with over half a million new cases reported each year. Different therapeutic regimens have been suggested in various regions of Africa, however, over a quarter of a million women die of cervical cancer, annually. This makes it the most lethal cancer amongst black women and calls for urgent therapeutic strategies. In this study we compare the anti-proliferative effects of crude extract of *Cannabis sativa* and its main compound cannabidiol on different cervical cancer cell lines.

Methods: To achieve our aim, phytochemical screening, MTT assay, cell growth analysis, flow cytometry, morphology analysis, Western blot, caspase 3/7 assay, and ATP measurement assay were conducted.

Results: Results obtained indicate that both cannabidiol and *Cannabis sativa* extracts were able to halt cell proliferation in all cell lines at varying concentrations. They further revealed that apoptosis was induced by cannabidiol as shown by increased subG0/G1 and apoptosis through annexin V. Apoptosis was confirmed by overexpression of p53, caspase 3 and bax. Apoptosis induction was further confirmed by morphological changes, an increase in Caspase 3/7 and a decrease in the ATP levels.

Conclusions: In conclusion, these data suggest that cannabidiol rather than Cannabis sativa crude extracts prevent cell growth and induce cell death in cervical cancer cell lines.

Endocannabinoid System In Brain

Cannabinoid and cannabinoid-like receptors in microglia, astrocytes, and astrocytomas.

Stella N[1].

Author information

1
University of Washington, Seattle, Washington (https://www.ncbi.nlm.nih.gov/pubmed/20468046)

Abstract: CB1 and CB2 receptors are activated by a plethora of cannabinoid compounds, be they endogenously-produced, plant-derived or synthetic. These receptors are expressed by microglia, astrocytes and astrocytomas, and their activation regulates these cells' differentiation, functions and viability. Recent studies show that glial cells also express cannabinoid-like receptors, and that their activation regulates different cell functions, but also control cell viability. This review summarizes this evidence, and discusses how selective compounds targeting cannabinoid-like receptors constitute promising therapeutics to manage neuroinflammation and eradicate malignant astrocytomas. Importantly, the selective targeting of cannabinoid-like receptors should provide therapeutic relieve [sic] without inducing the typical psychotropic effects and possible addictive properties associated with the use of Delta9-tetrahydrocannabinol, the main psychotropic ingredient produced by the plant Cannabis sativa.

CBD: Herpes-type viruses

“Cannabidiol inhibits growth and induces programmed cell death in kaposi sarcoma-associated herpesvirus-infected endothelium.”

https://www.ncbi.nlm.nih.gov/pubmed/23264851 Genes Cancer. 2012 Jul;3(7-8):512-20. doi: 10.1177/1947601912466556.

Abstract Kaposi sarcoma is the most common neoplasm caused by Kaposi sarcoma-associated herpesvirus (KSHV). It is prevalent among the elderly in the Mediterranean, inhabitants of sub-Saharan Africa, and immunocompromised individuals such as organ transplant recipients and AIDS patients. Current treatments for Kaposi sarcoma can inhibit tumor growth but are not able to eliminate KSHV from the host. When the host's immune system weakens, KSHV begins to replicate again, and active tumor growth ensues. New therapeutic approaches are needed. Cannabidiol (CBD), a plant-derived cannabinoid, exhibits promising antitumor effects without inducing psychoactive side effects. CBD is emerging as a novel therapeutic for various disorders, including cancer. In this study, we investigated the effects of CBD both on the infection of endothelial cells (ECs) by KSHV and on the growth and apoptosis of KSHV-infected ECs, an in vitro model for the transformation of normal endothelium to Kaposi sarcoma. While CBD did not affect the efficiency with which KSHV infected ECs, it reduced proliferation and induced apoptosis in those infected by the virus. CBD inhibited the expression of KSHV viral G protein-coupled receptor (vGPCR), its agonist, the chemokine growth-regulated protein α (GRO-α), vascular endothelial growth factor receptor 3 (VEGFR-3), and the VEGFR-3 ligand, vascular endothelial growth factor C (VEGF-C). This suggests a potential mechanism by which CBD exerts its effects on KSHV-infected endothelium and supports the further examination of CBD as a novel targeted agent for the treatment of Kaposi sarcoma.

CBD: Glioma

Cell Mol Life Sci. 2006 Sep;63(17):2057-66.

The non-psychoactive cannabidiol triggers caspase activation and oxidative stress in human glioma cells.

Massi P[1], Vaccani A, Bianchessi S, Costa B, Macchi P, Parolaro D.

Author information

Abstract

Recently, we have shown that the non-psychoactive cannabinoid compound cannabidiol (CBD) induces apoptosis of glioma cells in vitro and tumor regression in vivo. The present study investigated a possible involvement of caspase activation and reactive oxygen species (ROS) induction in the apoptotic effect of CBD. CBD produced a gradual, time-dependent activation of caspase-3, which preceded the appearance of apoptotic death. In addiction, release of cytochrome c and caspase-9 and caspase-8 activation were detected. The exposure to CBD caused in glioma cells an early production of ROS, depletion of intracellular glutathione and increase activity of glutathione reductase and glutathione peroxidase enzymes. Under the same experimental condition, CBD did not impair primary glia. Thus, we found a different sensitivity to the anti-proliferative effect of CBD in human glioma cells and non-transformed cells that appears closely related to a selective ability of CBD in inducing ROS production and caspase activation in tumor cells.

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16909207

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