Cannabis Health Science Studies Index

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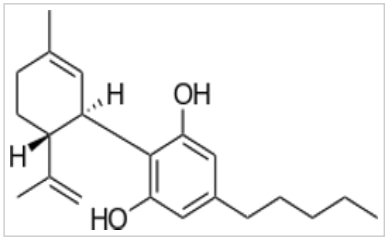

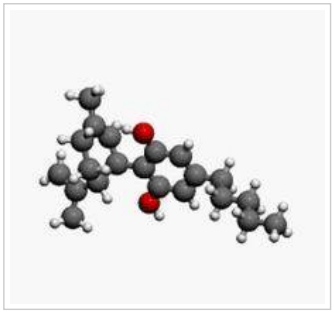

Cannabidiol (CBD) is one of at least 85 active cannabinoids identified in cannabis. It is a major phytocannabinoid, accounting for up to 40% of the plant's extract. CBD is considered to have a wider scope of medical applications than tetrahydrocannabinol (THC).

An orally-administered liquid containing CBD has received orphan drug status in the US, for use as a treatment for Dravet syndrome, under the brand name **Epidiolex** (wikipedea).

There are seed banks specializing in cannabis strains with **high CBD concentrations.**

CBD Medi Haze is Super Silver Haze crossed with old time classic of Nevil Haze then bred with the CBD parents for enrichment....read more
also see CHEMICAL COMPOSITION of Cannabis and Hemp

Science & Research

Undated - Study ~ Effects of cannabidiol derivatives on intestinal motility.
Undated - News ~ Phytocannabinoids.
Undated - News ~ ACCESSING 0.5 to 2.0 GRAMS CBD FRACTIONATING THE PHYTOCANNABINOIDS BY THEIR VAPORIZATION POINTS.
1946 - Study ~ STUDIES ON THE PHARMACOLOGY AND ACUTE TOXICITY OF COMPOUNDS WITH MARIHUANA ACTIVITY.
1971 - Study ~ Some actions of delta-1 tetrahydrocannabinol and cannabidiol at cholinergic junctions.
1972 - Study ~ A metabolic interaction in vivo between cannabidiol and Δ1-tetrahydrocannabinol.
1975 - Study ~ Interactions in man of delta-9-tetrahydrocannabinol. II. Cannabinol and cannabidiol.
1975 - Study ~ Differential effect of cannabinol and cannabidiol on THC-induced responses during abstinence in morphine-dependent rats.
1975 - Study ~ Constituents of Cannabis sativa L. VIII: Possible biological application of a new method to separate cannabidiol and cannabichromene.
1975 - Study ~ The influence of delta9-tetrahydrocannabinol, cannabinol and cannabidiol on tissue oxygen consumption.

1975 - Study ~ Absence of interaction between delta9-tetrahydrocannabinol (delta-THC) and

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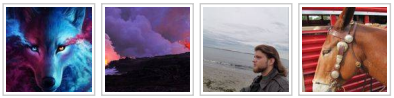

Other known Cannabinoids

2-AG
2-AGE, Noladin ether
AEA
CBC
CBL
CBDV CBG
CBN
CBV
NADA
THC
THCV
Virodhamine

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cannabidiol (CBD) in aggression, muscle control and body temperature experiments in mice.
1975 - Study ~ Anticonvulsant activity of four oxygenated cannabidiol derivatives.
1976 - Study ~ Antibacterial activity of delta9-tetrahydrocannabinol and cannabidiol.
1977 - Study ~ Cannabidiol--antiepileptic drug comparisons and interactions in experimentally induced seizures in rats.
1977 - Study ~ In vivo effects of cannabinoids on macromolecular biosynthesis in Lewis lung carcinomas.
1979 - Study ~ Interaction of cannabidiol and alcohol in humans.
1980 - Study - CHRONIC ADMINISTRATION OF CANNABIDIOL TO HEALTHY VOLUNTEERS AND EPILEPTIC PATIENTS.
1981 - Study ~ Sedative activity of cannabis in relation to its delta'-trans-tetrahydrocannabinol and cannabidiol content.
1981 - Study ~ Antiepileptic potential of cannabidiol analogs.
1981 - Study ~ The cannabinoids as potential antiepileptics.
1982 - Study ~ Effects of cannabidiol on behavioral seizures caused by convulsant drugs or current in mice.
1982 - Study ~ Anticonvulsant effects of the (-) and (+)isomers of cannabidiol and their dimethylheptyl homologs.
1983 - Study ~ Allergenic properties of naturally occurring cannabinoids.
1984 - Study ~ Ocular Hypotension, Ocular Toxicity, and Neurotoxicity in Response to Marihuana Extract and Cannabidiol.
1984 - Study ~ Stimulation of Sphingomyelin Hydrolysis by Cannabidiol in Fibroblasts from a Niemann-pick Patient.
1984 - Study -Treatment of Meige's syndrome with cannabidiol.
1985 - Study - Beneficial and adverse effects of cannabidiol in a Parkinson patient.
1985 - Study ~ The quasi-morphine withdrawal syndrome: effect of cannabinol, cannabidiol and tetrahydrocannabinol.
1986 - Study - Evaluation of cannabidiol in dystonic movement disorders.
1986 - Study - EFFECTS OF CANNABIDIOL IN HUNTINGTON'S DISEASE.
1986 - Study - Cannabidiol in dystonic movement disorders.
1986 - Study ~ Open label evaluation of cannabidiol in dystonic movement disorders.
1989 - Study ~ The inhibitory effects of cannabinoids, the active constituents of Cannabis sativa L. on human and rabbit platelet aggregation.
1990 - Study ~ Antianxiety effect of cannabidiol in the elevated plus-maze.
1994 - Study ~ Mammary excretion of cannabidiol in rabbits after intravenous administration.
1997 - Study - Neuroprotective effect of Delta9-tetrahydrocannabinol and cannabidiol.
1998 - Study ~ Cannabidiol and (−)Δ9-tetrahydrocannabinol are neuroprotective antioxidants.
1998 - News ~ Marijuana chemical tapped to fight strokes?
1998 - News ~ Cannabinoid Antioxidant Protects Brain Cells - Without the High.
2000 - Study - The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis.
2000 - Study ~ Cannabinoids might reduce spasticity in multiple sclerosis.
2000 - Study ~ Advantages of polypharmaceutical herbal cannabis compared to single ingredient, synthetic tetrahydrocannabinol.
2000 - Study ~ Variations of D9-THC content in single plants of hemp varieties.
2000 - Study ~ Neuroprotective Antioxidants from Marijuana.
2000 - Study ~ Different effects of nabilone and cannabidiol on binocular depth inversion in Man.
2000 - Study ~ Synthesis of a primary metabolite of cannabidiol.
2000 - Study ~ Cannabinoids in clinical practice.
2000 - News ~ Marijuana Extract Helps Arthritis Pain.
2001 - Study ~ Cannabinoid effects on anxiety-related behaviours and hypothalamic neurotransmitters.
2003 - Study - Anti-tumor effects of cannabidiol.
2003 - Study - Composition of the essential oils and extracts of two populations of Cannabis sativa L. ssp. spontanea from Austria.
2003 - Study ~ Composition of the essential oils and extracts of two populations of Cannabis sativa L. ssp. spontanea from Austria.
2003 - Study ~ Vasodilator actions of abnormal-cannabidiol in rat isolated small mesenteric artery.
2003 - Study ~ Cannabis and the brain.
2003 - Study ~ Post-ischemic Treatment with Cannabidiol Prevents Electroencephalographic Flattening, Hyperlocomotion and Neuronal Injury in Gerbils.
2003 - Study ~ Therapeutic potential of cannabinoids in CNS disease.
2003 - Study ~ Gamma-irradiation enhances apoptosis induced by cannabidiol, a non-psychotropic cannabinoid, in cultured HL-60 myeloblastic leukemia cells.
2003 - Study ~ Cannabidiol-transdermal delivery and anti-inflammatory effect in a murine model.

2003 - Study ~ Anti-tumor effects of cannabidiol, a non-psychotropic cannabinoid, on human glioma cell lines.
2004 - Study ~ Initial experiences with medicinal extracts of cannabis for chronic pain: Results

What is CBD?

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2004 - Study ~ Cannabidiol prevents infarction via the non-CB1 cannabinoid receptor mechanism.
2004 - Study ~ Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults.
2004 - Study - Cannabinoids Induce Cancer Cell Proliferation via Tumor Necrosis Factor {alpha}-Converting Enzyme (TACE/ADAM17)-Mediated Transactivation of the Epidermal Growth Factor Receptor.
2004 - News ~ Marijuana-like compounds may aid array of debiliating conditions ranging from Parkinson's to pain.
2005 - Study - Comparison of Cannabidiol, Antioxidants, and Diuretics in Reversing Binge Ethanol-Induced Neurotoxicity.
2005 - Study - Cannabidiol lowers incidence of diabetes in non-obese diabetic mice.
2005 - Study - Treatment with CBD in oily solution of drug-resistant paediatric epilepsies.
2005 - Study - Cannabidiol as an antipsychotic. A double-blind, controlled clinical trial on cannabidiol vs. amisulpride in acute schizophrenia.
2005 - Study ~ Cannabidiol inhibits human glioma cell migration through a cannabinoid receptor-independent mechanism.
2005 - Study ~ Cannabidiol Prevents Cerebral Infarction Via a Serotonergic 5-Hydroxytryptamine1A Receptor–Dependent Mechanism.
2005 - Study ~ Cannabinol delays symptom onset in SOD1 (G93A) transgenic mice without affecting survival.
2005 - Study ~ Peripheral, but not central effects of cannabidiol derivatives: mediation by CB(1) and unidentified receptors.
2005 - Study ~ Treatment with CBD in oily solution of drug-resistant paediatric epilepsies.
2005 - Study ~ Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease.
2005 - News ~ Chemicals in Cannabis may help mentally ill.
2006 - Study - Cannabidiol-Induced Apoptosis in Human Leukemia Cells.
2006 - Study - The non-psychoactive cannabidiol triggers caspase activation and oxidative stress in human glioma cells.
2006 - Study - Neuroprotective and Blood-Retinal Barrier-Preserving Effects of Cannabidiol in Experimental Diabetes.
2006 - Study - The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. Cannabidiol has a cerebroprotective action.
2006 - Study - Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug.
2006 - Study ~ Role of the Cannabinoid System in Pain Control and Therapeutic Implications for the Management of Acute and Chronic Pain Episodes.
2006 - Study ~ A tale of two cannabinoids: The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol.
2006 - Study ~ The effects of cannabinoids on P-glycoprotein transport and expression in multidrug resistant cells.
2006 - Study ~ Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats.
2006 - Study ~ Anxiolytic-like effect of cannabidiol in the rat Vogel conflict test.
2006 - Study ~ Differential effects of cannabis extracts and pure plant cannabinoids on hippocampal neurones and glia.
2006 - Study ~ The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells.
2006 - Study ~ Cannabidiol inhibits inducible nitric oxide synthase protein expression and nitric oxide production in beta-amyloid stimulated PC12 neurons through p38 MAP kinase and NF-kappaB involvement.
2006 - News ~ Compound found in marijuana may defend against diabetic retinopathy.
2006 - News - Cannabidiol inhibits tumour growth in leukaemia and breast cancer.
2007 - Study - The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin.
2007 - Study - Cannabidiol and (delta)9-tetrahydrocannabinol are neuroprotective antioxidants.
2007 - Study - Cannabidiol in vivo blunts B-amyloid induced neuroinflammation by suppressing IL-1B and iNOS expression.
2007 - Study - Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption.
2007 - Study ~ Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells.

2007 - Study ~ The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin.
2007 - Study ~ Cannabidiol, a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury.

2007 - Study ~ Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro.
2007 - Study ~ Delayed treatment with cannabidiol has a cerebroprotective action via a cannabinoid receptor-independent myeloperoxidase-inhibiting mechanism.
2007 - Study ~ Cannabidiol, unlike synthetic cannabinoids, triggers activation of RBL-2H3 mast cells.
2007 - Study ~ The multidrug transporter ABCG2 (BCRP) is inhibited by plant-derived cannabinoids.
2007 - Study ~ US Patent Application 20070099987 - Treating or preventing diabetes with cannabidiol.
2007 - Study ~ Repeated Treatment with Cannabidiol but Not Delta9-tetrahydrocannabinol Has a Neuroprotective Effect Without the Development of Tolerance.
2007 - Study ~ Interactions of cannabidiol with endocannabinoid signalling in hippocampal tissue.
2007 - Study ~ Cannabidiol--recent advances.
2007 - News - Who's Afraid of Cannabidiol?
2007 - News ~ Cannabidiol May be Effective in Preventing Bovine Spongiforme Enzephalopathy (Mad Cow Disease).
2007 - News ~ Marijuana Compound Shows Promise In Fighting Breast Cancer.
2007 - News ~ Cannabis may stop Breast Cancer from spreading in the Body.
2007 - News ~ Cannabis compound cannabidiol CBD 'halts cancer.
2007 - News ~ Cannabis compound stops spread of breast cancer: researchers.
2008 - Study - Cannabidiol, extracted from Cannabis sativa, selectively inhibits inflammatory hypermotility in mice.
2008 - Study - Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action.
2008 - Study - Divergent effects of cannabidiol on the discriminative stimulus and place conditioning effects of delta9-tetrahydrocannabinol.
2008 - Study - The nonpsychoactive cannabis constituent cannabidiol is a wake-inducing agent.
2008 - Study - Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders.
2008 - Study ~ US Patent Application 20080262099 - Inhibition of Tumour Cell Migration.
2008 - Study ~ Mediation of Cannabidiol anti-inflammation in the Retina by Equilibrative Nucleoside Transporter and A2A Adenosine Receptor.
2008 - Study ~ Antibacterial cannabinoids from Cannabis sativa: a structure-activity study.
2008 - Study ~ Neuroprotective effects of cannabidiol in endotoxin-induced uveitis: critical role of p38 MAPK activation.
2008 - Study ~ Effects of cannabidiol on schizophrenia-like symptoms in people who use cannabis.
2008 - Study ~ The role of the endocannabinoid system in Alzheimer's disease: facts and hypotheses.
2008 - Study ~ A comparative study on cannabidiol-induced apoptosis in murine thymocytes and EL-4 thymoma cell.
2008 - Study ~ 5-Lipoxygenase and anandamide hydrolase (FAAH) mediate the antitumor activity of cannabidiol, a non-psychoactive cannabinoid.
2008 - Study ~ Inhibition of Breast Cancer Aggressiveness by Cannabidiol.
2009 - Study - Cannabidiol decreases bone resorption by inhibiting RANK/RANKL expression and pro-inflammatory cytokines during experimental periodontitis in rats.
2009 - Study - Cannabidiol-2,6-Dimethyl Ether, a Cannabidiol Derivative, Is a Highly Potent and Selective 15-Lipoxygenase Inhibitor.
2009 - Study - Beneficial effects of a Cannabis sativa extract treatment on diabetes-induced neuropathy and oxidative stress.
2009 - Study - Opposite Effects of Delta-9-Tetrahydrocannabinol and Cannabidiol on Human Brain Function and Psychopathology.
2009 - Study - Cannabidiol: a promising drug for neurodegenerative disorders.
2009 - Study - Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis.
2009 - Study - Cannabidiol ameliorates cognitive and motor impairments in mice with bile duct ligation.
2009 - Study - Modulation of effective connectivity during emotional processing by Delta9-tetrahydrocannabinol and cannabidiol.
2009 - Study ~ Therapeutic time window of cannabidiol treatment on delayed ischemic damage via high-mobility group box1-inhibiting mechanism.
2009 - Study ~ Cannabinoids Δ9-Tetrahydrocannabinol and Cannabidiol Differentially Inhibit the Lipopolysaccharide-activated NF-κB and Interferon-β/STAT Proinflammatory Pathways in BV-2 Microglial Cells.
2009 - Study ~ Non-psychotropic plant cannabinoids:new therapeutic opportunities from an ancient herb.
2009 - Study ~ Cannabinoids, Endocannabinoids, and Related Analogs in Inflammation.
2009 - Study ~ Evaluation of Prevalent Phytocannabinoids in the Acetic Acid Model of Visceral Nociception.

2009 - Study ~ The putative cannabinoid receptor GPR55 affects osteoclast function in vitro and bone mass in vivo.
2009 - Study ~ Cannabinoids as novel anti-inflammatory drugs.
2009 - Study ~ Cannabidiol, a Nonpsychotropic Component of Cannabis, Inhibits Cue-Induced Heroin Seeking and Normalizes Discrete Mesolimbic Neuronal Disturbances.
2009 - Study ~ Cannabidiol As a Putative Novel Therapy for Diabetic Retinopathy: A Postulated Mechanism of Action as an Entry Point for Biomarker-Guided Clinical Development.
2009 - Study ~ Cannabidiol Attenuates Cisplatin-Induced Nephrotoxicity by Decreasing Oxidative/Nitrosative Stress, Inflammation, and Cell Death.
2009 - Study ~ The nonpsychotropic cannabinoid cannabidiol modulates and directly activates alpha-1 and alpha-1-Beta glycine receptor function.
2009 - Study ~ Cannabidiol-induced lymphopenia does not involve NKT and NK cells.
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2009 - Study ~ Cannabidiol reverses the reduction in social interaction produced by low dose Delta(9)-tetrahydrocannabinol in rats.
2009 - Study ~ Opposite Effects of Delta-9-Tetrahydrocannabinol and Cannabidiol on Human Brain Function and Psychopathology.
2009 - Study ~ Time-dependent vascular actions of cannabidiol in the rat aorta.
2009 - Study ~ Cannabidiol targets mitochondria to regulate intracellular Ca2+ levels.
2009 - Study ~ Cannabidiol for the treatment of psychosis in Parkinson's disease.
2009 - Study ~ Modulation of effective connectivity during emotional processing by Delta9-tetrahydrocannabinol and cannabidiol.
2009 - News - Cannabis by product helps reduce effects of Parkinson disease medication.
2009 - News ~ Cannabis compound can help cells.
2009 - News ~ Cannabis plant extracts could potentially form the basic ingredients for a market-leading diabetes drug.
2009 - News ~ Marijuana Chemicals Ease MS Symptoms, Review Confirms.
2010 - Study - Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb.
2010 - Study - Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT receptors.
2010 - Study - Effects of cannabidiol on amphetamine-induced oxidative stress generation in an animal model of mania.
2010 - Study ~ Cannabinoid-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain.
2010 - Study ~ Cannabinoid receptor CB1 mediates baseline and activity-induced survival of new neurons in adult hippocampal neurogenesis.
2010 - Study ~ Therapeutical use of the cannabinoids in psychiatry.
2010 - Study ~ Cannabidiol protects retinal neurons by preserving glutamine synthetase activity in diabetes.
2010 - Study ~ Therapeutic Potential of Non-Psychotropic Cannabidiol in Ischemic Stroke.
2010 - Study ~ Cannabidiol Displays Antiepileptiform and Antiseizure Properties In Vitro and In Vivo.
2010 - Study ~ Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion.
2010 - Study ~ Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis.
2010 - Study ~ Antitumorigenic Effects of Cannabinoids beyond Apoptosis.
2010 - Study ~ Cannabidiol Attenuates Cardiac Dysfunction, Oxidative Stress, Fibrosis, and Inflammatory and Cell Death Signaling Pathways in Diabetic Cardiomyopathy.
2010 - Study ~ Antidepressant-like effect of Delta(9)-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa L.
2010 - Study ~ Cannabidiol ameliorates cognitive and motor impairments in bile-duct ligated mice via 5-HT1A receptor activation.
2010 - Study ~ Anti-tumoural effects of cannabinoid combinations - Patent TW201002315 (A) — 2010-01-16.
2010 - Study ~ Diabetic retinopathy: Role of inflammation and potential therapies for anti-inflammation.
2010 - Study ~ A behavioural comparison of acute and chronic Delta9-tetrahydrocannabinol and cannabidiol in C57BL/6JArc mice.
2010 - Study ~ Intra-dorsal periaqueductal gray administration of cannabidiol blocks panic-like response by activating 5-HT1A receptors.
2010 - Study ~ Impact of cannabidiol on the acute memory and psychotomimetic effects of

2010 - Study ~ Impact of cannabidiol on the acute memory and psychotomimetic effects of smoked cannabis: naturalistic study.
2010 - Study ~ Decrease of plasminogen activator inhibitor-1 may contribute to the anti-invasive action of cannabidiol on human lung cancer cells.
2010 - Study ~ Regulation of nausea and vomiting by cannabinoids.
2010 - Study ~ Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion.
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2010 - Study ~ Cannabidiol inhibits cancer cell invasion via upregulation of tissue inhibitor of matrix metalloproteinases-1.
2010 - Study ~ Cannabidiol Enhances the Inhibitory Effects of Δ9-Tetrahydrocannabinol on Human Glioblastoma Cell Proliferation and Survival.
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2010 - Study ~ Effects of cannabidiol on amphetamine-induced oxidative stress generation in an animal model of mania.
2010 - Study ~ Cannabidiol Attenuates the Appetitive Effects of Δ9-Tetrahydrocannabinol in Humans Smoking Their Chosen Cannabis.
2010 - Study ~ Opposite Effects of Δ-9-Tetrahydrocannabinol and Cannabidiol on Human Brain Function and Psychopathology.
2010 - Study ~ Cannabidiol inhibitory effect on marble-burying behaviour: involvement of CB1 receptors.
2010 - Study ~ Cannabidiol attenuates delayed-type hypersensitivity reactions via suppressing T-cell and macrophage reactivity.
2010 - Study ~ Multicenter, double-blind, randomized, placebo-controlled, parallel-group study of the efficacy, safety, and tolerability of THC:CBD extract and THC extract in patients with intractable cancer-related pain.
2010 - Study ~ Disposition of Cannabichromene, Cannabidiol, and Δ9-Tetrahydrocannabinol and its Metabolites in Mouse Brain following Marijuana Inhalation Determined by High-Performance Liquid Chromatography-Tandem Mass Spectrometry.
2010 - Study ~ Treatment with cannabidiol reverses oxidative stress parameters, cognitive impairment and mortality in rats submitted to sepsis by cecal ligation and puncture.
2010 - Study ~ Anticonvulsant effects of GWP42006 in vitro and in vivo in rat.
2010 - Study ~ The neuroprotective effect of cannabidiol in an in vitro model of newborn hypoxic-ischemic brain damage in mice is mediated by CB(2) and adenosine receptors.
2010 - Study ~ Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report.
2010 - News ~ Non-psychoactive cannabis to be unveiled at Annual National Clinical Conference on Cannabis Therapeutics.
2010 - News ~ Prescription Marijuana Without "Intoxicating" Effect in Research Stage.
2010 - News ~ Key ingredient staves off marijuana memory loss.
2010 - News ~ Science: Cannabidiol enhances the anti-cancer effects of THC on human brain cancer cells.
2010 - News ~ Pot Compound Mitigates Diabetic Cardiomyopathy.
2010 - News ~ Cannabinoids inhibit and may prevent neuropathic pain in diabetes.
2010 - News ~ Lab Notes: Pot Has Benefits for Diabetic Hearts.
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2010 - News ~ Key ingredient dilutes marijuana's effect on memory.
2010 - News - Brazilian Scientists Show How Marijuana Can Help in Treating Parkinson.
2011 - Study ~ The potential for clinical use of cannabinoids in treatment of cardiovascular diseases.
2011 - Study ~ Acute administration of cannabidiol in vivo suppresses ischaemia-induced cardiac arrhythmias and reduces infarct size when given at reperfusion.
2011 - Study ~ Cannabidiol reduces lipopolysaccharide-induced vascular changes and inflammation in the mouse brain: an intravital microscopy study.
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2011 - Study ~ Cannabidiol and other cannabinoids reduce microglial activation in vitro and in vivo: relevance to Alzheimers' disease.
2011 - Study ~ Evaluation of the Cyclooxygenase Inhibiting Effects of Six Major Cannabinoids Isolated from Cannabis sativa.
2011 - Study ~ Role of Myeloid-Derived Suppressor Cells in Amelioration of Experimental Autoimmune Hepatitis Following Activation of TRPV1 Receptors by Cannabidiol.
2011 - Study ~ Cannabidiol causes activated hepatic stellate cell death through a mechanism of endoplasmic reticulum stress-induced apoptosis.
2011 - Study ~ Cannabidiol, a Major Phytocannabinoid, as a Potent Atypical Inhibitor for Cytochrome P450 2D6.

2011 - Study ~ Brief Report: Cannabidiol Prevents the Development of Cold and Mechanical Allodynia in Paclitaxel-Treated Female C57Bl6 Mice.
2011 - Study ~ Cannabidiol Reduces Intestinal Inflammation through the Control of Neuroimmune Axis.
2011 - Study ~ Phytocannabinoids for use in the treatment of cancer - Patent GB2478595 (A) — 2011-09-14.
2011 - Study ~ US Patent Application 20110257256 - CANNABINOIDS FOR USE IN TREATING OR PREVENTING COGNITIVE IMPAIRMENT AND DEMENTIA.
2011 - Study ~ Influence of agroclimatic conditions on content of main cannabinoids in industrial hemp (Cannabis sativa L.).
2011 - Study ~ Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes.
2011 - Study ~ Identification of cytochrome P450 enzymes responsible for metabolism of cannabidiol by human liver microsomes.
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2011 - Study ~ Cannabidiol improves brain and liver function in a fulminant hepatic failure-induced model of hepatic encephalopathy in mice.
2011 - Study ~ Effects of intracisternal administration of cannabidiol on the cardiovascular and behavioral responses to acute restraint stress.
2011 - Study ~ Modulation of Auditory and Visual Processing by Delta-9-Tetrahydrocannabinol and Cannabidiol: an fMRI Study.
2011 - Study ~ CANNABIDIOL INHIBITS PATHOGENIC T-CELLS, DECREASES SPINAL MICROGLIAL ACTIVATION AND AMELIORATES MULTIPLE SCLEROSIS-LIKE DISEASE IN C57BL/6 MICE.
2011 - Study ~ Anti-Aversive Effects of Cannabidiol on Innate Fear-Induced Behaviors Evoked by an Ethological Model of Panic Attacks Based on a Prey vs the Wild Snake Epicrates cenchria crassus Confrontation Paradigm.
2011 - Study ~ Memory-rescuing effects of cannabidiol in an animal model of cognitive impairment relevant to neurodegenerative disorders.
2011 - Study ~ Interaction between non-psychotropic cannabinoids in marihuana: effect of cannabigerol (CBG) on the anti-nausea or anti-emetic effects of cannabidiol (CBD) in rats and shrews.
2011 - Study ~ Cannabidiol, a Non-Psychotropic Component of Cannabis, Attenuates Vomiting and Nausea-like Behaviour via Indirect Agonism of 5-HT(1A) Somatodendritic: Autoreceptors in the Dorsal Raphe Nucleus.
2011 - Study ~ A novel CB receptor GPR55 and its ligands are involved in regulation of gut movement in rodents.
2011 - Study ~ Cannabidiol inhibits the hyperphagia induced by cannabinoid-1 or serotonin-1A receptor agonists.
2011 - Study ~ Cannabidiol potentiates Δ(9)-tetrahydrocannabinol (THC) behavioural effects and alters THC pharmacokinetics during acute and chronic treatment in adolescent rats.
2011 - Study ~ Inhibitory Effect of Standardized Cannabis sativa Extract and Its Ingredient Cannabidiol on Rat and Human Bladder Contractility.
2011 - Study ~ Cannabidiol reduces the anxiety induced by simulated public speaking in treatment-naïve social phobia patients.
2011 - Study ~ Effects on sleep and dopamine levels of microdialysis perfusion of cannabidiol into the lateral hypothalamus of rats.
2011 - Study ~ Cannabidiol induces programmed cell death in breast cancer cells by coordinating the crosstalk between apoptosis and autophagy.
2011 - Study ~ Pathways mediating the effects of cannabidiol on the reduction of breast cancer cell proliferation, invasion, and metastasis.
2011 - Study ~ Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats.

2011 - Study ~ Cannabidiol, a Non-Psychotropic Component of Cannabis, Attenuates Vomiting and Nausea-like Behaviour via Indirect Agonism of 5-HT(1A) Somatodendritic: Autoreceptors in the Dorsal Raphe Nucleus.
2011 - Study ~ Regulation of nausea and vomiting by cannabinoids.
2011 - Study ~ The effects of cannabidiolic acid and cannabidiol on contractility of the gastrointestinal tract of Suncus murinus.
2011 - Study ~ Cannabidiol inhibits lung cancer cell invasion and metastasis via intercellular adhesion molecule-1.
2011 - Study ~ Cannabidiol Dampens Streptozotocin-Induced Retinal Inflammation by Targeting

of Microglial Activation.
2011 - Study ~ Plasma and brain pharmacokinetic profile of cannabidiol (CBD), cannabidivarine (CBDV), Δ(9)-tetrahydrocannabivarin (THCV) and cannabigerol (CBG) in rats and mice following oral and intraperitoneal administration and CBD action on obsessive-compulsive behaviour.
2011 - Study ~ Cannabis with high cannabidiol content is associated with fewer psychotic experiences.
2011 - Study ~ A novel CB receptor GPR55 and its ligands are involved in regulation of gut movement in rodents.
2011 - Study ~ Sub-chronic impact of cannabinoids in street cannabis on cognition, psychotic-like symptoms and psychological well-being.
2011 - Study ~ Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report.
2011 - Study ~ Endocannabinoid system and psychiatry: in search of a neurobiological basis for detrimental and potential therapeutic effects.
2011 - Study ~ The endocannabinoid system in the regulation of emotions throughout lifespan: a discussion on therapeutic perspectives.
2011 - Study ~ Cannabidiol protects against hepatic ischemia/reperfusion injury by attenuating oxidative stress, inflammatory response, and cell death.
2011 - Study ~ Therapeutic potential of cannabidiol against ischemia/reperfusion liver injury in rats.
2011 - Study ~ Cannabidiol as an emergent therapeutic strategy for lessening the impact of inflammation on oxidative stress.
2011 - Study ~ Cannabidiol reduces brain damage and improves functional recovery after acute hypoxia-ischemia in newborn pigs.
2011 - Study ~ Cannabidiol-treated Rats Exhibited Higher Motor Score After Cryogenic Spinal Cord Injury.
2011 - Study ~ Prospects for cannabinoid therapies in basal ganglia disorders.
2011 - Study ~ Phytocannabinoids as novel therapeutic agents in CNS disorders.
2011 - Study ~ Differential transcriptional profiles mediated by exposure to the cannabinoids cannabidiol and Δ(9) -tetrahydrocannabinol in BV-2 microglial cells.
2011 - Study ~ THC and CBD oromucosal spray (Sativex®) in the management of spasticity associated with multiple sclerosis.
2011 - Study ~ Plasma cannabinoid pharmacokinetics following controlled oral delta9-tetrahydrocannabinol and oromucosal cannabis extract administration.
2011 - Study ~ Memory-rescuing effects of cannabidiol in an animal model of cognitive impairment relevant to neurodegenerative disorders.
2011 - Study ~ The interplay of cannabinoid and NMDA glutamate receptor systems in humans: preliminary evidence of interactive effects of cannabidiol and ketamine in healthy human subjects.
2011 - Study ~ Induction of apoptosis by cannabinoids in prostate and colon cancer cells is phosphatase dependent.
2011 - Study ~ Heterogeneity in the composition of marijuana seized in California.
2011 - Study ~ Cannabidiol induced a contrasting pro-apoptotic effect between freshly isolated and precultured human monocytes.
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2011 - Study ~ A synthetic cannabinoid, CP55940, inhibits lipopolysaccharide-induced cytokine mRNA expression in a cannabinoid receptor-independent mechanism in rat cerebellar granule cells.
2011 - Study ~ Non-psychoactive cannabinoids modulate the descending pathway of antinociception in anaesthetized rats through several mechanisms of action.
2011 - Study ~ Cannabidiol (CBD) as an Anti-Arrhythmic.
2011 - News ~ Cannabis could help treat epilepsy #1.
2011 - News ~ Cannabis could be used to treat epilepsy #2.
2011 - News ~ Marijuana Extract Might Help Prevent Chemotherapy-Related Nerve Pain.
2011 - News ~ Another Study Confirms Anti-Cancer Effects of THC and CBD.
2011 - News ~ Cannabinoid 'Completely' Prevents Chemotherapy-Induced Neuropathy, Study Says.
2011 - News ~ Cannabidiol May Fight Alzheimer's Disease.
2011 - News ~ Marijuana Compound Induces Cell Death In Hard-To-Treat Brain Cancer.
2011 - News ~ Marijuana component may ease pain from chemo therapy drugs.
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2011 - News ~ New research provides hope for those with epilepsy.
2011 - News ~ Cannabis Compound Induces Death Of Cells Associated With Liver Fibrosis.
2011 - News ~ CBD Tops The Chart.
2012 - Study ~ Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug.
2012 - Study ~ Topical and Systemic Cannabidiol Improves Trinitrobenzene Sulfonic Acid Colitis in Mice.
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2012 - Study ~ Chemopreventive effect of the non-psychotropic phytocannabinoid cannabidiol

2012 - Study ~ Chemopreventive effect of the non-psychotropic phytocannabinoid cannabidiol on experimental colon cancer.
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2012 - Study ~ Heat Exposure of Cannabis sativa Extracts Affects the Pharmacokinetic and Metabolic Profile in Healthy Male Subjects.
2012 - Study ~ The therapeutic potential of the endocannabinoid system for Alzheimer's disease.
2012 - Study ~ On Disruption of Fear Memory by Reconsolidation Blockade: Evidence from Cannabidiol Treatment.
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2012 - Study ~ Cannabidiol for neurodegenerative disorders: important new clinical applications for this phytocannabinoid?
2012 - Study ~ CANNABIDIOL INHIBITS ANGIOGENESIS BY MULTIPLE MECHANISMS.
2012 - Study ~ Non-THC cannabinoids counteract prostate carcinoma growth in vitro and in vivo: pro-apoptotic effects and underlying mechanisms.
2012 - Study ~ Cannabinoids suppress inflammatory and neuropathic pain by targeting α3 glycine receptors.
2012 - Study ~ Poly-ε-caprolactone microspheres as a drug delivery system for cannabinoid administration: Development, characterization and in vitro evaluation of their antitumoral efficacy.
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2012 - Study ~ Antipsychotic Profile of Cannabidiol and Rimonabant in an Animal Model of Emotional Context Processing in Schizophrenia.
2012 - Study ~ Cannabidiol enhances anandamide signaling and alleviates psychotic symptoms of schizophrenia.
2012 - Study ~ Cannabidiol-induced apoptosis in murine microglial cells through lipid raft.
2012 - Study ~ Cannabis derivatives therapy for a seronegative stiff-person syndrome: a case report.
2012 - Study ~ A critical review of the antipsychotic effects of Cannabidiol: 30 years of a translational investigation.
2012 - Study ~ Acute effects of a single, oral dose of d9-tetrahydrocannabinol (THC) and cannabidiol (CBD) administration in healthy volunteers.
2012 - Study ~ Cannabidiol exerts anti-convulsant effects in animal models of temporal lobe and partial seizures.
2012 - Study ~The potential use of cannabidiol in the therapy of metabolic syndrome.
2012 - Study ~ Cannabinoid-like anti-inflammatory compounds from flax fiber.
2012 - Study ~ Cannabidiol in Inflammatory Bowel Diseases: A Brief Overview.
2012 - News ~ Medical Marijuana: A "Cure" for Autism?
2012 - News ~ How marijuana could help cure obesity-related diseases.
2012 - News ~ Cannabis can help treat obesity.
2012 - News ~ Researchers study neuroprotective properties in cannabis.
2012 - Forum Post ~ Simple Method: Isolating & Extracting INDIVIDUAL Cannabinoids... from BadKittySmiles.

Comparison of Cannabidiol, Antioxidants, and Diuretics in Reversing Binge Ethanol-Induced Neurotoxicity

1. Carol Hamelink
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Abstract

Binge alcohol consumption in the rat induces substantial neurodegeneration in the hippocampus and entorhinal cortex.

Oxidative stress and cytotoxic edema have both been shown to be involved in such

Oxidative stress and cytotoxic edema have both been shown to be involved in such neurotoxicity, whereas *N*-methyl-d-aspartate (NMDA) receptor activity has been implicated in alcohol withdrawal and excitoxic injury.

Because the nonpsychoactive cannabinoid cannabidiol (CBD) was previously shown in vitro to prevent glutamate toxicity through its ability to reduce oxidative stress, we evaluated CBD as a neuroprotectant in a rat binge ethanol model. When administered concurrently with binge ethanol exposure, CBD protected against hippocampal and entorhinal cortical neurodegeneration in a dose-dependent manner.

Similarly, the common antioxidants butylated hydroxytoluene and α-tocopherol also afforded significant protection. In contrast, the NMDA receptor antagonists dizocilpine (MK-801) and memantine did not prevent cell death. Of the diuretics tested, furosemide was protective, whereas the other two anion exchanger inhibitors, L-644,711 [(*R*)-(+)-(5,6-dichloro2,3,9,9*a*-tetrahydro 3-oxo-9*a*-propyl-1*H*-fluoren-7-yl)oxy acetic acid] and bumetanide, were ineffective.

In vitro comparison of these diuretics indicated that furosemide is also a potent antioxidant, whereas the nonprotective diuretics are not. The lack of efficacy of L-644,711 and bumetanide suggests that the antioxidant rather than the diuretic properties of furosemide contribute most critically to its efficacy in reversing ethanol-induced neurotoxicity in vitro, in our model. This study provides the first demonstration of CBD as an in vivo neuroprotectant and shows the efficacy of lipophilic antioxidants in preventing binge ethanol-induced brain injury.

Footnotes

- Article, publication date, and citation information can be found at http://jpet.aspetjournals.org.

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The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis

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1. Edited by Anthony Cerami, The Kenneth S. Warren Laboratories, Tarrytown, NY, and approved June 2, 2000 (received for review March 10, 2000)

Abstract

The therapeutic potential of cannabidiol (CBD), the major nonpsychoactive component of cannabis, was explored in murine collagen-induced arthritis (CIA). CIA was elicited by immunizing DBA/1 mice with type II collagen (CII) in complete Freund's adjuvant.

The CII used was either bovine or murine, resulting in classical acute CIA or in chronic relapsing CIA, respectively. CBD was administered after onset of clinical symptoms, and in both models of arthritis the treatment effectively blocked progression of arthritis. CBD was equally effective when administered i.p. or orally. The dose dependency showed a bell-shaped curve, with an optimal effect at 5 mg/kg per day i.p. or 25 mg/kg per day orally.

Clinical improvement was associated with protection of the joints against severe damage. *Ex vivo,* draining lymph node cells from CBD-treated mice showed a diminished CII-specific proliferation and IFN-γ production, as well as a decreased release of tumor necrosis factor by knee synovial cells.

In vitro effects of CBD included a dose-dependent suppression of lymphocyte proliferation, both mitogen-stimulated and antigen-specific, and the blockade of the Zymosan-triggered reactive oxygen burst by peritoneal granulocytes.

It also was found that CBD administration was capable of blocking the lipopolysaccharide-induced rise in serum tumor necrosis factor in C57/BL mice. Taken together, these data show that CBD, through its combined immunosuppressive and anti-inflammatory actions, has a

potent anti-arthritic effect in CIA....read more

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Cannabidiol inhibits tumour growth in leukaemia and breast cancer

Italian researchers investigated the anti-tumour effects of five natural cannabinoids of the cannabis plant (cannabidiol, cannabigerol, cannabichromene, cannabidiol-acid and THC-acid) in breast cancer. Cannabidiol (CBD) was the most potent cannabinoid in inhibiting the growth of human breast cancer cells that had been injected under the skin of mice. CBD also reduced lung metastases deriving from human breast cancer cells that had been injected into the paws of the animals.

Researchers found that the anti-tumour effects of CBD were caused by induction of apoptosis (programmed cell death). They concluded that their data "support the further testing of cannabidiol and cannabidiol-rich extracts for the potential treatment of cancer."

These observations are supported by investigations of US scientists who found out that exposure of leukaemia cells to CBD led to a reduction in cell viability and induction of apoptosis. In living animals CBD caused a reduction in number of leukaemia cells. The scientists noted that CBD "may be a novel and highly selective treatment for leukemia."

(Sources: Ligresti A, Schiano Moriello A, Starowicz K, Matias I, Pisanti S, De Petrocellis L, Laezza C, Portella G, Bifulco M, Di Marzo V. Anti-tumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. J Pharmacol Exp Ther. 2006 May 25; [electronic publication ahead of print]; McKallip RJ, Jia W, Schlomer J, Warren JW, Nagarkatti PS, Nagarkatti M. Cannabidiol-induced apoptosis in human leukemia cells: A novel role of cannabidiol in the regulation of p22phox and Nox4 expression. Mol Pharmacol. 2006 Jun 5; [electronic publication ahead of print])

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Anti-tumor effects of cannabidiol

Anti-tumor effects of cannabidiol, a non-psychotropic cannabinoid, on human glioma cell lines

Paola Massi , Angelo Vaccani , Stefania Ceruti , Arianna Colombo , Maria Pia Abbracchio , Daniela Parolaro

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Abstract: Recently, cannabinoids have been shown to possess antitumor properties. Because the psycho-activity of cannabinoid compounds limits their medicinal usage, we undertook the present study to evaluate the in vitro antiproliferative ability of CBD, a non- psychoactive cannabinoid compound, on U87 and U373 human glioma cell lines. The addition of CBD to the culture medium led to a dramatic drop of mitochondrial oxidative metabolism (MTT test) and viability in glioma cells, in a concentration-dependent manner, already evident 24 h after CBD exposure with an apparent IC50 of 25 μM.

The antiproliferative effect of CBD was partially prevented by the CB2 receptor antagonist SR144528 and -tocopherol. By contrast, the CB1 cannabinoid receptor

antagonist SR141716, capsazepine (vanilloid receptor antagonist), the inhibitors of ceramide generation or PTX did not counteract CBD effects. We also show, for the first time, that the antiproliferative effect of CBD was correlated to induction of apoptosis, as determined by cytofluorimetric analysis and ssDNA staining, which was not reverted by cannabinoid antagonists. Finally, CBD administered s.c. to nude mice at the dose of 0.5 mg/mouse, significantly inhibited the growth of subcutaneously implanted U87 human glioma cells.

Concluding, the non-psychoactive CBD was able to produce a significant antitumor activity both in vitro and in vivo, thus suggesting a possible application of CBD as an antineoplastic agent.

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Cannabinol delays symptom onset

Amyotroph Lateral Scler Other Motor Neuron Disord. 2005 Sep;6(3):182-4.

Cannabinol delays symptom onset in SOD1 (G93A) transgenic mice without affecting survival.

Weydt P, Hong S, Witting A, Möller T, Stella N, Kliot M.

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Abstract

Therapeutic options for amyotrophic lateral sclerosis (ALS), the most common adult-onset motor neuron disorder, remain limited. Emerging evidence from clinical studies and transgenic mouse models of ALS suggests that cannabinoids, the bioactive ingredients of marijuana (Cannabis sativa) might have some therapeutic benefit in this disease.

However, Delta(9)-tetrahydrocannabinol (Delta(9)-THC), the predominant cannabinoid in marijuana, induces mind-altering effects and is partially addictive, compromising its clinical usefulness.

We therefore tested whether cannabinol (CBN), a non-psychotropic cannabinoid, influences disease progression and survival in the SOD1 (G93A) mouse model of ALS. CBN was delivered via subcutaneously implanted osmotic mini-pumps (5 mg/kg/day) over a period of up to 12 weeks.

We found that this treatment significantly delays disease onset by more than two weeks while survival was not affected.

Further research is necessary to determine whether non-psychotropic cannabinoids might be useful in ameliorating symptoms in ALS.

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Cannabidiol lowers incidence of diabetes in non-obese diabetic mice

Autoimmunity. 2006 May

Weiss L, Zeira M, Reich S, Har-Noy M, Mechoulam R, Slavin S, Gallily R.

Hadassah University Hospital, Department of Bone Marrow Transplantation & Cancer Immunotherapy, POB 12000, Jerusalem, 91120, Israel.

Abstract

Cannabidinoids are components of the Cannabis sativa (marijuana) plant that have been shown capable of suppressing inflammation and various aspects of cell-mediated immunity. Cannabidiol (CBD), a non-psychoactive cannabidinoid has been previously shown by us to suppress cell-mediated autoimmune joint destruction in an animal model of rheumatoid

arthritis.

We now report that CBD treatment significantly reduces the incidence of diabetes in NOD mice from an incidence of 86% in non-treated control mice to an incidence of 30% in CBD-treated mice. CBD treatment also resulted in the significant reduction of plasma levels of the pro-inflammatory cytokines, IFN-gamma and TNF-alpha.

Th1-associated cytokine production of in vitro activated T-cells and peritoneal macrophages was also significantly reduced in CBD-treated mice, whereas production of the Th2-associated cytokines, IL-4 and IL-10, was increased when compared to untreated control mice. Histological examination of the pancreatic islets of CBD-treated mice revealed significantly reduced insulitis.

Our results indicate that CBD can inhibit and delay destructive insulitis and inflammatory Th1-associated cytokine production in NOD mice resulting in a decreased incidence of diabetes possibly through an immunomodulatory mechanism shifting the immune response from Th1 to Th2 dominance.

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Neuroprotective and Blood-Retinal Barrier-Preserving Effects of Cannabidiol in Experimental Diabetes

El-Remessy AB, Al-Shabrawey M, Khalifa Y, Tsai NT, Caldwell RB, Liou GI.

Department of Pharmacology and Toxicology, Medical College of Georgia, 1120 15th St., Augusta, GA 30912, USA.

Abstract

Diabetic retinopathy is characterized by blood-retinal barrier (BRB) breakdown and neurotoxicity. These pathologies have been associated with oxidative stress and proinflammatory cytokines, which may operate by activating their downstream target p38 MAP kinase.

In the present study, the protective effects of a nonpsychotropic cannabinoid, cannabidiol (CBD), were examined in streptozotocin-induced diabetic rats after 1, 2, or 4 weeks. Retinal cell death was determined by terminal dUTP nick-end labeling assay; BRB function by quantifying extravasation of bovine serum albumin-fluorescein; and oxidative stress by assays for lipid peroxidation, dichlorofluorescein fluorescence, and tyrosine nitration.

Experimental diabetes induced significant increases in oxidative stress, retinal neuronal cell death, and vascular permeability. These effects were associated with increased levels of tumor necrosis factor-alpha, vascular endothelial growth factor, and intercellular adhesion molecule-1 and activation of p38 MAP kinase, as assessed by enzyme-linked immunosorbent assay, immunohistochemistry, and/or Western blot.

CBD treatment significantly reduced oxidative stress; decreased the levels of tumor necrosis factor-alpha, vascular endothelial growth factor, and intercellular adhesion molecule-1; and prevented retinal cell death and vascular hyperpermeability in the diabetic retina.

Consistent with these effects, CBD treatment also significantly inhibited p38 MAP kinase in the diabetic retina. These results demonstrate that CBD treatment reduces neurotoxicity, inflammation, and BRB breakdown in diabetic animals through activities that may involve inhibition of p38 MAP kinase.
PMID: 16400026 [PubMed - indexed for MEDLINE]PMCID: PMC1592672Free PMC Article

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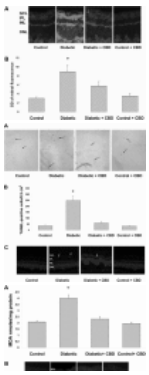

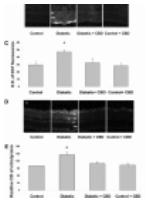

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Evaluation of cannabidiol in dystonic movement disorders

Consroe P, Sandyk R, Snider SR

International Journal of Neuroscience 1986;30(4):277-282

20-50% improvement of dystonia; deterioration of tremor and hypokinesia in 2 patients with Parkinson's disease

Indication Dystonia; Parkinson's disease

Medication Cannabidiol

Route(s) Oral

Dose(s)100-600 mg per day

Duration (days) 42

Participants 5 patients with dystonia

Design Open study

Address of author(s)

Department of Pharmacology/Toxicology, University of Arizona Health Sciences Center, Tucson, USA

Cannabidiol (CBD), a nonpsychoactive cannabinoid of Cannabis, was given to 5 patients with dystonic movement disorders in a preliminary open pilot study.

Oral doses of CBD rising from 100 to 600 mg/day over a 6 week period were administered along with standard medication. Dose-related improvement in dystonia was observed in all patients and ranged from 20 to 50%.

Side-effects of CBD were mild and included hypotension, dry mouth, psychomotor slowing, lightheadedness, and sedation. In 2 patients with coexisting Parkinsonian features, CBD at doses over 300 mg/day exacerbated the hypokinesia and resting tremor. CBD appears to have antidystonic and Parkinsonism-aggravating effects in humans.

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Cannabidiol in dystonic movement disorders

Title	**Cannabidiol in dystonic movement disorders.**
Author(s)	**Sandyk R, Snider SR, Consroe P, Elias SM.**
Journal, Volume, Issue	Psychiatry Res. 1986 Jul;18(3):291.
Major outcome(s)	Cannabidiol (CBD) reduced dystonic movements

Indication	Dystonia	**Abstract**
Medication	Cannabidiol	(Fulltext)

Route(s)	Oral
Dose(s)	200 mg
Duration (days)	
Participants	2 case reports
Design	Uncontrolled case report
Type of publication	Medical journal
Address of author(s)	
Full text	

Letter to the editors:
Evidence has recently accumulated to suggest that cannabidiol (CBD), a nonpsychoactive cannabinoid of marijuana, may be useful in the management of hyperkinetic movement disorders (Snider and Consroe, 1984, 1985).

We have therefore tested the efficacy of CBD in two patients with dystonic movement disorders.

A 65-year-old woman had idiopathic spasmodic torticollis of 2 years' duration.

Her condition was characterized by a lateral pulling of her neck to the right, which occurred at a frequency of 8-12/minute.

In addition, she had essential-type tremor affecting both hands, which was only partially relieved with atenolol (50mg/day). CBD (200mg, orally) produced an amelioration of the dystonic movements within 3 hours of the lateral neck movements to 2-4/minute.

The patient's improvement was confirmed by an evaluation of two independent neurologists.

A 31-year-old man had generalized torsion dystonia (dystonia musculorum deformans) of 20 years' duration.

He had obtained mild benefit from high doses (25-45 mg/day) of trihexyphenidyl, but was confirmed to a wheelchair.

CBD (200 mg, orally) produced an amelioration of his symptoms (especially of his more severely affected right leg) within two hours of administration.

Following CBD administration, he was able to walk without support, an effect that lasted about 24 hours. In both cases, CBD produced no adverse effects.

Cannabidiol (CBD) has been shown to have significant muscle relaxant effects and to reduce muscular spasms in humans (Petro, 1980). In rodents, CBD has been reported to reduce cholinergic transmission (Revuelta et al., 1978) and to increase turnover of gamma-aminobutyric acid (Revuelta et al., 1979).

Acute administration of delta-tetradydrocannabinol to rats greatly potentiated the hypokinetic effect of reserpine (Moss et al., 1984), suggesting that this compound may have antidyskinetic properties in humans and that further studies of CBD in other hyperkinetic movement disorders in humans and warranted.

All Conditions Benefited by Medical Marijuana

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Beneficial and adverse effects of cannabidiol in a Parkinson patient

Title	**Beneficial and adverse effects of cannabidiol in a Parkinson**

Title	**patient with sinemet-induced dystonic dyskinesia.**
Author(s)	**Snider SR, Consroe P.**
Journal, Volume, Issue	Neurology 1985;35(Suppl):201.
Major outcome(s)	Improvement of dyskinesia

Indication	Parkinson's disease
Medication	Cannabidiol
Route(s)	Oral
Dose(s)	100-400 mg
Duration (days)	
Participants	1 patient with parkinsonism and secondary dystonia.
Design	Uncontrolled case report
Type of publication	Medical journal
Address of author(s)	
Full text	

Abstract

(Fulltext)
In idiopathic dystonia, the terapeutic effect of marijuana smoking is reported to be comparable to diazepam (C.D. Marsden, in Disorders of Movement, 1981,81).

The non-psychoactive cannabis derivative, cannabidiol (CBD), also improves dystonia (Consroe and Snider, in Cannbinoids as Therapeutic Agents, in press).

We report the effect of CBD on dystonia secondary to Sinemet in parkinsonism, a disorder thought to be a relative contraindication for cannabinoids (D.Moss et al, Pharmacol Biochem Behav 1981, 1984).

The patient, a 42-year- old man with an 8-year history of parkinsonism, developed peak-dose dyskinesia about 4 years ago and action dystonia affecting all limbs more recently.

Trihexyphenidyl and bromocriptine each produced only slight improvement. To stable optimal dosages of the three drugs, CBD was added, starting with 100 mg/d and increasing by 100 mg weekly. At 100 to 200 mg/d, there was a decrease in clinical fluctuations and in dyskinesia scores (by 30%) without a significant worsening of the parkinsonism.

At 300 to 400 mg/d, there was no further improvement in the dyskinesia, and adverse effects (dizziness, drowsiness, increased Parkinson symptoms) appeared.

CBD withdrawal resulted in 3 days of severe generalized dystonia and several weeks of increased sensitivity to Sinemet, suggestive of a “drug holiday” effect.

All Conditions Benefited by Medical Marijuana

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Treatment of Meige’s syndrome with cannabidiol

Title	**Treatment of Meige's syndrome with cannabidiol.**
Author(s)	**Snider S.R, Consroe P.**
Journal, Volume, Issue	Neurology 1984;34(Suppl):147.
Major outcome(s)	50% improvement in spasm severity and frequency

Indication	Dystonia
Medication	Cannabidiol

Abstract

Cannabidiol (CBD) is the major nonpsychoactive cannabinoid in marijuana.

The anticonvulsant properties of CBD were demonstrated in humans 5 years ago.

Route(s)	Oral
Dose(s)	
Duration (days)	
Participants	A 42 year old Meige syndrome patient
Design	Uncontrolled case report
Type of publication	Medical journal
Address of author(s)	

Based on anecdotal reports of improvement of generalized dystonia with marijuana smoking, we decided to try CBD in a patient with severe cranial dystonia (Meige syndrome).

The patient, a 42-year-old man, first developed mild blepharospasm 9 years ago. The abnormal movements gradually spread to the oromandibular and neck muscles and worsened to the point that the patient was unable to drive.

Many drugs were tried, with disappointing results. CBD was initiated at 100 mg/day, in divided doses, and slowly increased over several weeks to 400 mg/day. Other drugs were kept the same. Spasm frequency, counted twice daily by a relative while the patient was either talking or driving, gradually decreased from 20 to 30 per min before CBD to 7 or 15 per min at a dosage of 400 mg/day.

Examinations at weekly intervals using a standard rating scale confirmed at least 50 % improvement in spasm severity and frequency.

Withdrawal of CBD for 24 hours resulted in reappearance of severe spasm at 25 to 30 per min. Side effects included dry mouth, transient morning headache, and slight sedation.

All Conditions Benefited by Medical Marijuana

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CHRONIC ADMINISTRATION OF CANNABIDIOL TO HEALTHY VOLUNTEERS AND EPILEPTIC PATIENTS (1980)

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Abstract.

In phase 1 of the study, 3 mg / kg daily of cannabidiol (CBD) was given for 30 days to 8 healthy human volunteers. Another 8 volunteers received the same number of identical capsules containing glucose as placebo in a double-blind setting.

Neurological and physical examinations, blood and urine analysis, ECG and EEG were performed atweekly intervals. In phase 2 of the study, 15 patients suffering from secondary generalized epilepsy with temporal focus were randomly divided into two groups. Each patient received, in a double-blind procedure, 200-300 mg daily of CBD or placebo. The drugs were administered for as long as 4 1/2 months.

Clinical and laboratory examinations, EEG and ECG were performed at 15- or 30-day intervals. Throughout the experiment the patients continued to take the antiepileptic drugs prescribed before the experiment, although these drugs no longer controlled the signs of the disease. All patients and volunteers tolerated CBD very well and no signs of toxicity or serious side effects were detected on examination. 4 of the 8 CBD subjects remained almost free of convulsive crises throughout the

6 CBD subjects remained almost free of convulsive crises throughout the experiment and 3 other patients demonstrated partial improvement in their clinical condition. CBD was ineffective in 1 patient.

The clinical condition of 7 placebo patients remained unchanged whereas the condition of 1 patient clearly improved. The potential use of CBD as an antiepileptic drug and its possible potentiating effect on other antiepileptic drugs are discussed.

Anecdotal reports on the antiepileptic properties of marihuana (Cannabis sativa) are known since ancient times (Li, 1974). Rosenthal (1971) mentioned medieval Arab manuscripts in which cannabis is described as a treatment for epilepsy. During the 19th century several medical reports were published on the ameliorative effects of cannabis extracts on several forms of convulsions (O'Shaughnessy, 1842; Shaw, 1843; Reynolds, 1890).

In spite of these promising results and its low toxicity, the use of cannabis preparations for medical purposes progressively decreased. This was due to the absence of standardized preparations, the unknown chemical composition, and the psychotropic secondary effects produced by cannabis.

Cannabidiol (CBD) is the major neutral nonpsychoactive cannabinoid in most cannabis preparations. It was first isolated by Adams et al, in 1940 but its structure was elucidated only 23 years later (Mechoulam and Shvo, 1963). The main active component of cannabis is delta-1-tetrahydrocannabinol (delta-1-THC) which was isolated in pure form and its structure was determined by Gaoni and Mechoulam in 1964. It is also named delta-9-THC. Numerous other natural cannabinoids are known today (Mechoulam, 1973; Mechoulam et al, 1976).

The unraveling of the chemistry of C. sativa brought a new interest in its pharmacology, and quite expectedly many laboratories studied the anticonvulsant properties of its components especially since early reports had shown that some natural and synthetic cannabinoids protected rats from convulsions (Loewe and Goodman, 1947) and were of therapeutic value in epileptic children (Davis and Ramsey, 1949).

More recently many reports have appeared attributing anticonvulsant properties to delta-1-THC and other cannabinoids, in a variety of experimental procedures (Garriott et al, 1968; Sofia et al, 1971; Consroe and Man, 1973; Karler et al, 1973, 1974; Plotnikoff, 1976). As a rule, delta-1-THC was the most studied compound. Most of the results obtained confirmed the rather potent anticonvulsant property of this drug. Its possible use as an antiepileptic drug in humans has, however, been hindered by its known psychotropic effects.

Since Brazilian workers (Carlini et al, 1973; Izquierdo et al, 1973) first demonstrated the anticonvulsant effects of CBD, there have been several additional reports on the effectiveness of CBD and its derivatives in protecting experimental animals from convulsions induced by various procedures (Karler et al, 1973; Turkanis et al, 1974; Carlini et al, 1975; Karler and Turkanis, 1976; Consroe and Wolkin, 1977). Consroe and Wolkin (1977) demonstrated that CBD has a high protective index comparable to that of phenobarbital and a spectrum of anticonvulsant activity in rodents similar to that of phenytoin. CBD also enhances the anti-convulsant potency of both phenytoin and phenobarbital (Consroe and Wolkin, 1977; Chesher and Jackson, 1974; Chesher et al., 1975).

In addition to its favorable anticonvulsant effects and absence of toxicity in animals, CBD seems to be devoid of psychotropic activity and other undesirable side effects in humans. The lack of toxicity of CBD in animals was demonstrated by intraperitoneal injection of 50 mg / kg daily for 90 days in mice, oral ingestion of 5-20 mg / kg daily for 90 days and 50 mg / kg for 27 days by rats and intravenous injection of 1,000 mg / kg in rabbits. No toxicity was observed (Cunha and Carlini, to be published). In man, oral intake of doses from 15 to 160 mg / day (Karniol et al, 1974; Hollister, 1973; Carlini et al, 1979), inhalation of 0.15 mg / kg (Dalton et al, 1976a), and intravenous injection of 30 mg (Perez-Reyes et al, 1973; Hollister, 1973) were not followed by ill effects. Chronic oral administration of 10 mg daily for 21 days did not induce any change in neurological (including EEG), clinical (including ECG), psychiatric, blood and urine examinations (Mincis et al, 1973).

Another recent investigation in our laboratory (Consroe et al., 1979) showed that CBD neither interferes with several psychomotor and psychological functions in humans nor potentiates alcohol effects on these functions.

The above data led us to undertake the present investigation which was performed in two phases. In phase 1, 3--6 mg / kg of CBD (roughly corresponding to 200--400 mg / subject) was administered daily to healthy human volunteers for 30 days. In phase 2, patients suffering from secondary generalized epilepsy with temporal irritative activity received 200--300 mg of the drug for periods of up to 4.5 months.

Experiment 1 (Phase 1 of Study)

Material and Methods

Subjects
16 adult volunteers (11 men and 5 women) aged 22-35, with an average weight of 65 kg were chosen from the staff of Escola Paulista de Medicina. They were in good health showing neither clinical nor laboratory evidence of cardiovascular, renal, hepatic or other impairments. The institutional review committee at Escola Paulista de Medicina previously approved the protocol of the experiments.

On the first day of the experiment the patients were submitted to a complete medical check-up, including clinical and neurological examinations, EEG, ECG, blood tests (hematocrit, hemoglobin, leukocyte and erythrocyte counts, bilirubin, oxaloacetic and puruvic transaminases and creatinine) and urine tests ; (osmolarity, pH, albumin, leukocyte and erythrocyte counts, cylinders and crystals) in the Department of Medicine of the Hospital Sao Paulo of Escola Paulista de Medicina. On the 7th day, they returned to the hospital, signed the informed consent and were randomly divided in two groups of 8. Each group started the ingestion of identical gelatine capsules containing either glucose as placebo (control group) or CBD (experimental group). The experiment was performed on a double-blind basis and the subjects were instructed to ingest the assigned capsules, one in the morning and the second in the afternoon for 30 days. Each capsule contained an amount of CBD (or glucose) equivalent to 1.5 mg / kg, i.e. a daily dosage of 3.0 mg / kg. 1 volunteer took 4 capsules of CBD daily (6 mg / kg) on the last 3 days of the experiment.

On the 3rd, 7th, 15th, 31st and 37th days after the beginning of drug ingestion, the subjects returned to the hospital to undergo the examinations described above.

Drug

Cannabidiol, in crystalline from (m.p. 66--67) was isolated from hashish of undetermined age. It was of Lebanese origin and was supplied by the Israeli Police. The isolation procedure has been described (Gaoni and Mechoulam, 1971). Part of the CBD was a gift from Makor Chemicals, P.O.B. 6570, Jerusalem

Results

General Observations
During the entire period of the experiment, the subjects did not report any symptoms suggestive of psychotropic effect of CBD. Of the 8 volunteers receiving the placebo, 1 gave up on the 21st day of the experiment for personal reasons; a second placebo subject reported sudoresis and 'palpitations' from the 7th to the 10th day in the veins of the feet, legs and head, stating that he had to uncover his feet to feel the palpitations less in order to sleep. Clinical and laboratory examinations were normal and the symptoms subsided after the 11th day without any measures on the part of the investigators.

Of the 8 volunteers receiving CBD, 2 reported somnolence, 1 during the first week and the other throughout the entire period of the experiment. A 3rd subject, with a history of mild insomnia, reported being able to sleep better during the first week of medication.

Neurological and clinical examinations, EEG and ECG tracings, and blood and urine analyses (detailed above) were within normal limits in the 16 subjects before, during and after the experiment.

Comments

It has been suggested that delta-1-THC and other cannabinoids may possess therapeutic potential as antidepressive drugs in patients with cancer (Regelson et al., 1975) or in the treatment of glaucoma (Hepler and Frank, 1971), asthma (Tashkin et al., 1972), etc. For a recent review see Mechoulam and Carlini (1978). However, acute administration of 20--60 mg of delta-1-THC induces a marked psychic change and has peripheral effects such as an increase in heart rate (Isbell et al., 1967; Kiplinger et al., 1971; Karniol et al., 1975) which would limit its therapeutic use.

In contrast, the present experiment shows that 3 mg / kg / day of CBD administered for 30 days (1 volunteer received 6 mg / kg / day during the last 3 days of experiment) did not induce any psychic or other side effects and was well tolerated by the 8 subjects. Thus CBD does not appear to have any toxic effect in humans when administered at the above dosage over a long period. This confirms our previous data obtained in animal (Cunha and Carlini, to be published).

In our opinion these findings justified the trial of the drug in

epileptic patients.
Experiment 2 (Phase 2 of Study)

Material and Methods

Subjects
15 Epileptic patients, 11 women and 4 men, aged 14-49 (average 24 years), with a documented history of frequent convulsions for at least 1 year, were selected. These patients were not reacting satisfactorily to the prescribed antiepileptic drugs they were receiving (table 1) in spite of special care to assure that the patients were taking them properly. The patients were diagnosed as cases of secondary generalized epilepsy; EEG tracings revealed irritative activity with temporal projection. They had at least one generalized convulsive crisis weekly.

Clinical and laboratory
examinations showed no signs of renal, cardiovascular or hepatic disease. The experiment was performed in the Neurology Out-Patient Clinics of the Hospital Sao Paulo (8 patients) and the Hospital da Santa Case (t patients). Each patient was followed by the same investigator, beginning 2 weeks before first drug administration and then throughout the whole period of drug administration.

In the 2 weeks before CBD or placebo
administration, the number of focal and generalized convulsive crises was recorded and considered as the baseline to evaluate treatment. On the first day of the experiment, the patients were submitted to the examinations described in experiment 1. They were randomly divided into one group of 8 (control group) and another group of 7 (CBD group) and returned to the hospital for 2 more days. After 1 week each group received placebo or CBD capsules in a double-blind procedure in addition to the antiepileptic drugs they were already receiving (see table 1). 1 placebo patient (Z.S.M.) was transferred to the CBD group after 1 month. Half of each group of patients was treated in each hospital. The patients were instructed to take 2 or 3 capsules daily (containing 100 mg of CBD or glucose) and to return to the hospital every week for clinical and / or laboratory examinations.

Clinical evaluation of drug treatment was made weekly using a scale with score 0-3, which took into consideration absence of convulsive crises or absence of generalization and self-reported subjective improvement (see tableII). According to this criterion all patients were scored 3 during the predrug phase (baseline).

Results

General Observations
During the curse of the experiment none of the 8 patients receiving CBD showed evidence of behavioral alterations which could be suggestive of a psychotropic effect. The minimum and maximum times of drug administration were 8 and 18 weeks for most patients (control and CBD groups). 2 of the placebo patients did not return after the end of the 4th week and 1 CBD patient after the 6th week. 1 placebo patient (Z.S.M.) whose condition remained unaltered during 4 weeks, wanted to give up the experiment, but remained in it after crossing over to the CBD group.

4 patients under CBD and 1 receiving placebo complained of somnolence during the experiment. Another CBD patient (M.C.P.) complained of painful gastric sensations after drug ingestion at the 6th week. These symptoms disappeared after prescription of an antacid and did not return throughout the experiment.

Table II. Criteria used to evaluate clinical efficacy of cannabidiol in epileptic patients

Score 0.....complete improvement
Score 1.....partial improvement
Score 2.....small improvement
Score 3.....without improvement

0 = Total absence of convulsive crises and self-reported subjective improvement.
1 = Absence of generalization of crises and self-reported subjective improvement.
2 = Only self-reported subjective improvement.
3 = No reduction in crises and no self-reported improvement.

Neurological Examination and EEG
Before drug treatment 1 CBD patient (N.D.) showed paresthetic walking towards the right, with spastic hypomotility of the right arm and leg, mainly of the right hand. He also presented a decrease in psychomotor functions. 2 other patients in the CBD group (A.A.S. and Z.S.M.) showed in examinations prior to the experiment some mental underdevelopment. Neurological examinations of all other patients were within normal limits.

Table III shows the results of the EEG analysis in a condensed

Table III shows the results of the EEG analysis in a condensed form. Of the patients receiving CBD, 3 showed improvement in EEG pattern with signs of decrease in frequency of crises throughout the experiment. 2 placebo patients also had improved EEG patterns (J.O.R., and J.S.V.) on one occasion, with a return to their previous condition on subsequent examination.

Clinical Evaluation of Treatment
Clinical evaluation was performed weekly, scoring 0 - 3 points to each patient compared to its own baseline (see table II and 'methods' for details). At the end of the treatment, the median of weekly score for each patient was calculated. The results are presented in table IV. During the first week of treatment there was general improvement in almost all patients (placebo and CBD groups), but from the second week, all placebo patients with one exception (M.D.M.S.) returned to their previous clinical state. At the end of the placebo treatment, 7 patients had a median of 3 (i.e. no improvement) whereas patient M.D.M.S. showed complete improvement (median 0). 2 placebo patients (J.S. and M.G.S.) with no improvement received the capsules for the 4th week of treatment but did not return. 3 other placebo patients (J.O.R.; J.S.V.; M.L.M.) remained under treatment for the period stated in table IV, after which it was decided to withdraw them from the experiment and to change the antiepileptic drugs they were receiving (see table I) in an attempt to improve their condition. Patient R.C. remained in the placebo group for 18 weeks and received all known antiepileptic drugs without success. Patient Z.S.M. was on placebo for 4 weeks without improvement and was subsequently transferred to 200 mg of CBD daily for 6 weeks (without her knowledge) with a small improvement (median 2).

Of the 8 patients receiving CBD, 4 showed considerable improvement in their clinical condition (median 0). However, in 1 case (M.C.P.) this was achieved by increasing the dosage to 300 mg daily. Patient A.A.S., who showed much improvement from the first week, unfortunately moved to another city after completing 6 weeks of treatment with CBD. The 5th patient (F.R.F.) improved only partially (median 1) although he attained score 0 in clinical evaluation (no convulsive crisis and subjective improvement) in 7 out of the 16 weeks of treatment. 2 of the 3 remaining patients showed improvement (score 2) whereas the last patient (N.D.) did not improve at all in spite of increasing CBD to 300 mg daily for the last 2 weeks of treatment.

Table IV

JOR placebo 3
JS placebo 3
MGS Placebo 3
JSV placebo 3
MLM placebo 3
RC placebo 3
MDMSplacebo 0
ZSM placebo 3

ZSM CBD200 2
FRF CBD200 1
OEBNCBD200 0
AAS CBD200 0
ASR CBD200 2
NP CBD200
300 3
MCP CBD200
300 0

0 = complete improvement
3 = no improvement

Discussion

Treatment of epilepsy is based mainly on anticonvulsant drugs. However, even when properly administered in well-diagnosed cases, these drugs succeed in helping only about 70-75% of the epileptic patients, whereas about 30% of the patients do not benefit at all (Robb, 1975). Furthermore, all clinically effective antiepileptic drugs induce undesirable side effects at normal dosage (osteomalacia, megaloblastic anemia; gingival hyperplasia) or due to overdose (nystagmus, motor incoordination, coma and death) or to idiosyncratic reactions (Kutt and Louis, 1972).

As already stated in the introduction, many ancient reports mention the antiepileptic properties of cannabis. More recently Consroe et al. (1975) described an epileptic patient receiving phenobarbital and phenytoin without good results, who benefited by smoking marihuana. These accounts indicate that marihuana contains chemical entities which may possess anti-epileptic properties.

According to the present data, CBD may turn out to be a useful drug for the treatment of some cases of epilepsy. There is hardly any

toxicity as shown in our phase 1 study; there were no changes in EEG, ECG, blood and urine analyses and neurological and clinical examinations were normal in 8 healthy volunteers receiving 3 mg / kg of CBD daily for 30 days. A similar absence of toxicity was also noted in our phase 2 study in which 8 epileptic patients received 200 or 300 mg for up to 4 1/2 months. Furthermore, none of the 16 subjects receiving CBD showed any psychic delta-1-THC-type effects. The present data obtained after long-term administration also confirm previous reports showing the absence of toxicity in acute studies (Hollister, 1973; Carlini et al, 1979).

Somnolence reported by 3 healthy volunteers and 4 epileptic patients (43% of the subjects receiving the drug) was the only CBD side effect noted. A certain hypnotic effect is frequently observed with drugs which possess antiepileptic properties. We have in fact recently demonstrated that CBD does induce better sleep in human volunteers (Carlini et al., 1979). On the other hand, CBD induced a remarkable improvement (median 0) in 4 of 8 epileptic patients who remained almost free of convulsive crises during the entire period of the experiment. In a 5th patient (median 1), the crises were absent in 7 of the 16 weeks of treatment. All of these patients (as well as their relatives) reported subjective improvement. A similar subjective effect was also reported by 2 more patients and only in 1 patient CBD failed to induce any form of clinical benefit. This is in striking contrast to the results obtained with the 8 patients receiving placebo of whom 7 showed no improvement in their clinical condition.

However, EEG results were not as consistent as the clinical evaluation. As seen in table III, clinical improvement was not always followed by positive changes in the tracings. As the International League against Epilepsy (Commission on Antiepileptic Drugs) does not consider EEG mandatory in this type of research (Penry, 1973), EEG data were not included in the overall clinical evaluation of CBD effects. It should also be emphasized that the abnormal EEGs were present from the beginning of the experiment even though all patients were receiving known antiepileptic drugs. Furthermore, phenytoin and barbiturates fail to control the EEG abnormalities of epileptics in spite of being able to abolish their behavioral convulsions; phenytoin may even increase the prominence of focal spikes (Morrel et al., 1959; Millichap, 1969).

Wall et al. (1976) have reported pharmacokinetic studies in man with 3H-CBD injected intravenously into 5 healthy volunteers. They observed that 8% of the total initial dose (20 mg of CBD) was present in plasma 30 min after injection, to fall to 3% after 60 minutes. 3 days later, 33% was excreted in the feces and 16% in the urine, with 50% remaining in tissues and organs. Therefore, CBD seems to have a relatively long half-life, which favors its use as a drug in epileptics.

However, in spite of the large number of reports showing beneficial effects of cannabis and its preparations in many forms of experimental convulsions and in human epilepsy, a few reports claim the contrary. Feeney et al. (1976) showed that delta-1-THC in cats induced EEG changes resembling those observed in convulsions, and Perez-Reyes and Wingfield (1974) described a similar effect of CBD in man. In neither case, however, were behavioral convulsions observed. It is interesting in this context that phenytoin may increase activity of focal spikes (Millichap, 1969). To the best of our knowledge there is only one report attributing a worsening of an epileptic convulsive crisis (grand mal) following use of marihuana smoking (Keeler and Reifler, 1967), and we do not know of any cases described for CBD. Furthermore, in none of our 8 epileptic patients did we observe deterioration of clinical symptomatology or of EEG, but rather the opposite effect was true.

The mechanism by which CBD benefited our epileptic patients is not known. All 8 patients were also receiving known antiepileptic drugs which were by themselves, however, ineffective. One possibility is that CBD potentiated their action since enhancement by CBD of anticonvulsant activity of phenobarbital and phenytoin in animals has been demonstrated (Consroe and Wolkin, 1977; Chesher and Jackson, 1974; Chesher et al., 1975). In man, however, 50--500 mcg / kg CBD given in cigarette form is not able to alter plasma concentrations of secobarbital (Dalton et al., 1976b). The possibility that CBD acts per se should also be taken into consideration, as shown by several reports describing its direct anticonvulsant effects in animals.

In conclusion, we have found that CBD had a beneficial effect in patients suffering from secondary generalized epilepsy with temporal foci, who did not benefit from know anti-epileptic drugs. Further research with more patients and other forms of epilepsy is needed to establish the scope of the antiepileptic effects of CBD in humans.

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Neuroprotective effect of (-)Delta9-tetrahydrocannabinol and cannabidiol

El-Remessy AB, Khalil IE, Matragoon S, Abou-Mohamed G, Tsai NJ, Roon P, Caldwell RB, Caldwell RW, Green K, Liou GI
Neuroprotective effect of (-)Delta9-tetrahydrocannabinol and cannabidiol in N-methyl-D-aspartate-induced retinal neurotoxicity: involvement of peroxynitrite. [Comparative Study, Journal Article, Research Support, Non-U.S. Gov't, Research Support, U.S. Gov't, P.H.S.]
Am J Pathol 2003 Nov; 163(5):1997-2008.

In glaucoma, the increased release of glutamate is the major cause of retinal ganglion cell death. Cannabinoids have been demonstrated to protect neuron cultures from glutamate-induced death. In this study, we test the hypothesis that glutamate causes apoptosis of retinal neurons via the excessive formation of peroxynitrite, and that the neuroprotective effect of the psychotropic Delta9-tetrahydroxycannabinol (THC) or nonpsychotropic cannabidiol (CBD) is via the attenuation of this formation.

Excitotoxicity of the retina was induced by intravitreal injection of N-methyl-D-aspartate (NMDA) in rats, which also received 4-hydroxy-2,2,6,6-tetramethylpiperidine-n-oxyl (TEMPOL,a superoxide dismutase-mimetic), N-omega-nitro-L-arginine methyl ester (L-NAME, a nitric oxide synthase inhibitor), THC, or CBD. Retinal neuron loss was determined by TDT-mediated dUTP nick-end labeling assay, inner retinal thickness, and quantification of the mRNAs of ganglion cell markers.

NMDA induced a dose- and time-dependent accumulation of nitrite/nitrate, lipid peroxidation, and nitrotyrosine (foot print of peroxynitrite), and a dose-dependent apoptosis and loss of inner retinal neurons. Treatment with L-NAME or TEMPOL protected retinal neurons and confirmed the involvement of peroxynitrite in retinal neurotoxicity.

The neuroprotection by THC and CBD was because of attenuation of peroxynitrite. The effect of THC was in part mediated by the cannabinoid receptor CB1.

These results suggest the potential use of CBD as a novel topical therapy for the treatment of glaucoma.

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EFFECTS OF CANNABIDIOL IN HUNTINGTON'S DISEASE

Neurology 36 (Suppl 1) April 1986 p. 342

Reuven Sandyk, Paul Consroe, Lawrence Z. Stern, and Stuart R. Snider, Tucson, AZ

Cannabidiol (CBD) is a major nonpsychoactive cannabinoid of marijuana. Based on reports indicating possible efficacy of CBD in dystonic movements (Neurology 1984; 34 [Suppl 1]: 147 and 1985; 35 [Suppl 1]: 201), we tried CBD in three patients with Huntington's disease (HD).

The patients;, aged 30 to 56, had HD of 7 to 12 years' duration. Their condition has been slowly progressive and unresponsive to prior therapy with neuroleptics. Orally administered CBD was initiated at 300 mg/d and increased 1 week later to 600 mg/d for the next 3 weeks.

Mild improvement (5 to 15%) in the choreic movements was documented using the tongueprotrusion test (Neurology [Minneap} 1972; 22: 929-33) and a chorea severity evaluation scale (Br J Clin Pharmacol 1981; 11: 129-51) after the first week. Further improvement (20 to 40%) was noticed after the second week of CBD, and this remained stable for the following 2 weeks.

Except for transient, mild hypotension, no side effects were recorded, and laboratory tests were normal. Withdrawal of CBD after 48 hours resulted in return of choreic movements to the pre-CBD state.

(Supported in part by NINCDS grant #NS15441)

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The therapeutic rationale for combining tetrahydrocannabinol and cannabidiol.
(may need free registration)

Med Hypotheses. 2006; 66(2):234-46 (ISSN: 0306-9877)

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This study examines the current knowledge of physiological and clinical effects of tetrahydrocannabinol (THC) and cannabidiol (CBD) and presents a rationale for their combination in pharmaceutical preparations. Cannabinoid and vanilloid receptor effects as well as non-receptor mechanisms are explored, such as the capability of THC and CBD to act as anti-inflammatory substances independent of cyclo-oxygenase (COX) inhibition.

CBD is demonstrated to antagonise some undesirable effects of THC including intoxication, sedation and tachycardia, while contributing analgesic, anti-emetic, and anti-carcinogenic properties in its own right.

In modern clinical trials, this has permitted the administration of higher doses of THC, providing evidence for clinical efficacy and safety for cannabis based extracts in treatment of spasticity, central pain and lower urinary tract symptoms in multiple sclerosis, as well as sleep disturbances, peripheral neuropathic pain, brachial plexus avulsion symptoms, rheumatoid arthritis and intractable cancer pain. Prospects for future application of whole cannabis extracts in neuroprotection, drug dependency, and neoplastic disorders are further examined.

The hypothesis that the combination of THC and CBD increases clinical efficacy while reducing adverse events is supported.

Major Subject Heading(s)	Minor Subject Heading(s)	CAS Registry / EC Numbers
	• Animals • Cannabidiol [administration & dosage] • Clinical Trials as Topic • Drug Therapy, Combination • Humans • Neoplasms [drug therapy] • Tetrahydrocannabinol [administration & dosage]	• 13956-29-1 (Cannabidiol) • 1972-08-3 (Tetrahydrocannabinol)

- PreMedline Identifier: 16209908
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Cannabidiol-Induced Apoptosis in Human Leukemia Cells

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Abstract

In the current study, we examined the effects of the nonpsychoactive cannabinoid, cannabidiol, on the induction of apoptosis in leukemia cells.

Exposure of leukemia cells to cannabidiol led to cannabinoid receptor 2 (CB2)-mediated reduction in cell viability and induction in apoptosis.

Furthermore, cannabidiol treatment led to a significant decrease in tumor burden and an increase in apoptotic tumors in vivo. From a mechanistic standpoint, cannabidiol exposure resulted in activation of caspase-8, caspase-9, and caspase-3, cleavage of poly(ADP-ribose) polymerase, and a decrease in full-length Bid, suggesting possible cross-talk between the intrinsic and extrinsic apoptotic pathways. The role of the mitochondria was further suggested as exposure to cannabidiol led to loss of mitochondrial membrane potential and release of cytochrome *c*.

It is noteworthy that cannabidiol exposure led to an increase in reactive oxygen species (ROS) production as well as an increase in the expression of the NAD(P)H oxidases Nox4 and $p22^{phox}$. Furthermore, cannabidiol-induced apoptosis and reactive oxygen species (ROS) levels could be blocked by treatment with the ROS scavengers or the NAD(P)H oxidase inhibitors.

Finally, cannabidiol exposure led to a decrease in the levels of p-p38 mitogen-activated protein kinase, which could be blocked by treatment with a CB2-selective antagonist or ROS scavenger. Together, the results from this study reveal that cannabidiol, acting through CB2 and regulation of Nox4 and $p22^{phox}$ expression, may be a novel and highly selective treatment for leukemia.

Footnotes

- This work was supported in part by grants from National Institutes of Health (R01-DA016545, R21-DA014885, K12-DA14041, and P50-DA05274), The American Cancer Society (IRG-100036) and The Jeffress Memorial Trust Fund (J-741).

- **ABBREVIATIONS:** THC, Δ^9-tetrahydrocannabinol; CBD, cannabidiol; ROS, reactive oxygen species; PBS, phosphate-buffered saline; SR141716A; CB1, cannabinoid receptor 1; CB2, cannabinoid receptor 2; DPI, diphenylene iodinium; CPZ, capsazepine; VR1, vanilloid receptor 1; NAC, *N*-acetylcysteine; TUNEL, terminal deoxynucleotidyl transferase dUTP nick-end labeling; $DiOC_6$, 3,3′-dihexylcarbocyanine iodide; ERK, extracellular signal-regulated kinase; JNK, c-Jun NH_2-terminal kinase; MAPK, mitogen-activated protein kinase.

- Received February 28, 2006.
- Accepted June 5, 2006.
- The American Society for Pharmacology and Experimental Therapeutics

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Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats. (may need free registration)

Murillo-Rodríguez E ; Millán-Aldaco D ; Palomero-Rivero M ; Mechoulam R ; Drucker-Colín R
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Delta(9)-tetrahydrocannabinol (Delta(9)-THC) and cannabidiol (CBD) are two major constituents of Cannabis sativa. Delta(9)-THC modulates sleep, but no clear evidence on the role of CBD is available. In order to determine the effects of CBD on sleep, it was administered intracerebroventricular (icv) in a dose of 10 microg/5 microl at the beginning of either the lights-on or the lights-off period.

We found that CBD administered during the lights-on period increased wakefulness (W) and decreased rapid eye movement sleep (REMS).
No changes on sleep were observed during the dark phase. Icv injections of CBD (10 microg/5microl) induced an enhancement of c-Fos expression in waking-related brain areas such as hypothalamus and dorsal raphe nucleus (DRD). Microdialysis in unanesthetized rats was carried out to characterize the effects of icv administration of CBD (10 microg/5 microl) on extracellular levels of dopamine (DA) within the nucleus accumbens. CBD induced an increase in DA release.

Finally, in order to test if the waking properties of CBD could be blocked by the sleep-inducing endocannabinoid anandamide (ANA), animals received ANA (10 microg/2.5 microl, icv) followed 15 min later by CBD (10 microg/2.5 microl).

Results showed that the waking properties of CBD were not blocked by ANA. In conclusion, we found that CBD modulates waking via activation of neurons in the hypothalamus and DRD.

Both regions are apparently involved in the generation of alertness. Also, CBD increases DA levels as measured by microdialysis and HPLC procedures. Since CBD induces alertness, it might be of therapeutic value in sleep disorders such as excessive somnolence.

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Who's Afraid of Cannabidiol?

Ronen Durst, Haim Danenberg, Ruth Gallily, Raphael Mechoulam, Keren Meir, Etty Grad, Ronen Beeri, Thea Pugatsch, Elizabet Tarsish, and Chaim Lotan

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Submitted 24 January 2007 ; accepted in final form 19 September 2007

ABSTRACT

Cannabidiol (CBD) is a major, nonpsychoactive *Cannabis* constituent with anti-inflammatory activity mediated by enhancing adenosine signaling. Inasmuch as adenosine receptors are promising pharmaceutical targets for ischemic heart diseases, we tested the effect of CBD on ischemic rat hearts. For the in vivo studies, the left anterior descending coronary artery was transiently ligated for 30 min, and the rats were treated for 7 days with CBD (5 mg/kg ip) or vehicle. Cardiac function was studied by echocardiography.

Infarcts were examined morphometrically and histologically. For ex vivo evaluation, CBD was administered 24 and 1 h before the animals were killed, and hearts were harvested for physiological measurements.

In vivo studies showed preservation of shortening fraction in CBD-treated animals: from 48 ± 8 to 39 ± 8% and from 44 ± 5 to 32 ± 9% in CBD-treated and control rats, respectively (n = 14, $P < 0.05$). Infarct size was reduced by 66% in CBD-treated animals, despite nearly identical areas at risk (9.6 ± 3.9 and 28.2 ± 7.0% in CBD and controls, respectively, $P < 0.001$) and granulation tissue proportion as assessed qualitatively.

Infarcts in CBD-treated animals were associated with reduced myocardial inflammation and reduced IL-6 levels (254 ± 22 and 2,812 ± 500 pg/ml in CBD and control rats, respectively, $P < 0.01$). In isolated hearts, no significant difference in infarct size, left ventricular developed pressures during ischemia and reperfusion, or coronary flow could be detected between CBD-treated and control hearts.

Our study shows that CBD induces a substantial in vivo cardioprotective effect from ischemia that is not observed ex vivo. Inasmuch as CBD has previously been administered to humans without causing side effects, it may represent a promising novel treatment for myocardial ischemia....read more

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Cannabidiol May be Effective in Preventing Bovine Spongiforme Enzephalopathy (Mad Cow Disease)

J Neurosci 2007;27

Cannabidiol (CBD) may prevent the development of prion diseases, the most known being BSE (bovine spongiforme enzephalopathy), which is often called mad cow disease. It is believed that the BSE may be transmitted to human beings. In humans, it is known as Creutzfeldt-Jakob disease.

The infectious agent in prion diseases is believed to be a specific type of misfolded protein called prion. Misfolded prion proteins carry the disease between individuals and cause deterioration of the brain. The French researchers reported that the non- psychoactive cannabis constituent CBD inhibited the accumulation of prion proteins in both mouse and sheep prion- infected cells, whereas other cannabinoids were either weak or not effective.

Moreover, after infection with mouse scrapie, a prion disease, CBD limited accumulation of the prion protein in the brain and significantly increased the survival time of infected mice. CBD inhibited the nerve damaging effects of prions in a concentration-dependent manner. Researchers noted that CBD may be a promising agent for the treatment of prion diseases.

(Source: Dirikoc S, Priola SA, Marella M, Zsuerger N, Chabry J. Nonpsychoactive cannabidiol prevents prion accumulation and protects neurons against prion toxicity. J Neurosci 2007;27(36):9537-44.)

Click here to view original article

Prion diseases are transmissible neurodegenerative disorders characterized by the accumulation in the CNS of the protease-resistant prion protein (PrPres), a structurally misfolded isoform of its physiological counterpart PrPsen. Both neuropathogenesis and prion infectivity are related to PrPres formation. Here, we report that the nonpsychoactive cannabis constituent cannabidiol (CBD) inhibited PrPres accumulation in both mouse and sheep scrapie-infected cells, whereas other structurally related cannabinoid analogs were either weak inhibitors or noninhibitory. Moreover, after intraperitoneal infection with murine scrapie, peripheral injection of CBD limited cerebral accumulation of PrPres and significantly increased the survival time of infected mice. Mechanistically, CBD did not appear to inhibit PrPres accumulation via direct interactions with PrP, destabilization of PrPres aggregates, or alteration of the expression level or subcellular localization of PrPsen.

However, CBD did inhibit the neurotoxic effects of PrPres and affected PrPres-induced microglial cell migration in a concentration-dependent manner. Our results suggest that CBD may protect neurons against the multiple molecular and cellular factors involved in the

may protect neurons against the multiple molecular and cellular factors involved in the different steps of the neurodegenerative process, which takes place during prion infection. When combined with its ability to target the brain and its lack of toxic side effects, CBD may represent a promising new anti-prion drug.

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Cannabidiol, extracted from Cannabis sativa, selectively inhibits inflammatory hypermotility in mice

Capasso R, Borrelli F, Aviello G, Romano B, Scalisi C, Capasso F, Izzo AA

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Background and purpose:Cannabidiol is a Cannabis-derived non-psychotropic compound that exerts a plethora of pharmacological actions, including anti-inflammatory, neuroprotective and antitumour effects, with potential therapeutic interest. However, the actions of cannabidiol in the digestive tract are largely unexplored. In the present study, we investigated the effect of cannabidiol on intestinal motility in normal (control) mice and in mice with intestinal inflammation.

Experimental approach:

Motility in vivo was measured by evaluating the distribution of an orally administered fluorescent marker along the small intestine; intestinal inflammation was induced by the irritant croton oil; contractility in vitro was evaluated by stimulating the isolated ileum, in an organ bath, with ACh.Key results:In vivo, cannabidiol did not affect motility in control mice, but normalized croton oil-induced hypermotility. The inhibitory effect of cannabidiol was counteracted by the cannabinoid CB(1) receptor antagonist rimonabant, but not by the cannabinoid CB(2) receptor antagonist SR144528 (N-[-1S-endo-1,3,3-trimethyl bicyclo [2.2.1] heptan-2-yl]-5-(4-chloro-3-methylphenyl)-1-(4-methylbenzyl)-pyrazole-3-carboxamide), by the opioid receptor antagonist naloxone or by the alpha(2)-adrenergic antagonist yohimbine.

Cannabidiol did not reduce motility in animals treated with the fatty acid amide hydrolase (FAAH) inhibitor N-arachidonoyl-5-hydroxytryptamine, whereas loperamide was still effective. In vitro, cannabidiol inhibited ACh-induced contractions in the isolated ileum from both control and croton oil-treated mice.Conclusions and implications:Cannabidiol selectively reduces croton oil-induced hypermotility in mice in vivo and this effect involves cannabinoid CB(1) receptors and FAAH. In view of its low toxicity in humans, cannabidiol may represent a good candidate to normalize motility in patients with inflammatory bowel disease.British Journal of Pharmacology (2008) 154, 1001-1008; doi:10.1038/bjp.2008.177; published online 12 May 2008.

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Full-text of this article is available online (may require subscription).

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Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug

A.W. Zuardi, J.A.S. Crippa, J.E.C. Hallak, F.A. Moreira and F.S. Guimarães

Braz J Med Biol Res, April 2006, Volume 39(4) 421-429 (Review)

Abstract

A high dose of D^9-tetrahydrocannabinol, the main *Cannabis sativa* (cannabis) component, induces anxiety and psychotic-like symptoms in healthy volunteers. These effects of D^9-tetrahydrocannabinol are significantly reduced by cannabidiol (CBD), a cannabis constituent

tetrahydrocannabinol are significantly reduced by cannabidiol (CBD), a cannabis constituent which is devoid of the typical effects of the plant.

This observation led us to suspect that CBD could have anxiolytic and/or antipsychotic actions. Studies in animal models and in healthy volunteers clearly suggest an anxiolytic-like effect of CBD. The antipsychotic-like properties of CBD have been investigated in animal models using behavioral and neurochemical techniques which suggested that CBD has a pharmacological profile similar to that of atypical antipsychotic drugs.

The results of two studies on healthy volunteers using perception of binocular depth inversion and ketamine-induced psychotic symptoms supported the proposal of the antipsychotic-like properties of CBD. In addition, open case reports of schizophrenic patients treated with CBD and a preliminary report of a controlled clinical trial comparing CBD with an atypical antipsychotic drug have confirmed that this cannabinoid can be a safe and well-tolerated alternative treatment for schizophrenia.

Future studies of CBD in other psychotic conditions such as bipolar disorder and comparative studies of its antipsychotic effects with those produced by clozapine in schizophrenic patients are clearly indicated.

Key words: Cannabidiol, D^9-Tetrahydrocannabinol, Cannabinoid, Anxiety, Antipsychotic, Schizophrenia

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Introduction

The use *Cannabis sativa* (cannabis) extracts as medicine was described in China and India before the birth of Christ.

The therapeutic use of cannabis was introduced in Western medicine in the first half of the 19th century and reached its climax in the last two decades of the same century.

At the turn of the century, several pharmaceutical companies were marketing cannabis extracts and tinctures which were prescribed by doctors for many different complaints including pain, whooping cough and asthma, and as a sedative/hypnotic agent.

However, the use of cannabis as a medicine almost completely disappeared at about the middle of the 20th century.

The main reasons for this disappearance were the variable potency of cannabis extracts, the erratic and unpredictable individual responses, the introduction of synthetic and more stable pharmaceutical substitutes such as aspirin, chloral hydrate and barbiturates, the recognition of important adverse effects such as anxiety and cognitive impairment, and the legal restrictions to the use of cannabis-derived medicines .

Today this situation has changed considerably. The main active psychotropic constituent of cannabis, D^9-tetrahydrocannabinol (D^9-THC), was isolated, identified and synthesized in the 1960's. Almost three decades later, cannabinoid receptors in the brain were described and cloned and the endogenous cannabinoids were isolated and identified.

As a result of these discoveries the interest in cannabis research has remarkably increased. For instance, the number of publications using the key word "brain", compiled by the ISI Web of Knowledge, increased 26 times from 1960-1964 to 2000-2004, while the number of publications about `cannabis' increased 78.5 times during the same period.

As a consequence, the research on the use of cannabis as medicine has been renewed.

Although D^9-THC is commonly accepted as the main factor responsible for the effects of cannabis, several reports have demonstrated that other components of the plant influence its pharmacological activity.

One of these components is cannabidiol (CBD), which may constitute up to 40% of cannabis extracts and is devoid of the typical psychological effects of cannabis in humans.

Studies on the interaction between D^9-THC and CBD have produced apparently contradictory results (7). Although potentiation of the effects of D^9-THC has been observed (8,9), this phenomenon probably involves pharmacokinetic interactions since CBD is a potent inhibitor of hepatic drug metabolism (10) and increases D^9-THC concentrations in the brain.

Several studies, however, have reported antagonism of the effects of D^9-THC when both compounds are administered simultaneously to animals or humans.

CBD (1 mg/kg) co-administered with D^9-THC (0.5 mg/kg) significantly reduced the anxiety and the psychotomimetic symptoms induced by the latter drug in healthy volunteers.

Since the dose of CBD used in that study did not change D^9-THC levels in blood, it was suggested that CBD blocked the effects of D^9-THC by some intrinsic pharmacological properties.

Actually, when administered alone CBD produced its own effects, including hypnotic, anticonvulsive, neuroprotective, and hormonal (increased corticosterone and cortisol levels) effects (19,20).

These effects led to the hypothesis that CBD could have anxiolytic and/or antipsychotic effects.

Anxiolytic effect of cannabidiol

The anxiolytic properties of CBD has been demonstrated by several pre-clinical studies that employed different paradigms such as the conditioned emotional response, the Vogel conflict test and the elevated plus-maze.

In the later study, the effective doses of CBD ranged from 2.5 to 10 mg/kg, and the drug produced an inverted U-shaped dose-response curve, the higher doses being no longer effective in rats. This could explain the negative results obtained with high doses of CBD (above 100 mg/kg) in a previous study employing the Geller-Seifter conflict test.

To evaluate a possible anxiolytic effect of CBD in humans, a double-blind study was conducted on healthy volunteers submitted to a simulation of the public speaking test. CBD (300 mg, *po*) was compared to ipsapirone (5 mg), diazepam (10 mg) or placebo. The results showed that both CBD and the two other anxiolytic compounds attenuated the anxiety induced by the test.

The anxiolytic-like effect of CBD in healthy volunteers was also observed in a more recent double-blind study that investigated its effects on regional cerebral blood flow by single-photon emission computed tomography.

Because the procedure, by itself, can be interpreted as an anxiogenic situation, it permits the evaluation of anxiolytic drugs. CBD induced a clear anxiolytic effect and a pattern of cerebral activity compatible with an anxiolytic activity.

Therefore, similar to the data obtained in animal models, results from studies on healthy volunteers have strongly suggested an anxiolytic-like effect of CBD.

Antipsychotic effect

Studies employing animal models

Animal models used for screening antipsychotic drugs are based on the neurochemical hypothesis of schizophrenia, involving mainly the neurotransmitters dopamine and glutamate.

Antagonism of dopamine D_2 receptors may be a common feature of most clinically effective antipsychotic drugs, especially those active against hallucinations and delusions.

The dopamine-based models usually employ apomorphine, a direct agonist, or amphetamine, a drug that increases the release of this neurotransmitter and blocks its re-uptake.

Another common effect of antipsychotic drugs is hyperprolactinemia that results from the antagonism of D_2 receptors on anterior-pituitary mammotrophic cells. These cells are tonically inhibited by dopamine produced in the hypothalamic arcuate nucleus.

Conventional or typical antipsychotic drugs, especially those with high affinity for D_2 receptors (haloperidol being the standard compound), induce motor side effects characterized by a Parkinson-like syndrome.

On the contrary, atypical antipsychotic drugs, of which clozapine is the prototype, are therapeutically effective at doses that induce fewer or no Parkinson-like effects.

The probability of an antipsychotic agent to induce Parkinson-like symptoms may be evaluated in the catalepsy test.

Atypical antipsychotics inhibit the stereotypies and hyperlocomotion induced by dopamine agonists at lower doses than those that produce catalepsy.

As a first step in the investigation of possible antipsychotic-like properties of CBD, the drug was compared to haloperidol in rats submitted to dopamine-based models.

However, blocking D_2 receptors is not necessarily the only mechanism for the antipsychotic activity. Several lines of evidence suggest that the glutamatergic N-methyl-D-aspartate (NMDA) receptor is involved in the mechanism of action of clozapine.

The glutamate-based models of schizophrenia employ sub-anesthetic doses of ketamine, a glutamate NMDA receptor antagonist, or its related compound phencyclidine, to induce psychotic symptoms. A more recent study investigated the effects of CBD in both dopamine and glutamate-based models predictive of antipsychotic activity.

The study compared the ability of CBD, haloperidol and clozapine to prevent the hyperlocomotion induced by amphetamine or ketamine in mice (34). The results of these two studies are summarized in Table 1.

TABLE

Table 1. Summary of two studies employing animal models for the screening of antipsychotic drugs, which compared cannabidiol, haloperidol and clozapine in rats and mice.

[View larger version of this table (87 K JPG file)]

CBD (15-60 mg/kg), like haloperidol (0.25-0.5 mg/kg), reduced the apomorphine-induced stereotyped behavior in rats in a dose-related manner. These drugs also increased the plasma levels of prolactin.

However, higher doses of CBD were needed (120 and 240 mg/kg) to obtain such effects. Moreover, in contrast to haloperidol, CBD did not induce catalepsy, even at doses as high as 480 mg/kg.

In agreement with the results obtained in rats, CBD (15-60 mg/kg) inhibited the hyperlocomotion induced by amphetamine in mice in a dose-related manner.

In addition, the drug also attenuated the hyperlocomotion induced by ketamine, expanding its antipsychotic-like effects to a glutamate-based model.

As expected, while both haloperidol (0.15-0.6 mg/kg) and clozapine (1.25-5.0 mg/kg) inhibited hyperlocomotion, only haloperidol induced catalepsy in this dose range. Therefore, similar to clozapine, CBD did not induce catalepsy at doses that inhibited hyperlocomotion in mice.

These results support the view that CBD exhibits a profile similar to that of atypical antipsychotic drugs.

In addition to being tested on behavioral models, typical and atypical antipsychotics may also be distinguished according to their pattern of neural activation.

This may be detected by the expression of the proto-oncogene *c-Fos*. For example, haloperidol induces Fos immunoreactivity in the dorsal striatum, probably reflecting its motor side effects, while clozapine induces Fos immunoreactivity in the prefrontal cortex but not in the dorsal striatum.

The Fos immunoreactivity pattern induced by CBD (120 mg/kg) was compared to that of haloperidol (1 mg/kg) and clozapine (20 mg/kg) in rats. Only haloperidol increased Fos immunoreactivity in the dorsal striatum, while both CBD and clozapine, but not haloperidol, induced Fos immunoreactivity in the prefrontal cortex (36,37).

These results are consistent with the behavioral data obtained when comparing CBD with these prototype antipsychotics.

In conclusion, animal models employing behavioral as well as neurochemical techniques suggest that CBD has a pharmacological profile similar to that of an atypical antipsychotic drug.

Safety studies

Safety studies of CBD were required before human tests. CBD was extensively investigated in laboratory animals to detect possible side or toxic effects.

Acute CBD administration by the oral, inhalatory or intravenous route did not induce any significant toxic effect in humans. In addition, chronic administration of CBD for 30 days to healthy volunteers, at daily doses ranging from 10 to 400 mg, failed to induce any significant alteration in neurological, psychiatric or clinical exams.

Finally, in patients suffering from Huntington's disease, daily doses of CBD (700 mg) for 6 weeks did not induce any toxicity.

Therefore, confirming results from animal studies, the available clinical data suggest that CBD can be safely administered over a wide dose range.

Clinical use

In 1848 the French psychiatrist Jacques-Joseph Moreau de Tour began to investigate the effects of cannabis. He proposed for the first time the use of the plant as an experimental psychotomimetic.

Results from a recent study, obtained with more appropriate measurements and scales, agreed with Moreau's observation that D^9-THC administration induces subjective, cognitive and behavioral changes that resemble endogenous psychosis, suggesting that D^9-THC can, indeed, be used as an experimental psychotomimetic drug.

In 1982, a study investigating a possible interaction between D^9-THC and CBD in healthy volunteers demonstrated that the latter drug could inhibit D^9-THC-induced subjective changes that resembled symptoms of psychotic diseases (Figure 1).

In the same year, it was observed that patients admitted to a psychiatric hospital in South Africa, after the use of a variety of cannabis virtually devoid of CBD, showed much higher frequency of acute psychotic episodes than in other countries.

These lines of evidence led to several investigations of a possible antipsychotic effect of CBD.

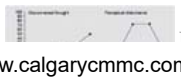
Figure 1. Percentage of healthy volunteers who exhibited psychotic-like

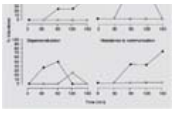

Figure 1. Percentage of healthy volunteers who exhibited psychotic-like effects after the ingestion of 0.5 mg/kg D^9-tetrahydrocannabinol (D^9-THC; lozenges) and a combination of 0.5 mg/kg D^9-THC + 1 mg/kg cannabidiol (circles).

[View larger version of this image (48 K JPG file)]

In order to evaluate the antipsychotic effects of new drugs in healthy volunteers, a useful model is the perception of binocular depth inversion. When a picture is presented separately to each eye, with a slight difference in the angle, it induces a three-dimensional perception.

The inversion of this picture from one eye to the other normally induces a change in convexity. This change may not be perceived if familiar objects (faces, for example) are presented, with the expected image predominating, which is illusory. Schizophrenic patients have difficulty in perceiving this illusory image, reporting a more veridical judgment.

During antipsychotic treatment, the inverted faces were seen as more illusionary.

This veridical judgment may also be obtained by the administration of psychotomimetic drugs such as nabilone, a D^9-THC analogue. In this model, impairment of the perception of the illusory image induced by nabilone was attenuated by CBD, suggesting an antipsychotic-like effect of this compound.

Another important model used to evaluate antipsychotic-like activity in healthy volunteers is the administration of sub-anesthetic doses of ketamine. This glutamate-based model induces a psychotic reaction that mimics both positive and negative symptoms of schizophrenia.

A double-blind crossover procedure was performed to study the effect of CBD in this model. Nine healthy volunteers were assigned randomly to the placebo or CBD (600 mg) groups in two experimental sessions separated by a 1-week interval.

After being submitted to psychiatric assessment scales, the volunteers received placebo orally or the drug and rested for 65 min.

An infusion pump was then installed and an intravenous bolus of S-ketamine (0.26 mg/kg) was administered during 1 min followed by a maintenance dose of 0.25 mg/kg for 30 min.

A Clinician-Administered Dissociative States Scale (CADSS) was applied at the beginning of the sessions and 90 min after the bolus injection.

The volunteers were asked to respond the scale according to the period during which they felt most symptomatic. CBD attenuated the effects of ketamine on the total score of the CADSS and also on each of its factors separately. This effect was significant for the depersonalization factor, further reinforcing the antipsychotic-like properties of CBD (Figure 2).

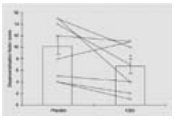

Figure 2. Depersonalization factor scores of the Clinician-Administered Dissociative States Scale for each healthy volunteer (lines) during intravenous ketamine infusion, after oral placebo or cannabidiol (CBD) (600 mg) administration. Bars indicate the mean ± SEM. *P < 0.05 compared to placebo (paired *t*-test) for 9 volunteers.

[View larger version of this image (35 K JPG file)]

In view of the safe profile of CBD administration in humans and in laboratory animals, we decided to perform open-label clinical trials in a reduced number of patients. In 1995, CBD was tested in a case study with a 19-year-old schizophrenic female patient who presented serious side effects after treatment with conventional antipsychotics.

Following a wash-out period of 4 days this patient received increasing oral doses of CBD dissolved in oil, reaching 1500 mg/day, for 4 weeks. After this period, CBD administration was interrupted and placebo was administered for 4 days.

Finally, the treatment was shifted to increasing doses of haloperidol that reached 12.5 mg/day. The psychiatric interviews were video-recorded and the symptoms were assessed by a blinded-psychiatrist using the Brief Psychiatric Rating Scale (BPRS).

A significant improvement was observed during CBD treatment, while a worsening was observed when the administration was interrupted. The improvement obtained with CBD was not increased by haloperidol (Figure 3, patient A).

Further supporting the safe profile of CBD, no side effects were observed, as assessed by the Ugvalg for Kliniske Undersgelser (UKU) scale.

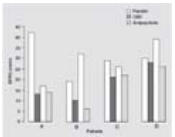

Figure 3. Brief Psychiatric Rating Scale (BPRS) scores for 4 schizophrenic patients treated with cannabidiol (CBD). Patient A received up to 1500 mg/day CBD and patients B, C, and D received up to 1280 mg/day. Bars indicate BPRS scores for each schizophrenic patient at the end point after the oral administration of placebo, CBD and

a control antipsychotic drug (haloperidol for patient A and olanzapine for patients B, C and D).

Placebo was administered before and after CBD treatment. Patient A is a woman who presented serious side effects with typical antipsychotics. Patients B, C, and D are men previously treated with typical antipsychotics with no response.

[View larger version of this image (41 K JPG file)]

More recently, CBD was administered to three 22- or 23-year-old male patients with a diagnosis of schizophrenia who had not responded to typical antipsychotic drugs (48). They received placebo for 5 days in the hospital followed by CBD from the 6th to the 35th day. After this period, they received placebo for an additional 5 days, followed by olanzapine for at least 15 days.

The dose of CBD was increased from 40 up to 1280 mg/day. The patients were assessed by two psychiatrists, who were blind to the doses administered, using the BPRS and UKU scales. No side effects were observed during CBD treatment, even at the higher dose of 1280 mg/day. A partial improvement was observed in one patient (Figure 3, patient B) while slight or no improvement was observed in the other two (Figure 3, patients C and D).

However, the patients (C and D) were considered to be refractory, since they did not even respond to clozapine, a fact that may explain the lack of CBD effectiveness (48). Figure 3 shows the results obtained with the 4 schizophrenic patients treated so far with CBD. These studies suggest, therefore, that CBD has an antipsychotic-like profile in healthy volunteers and may possess antipsychotic properties in schizophrenic patients, but not in the resistant ones.
Confirming this suggestion, a preliminary report from a 4-week, double-blind controlled clinical trial, using an adequate number of patients and comparing the effects of CBD with amisulpride in acute schizophrenic and schizophreniform psychosis, showed that CBD significantly reduced acute psychotic symptoms after 2 and 4 weeks of treatment when compared to baseline. In this trial CBD did not differ from amisulpride except for a lower incidence of side effects.

In conclusion, results from pre-clinical and clinical studies suggest that CBD is an effective, safe and well-tolerated alternative treatment for schizophrenic patients. Future trials of this cannabinoid in other psychotic conditions such as bipolar disorder (50) and comparative studies of its antipsychotic effects with those produced by clozapine in schizophrenic patients are clearly needed.

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Composition of the essential oils and extracts of two populations of Cannabis sativa L. ssp. spontanea from Austria

Journal of Essential Oil Research: JEOR, May/Jun 2003Novak, Johannes, Franz, Chlodwig

Abstract

The essential oil and the solvent extract of two populations of Cannabis sativa L. ssp. spontanea growing wild in Austria were analyzed comparatively. In the essential oil, myrcene (31% and 27%, respectively), (E)-beta-ocilnene (13% and 3%, respectively) and beta-caryophyllene (11 % and 16%, respectively) were found, while in the solvent extract the non-hallucinogeneous cannabidiol (77% and 59%, respectively) dominated.

The hallucinogeneous delta-9-tetrahydrocannabinol (THC) was also found in the solvent extract at a level of less than 1%.

The Plant

In Cannabis sativa L. ssp. spontanea (formerly Cannabis ruderalis) (Cannabaceae) the perianth of the female flowers is in contrast to C. sativa ssp. sativa still present; the fruit is brownish and has a peduncle-like ringbulge. It is a ruderal, but a rare plant in the east of Austria (1).

Source

Two populations of C. sativa L. ssp. spontanea ("Albrechtsfeld" and "Schoschtolacke") from the region of lake Neusiedl, Burgenland, eastern Austria were sampled in June, 1998, at the beginning of seed ripening.

At each population upper parts of approximately 10 plants were sampled. Voucher specimens were deposited in the Herbarium of the Institute for Applied Botany, University of Veterinary Medicine, Vienna.

Plant Part

For distillation and extraction, only fresh material was used, since drying results in a high loss (30-40%) of the essential oil.

Twenty g of fresh plant material (upper plant parts) were distilled in a modified Clevenger apparatus for 3 h. The solvent extracts were prepared by adding CH^sub 2^Cl^sub 2^ to 1 g fresh material of hemp (upper plant parts); extraction was performed in an ultrasonic bath for 15 min.

The essential oil (5 (mu)L) was diluted with CH^sub 2^Cl^sub 2^ (495 (mu)L) prior to analyses. GC/MS-analyses were performed on a HP 6890 coupled with a HP 5972 MSD and fitted with a HP 30 m x 0.25 mm capillary column coated with HP-5MS (0.25 (mu)m film thickness).

The analytical conditions were: carrier gas helium, injector temperature 250 deg C, split ratio 50:1, temperature programme 50 deg -140 deg C at 5 deg C/min and 140-170 deg C at 2 deg C/min. Components were identified by comparing their retention indices (RI) and mass spectra (3-5).

Previous Work

The essential oil of C. sativa has been the subject of previous studies (2, 6-15 and references cited therein).

Present Work

Mono- and sesquiterpenes: The oil of C. sativa L. ssp. spontanea contains as main compounds alpha-pinene (9% and 6%, respectively), myrcene (32% and 28%, respectively), beta-- caryophyllene (11% and 16%, respectively) and beta-caryophyllene oxide (7% and 8%, respectively) (Table I). However, the main differences between the two populations could be found in the high content of (E)-beta-ocimene with a very high content of 12.6% from "Albrechtsfeld" and a low content of 3% from "Schoschtolacke." Compared to "Schoschtolacke," the content of alpha-humulene was approximately the half at "Albrechtsfeld" (3.2%).

The oil compositions reported here differ very much from Ross et al., Hendriks et al. and Nigam where (E)-beta-ocimene was only found in traces or not at all. Hendriks et al. (8) and Nigam found alpha-pinene, beta-- pinene and myrcene at alevel of less than 1%, beta-caryophyllene instead reached 37% and 45%, respectively. In contrast, Ross et al. noticed

beta-caryophyllene to be present at only 1.3%. Myrcene (67%) and limonene (16%) were much higher than reported elsewhere (2). The Austrian populations of this report are within the range ofwhere different cultivars (especially European fiber cultivars) were analyzed.

Composition of cannabinoids: Regarding the cannabinoids in the oil, relatively high percentages of the non-- hallucinogeneous cannabidiol (CBD) (9.8% "Albrechtsfeld" and 10.9% "Schoschtolacke," respectively) could be found. The hallucinogenic delta-9-tetrahydrocannabinol (THC) was only present at "Schoschtolacke," and here only at low amounts (0.7%). CBD in the oil was still very high, but it's content was strictly dependant on the distillation conditions. The presence of cannabinoids in oils at higher amounts (11,17 and this report) as well as the almost absence of cannabinoids (12 and 16) are also dependant on distillation conditions and the state of the plant material being distilled. In the solvent extract, the content of CBD was extremely high (76.6% and 58.8%, respectively), while THC was always (even in the extract) below 1%. These can be regarded as being populations with a low content of THC, while the amount of CBD (especially in the extracts) was very high. So the ratio of CBD/THC, which is used for characterizing and distinguishing "fiber" from "drug" genotypes (18), is very much in favor of the fiber types.

Alkanes: Hendriks et al. (19) found nonacosane as main compound in the alkane-fraction obtained by extraction (55%) and at 11% in the oil. Nonacosane was also detected in the extracts of our study at 9% ("Albrechtsfeld") and 18% ("Schoschtolacke"), while it was absent in the oil

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Treatment with CBD in oily solution of drug-resistant paediatric epilepsies

Title	**Treatment with CBD in oily solution of drug-resistant paediatric epilepsies.**
Author(s)	**Pelliccia A, Grassi G, Romano A, Crocchialo P**
Journal, Volume, Issue	2005 Congress on Cannabis and the Cannabinoids, Leiden, The Netherlands: International Association for Cannabis as Medicine, p. 14.
Major outcome(s)	Improvement of EPILEPSY without side effects

Indication	Epilepsy
Medication	Cannabidiol
Route(s)	Oral
Dose(s)	
Duration (days)	
Participants	18 children with epilepsy
Design	Open study
Type of publication	Meeting abstract
Address of author(s)	II Facoltà di Medicina,Università “La Sapienza”, 00100 Rome, Italy, Istituto Sperimentale Colture Industriali, Sezione di Rovigo, Italy, American University of Rome, 00100, Italy
Full text	

Abstract

Introduction: As shown by Turkanis et al. (EPILEPSY, 1979), cannabidiol (CBD), similarly to d9-tetrahydrocannabinol (d9-THC) and Phenytoin (PHT) increases the “afterdischarge” and seizures threshold, mainly at the limbic level, without exhibiting the side effects induced by drugs such as PHT. Studies on rats were conducted that confirmed the anticonvulsant effects of both CBD (Chiu et al., 1979) and of d 9-THC (Cosroe and Mechoulam, 1987).

However, in spite of other studies having confirmed the anticonvulsant effect of cannabinoids, up to date no trials were conducted on man and, the less so, on the child.

Methods: We collected data on a population of children who presented with traditional antiepileptic drugs-resistant seizures, treated with a 2.5% corn oily solution of CBD as part of an open study, by modulating administration and titration schedules on a case by case basis, according to clinical response.

Results: On June 2002 we started to treat an eleven year-old girl affected with a
highly drug-resistant Lennox-Gastaut syndrome, with CBD, a substance not included in
the list of illicit drugs, in a 2.5% corn oily solution, administered at gradually increasing doses up to the present 20 drops daily.

Results have been encouraging: the girl, since she assumes CBD, did not need any longer to be admitted to hospital for her epileptic seizures, while her attacks decreased both in frequency and intensity, in addition her awareness, postural tone and speaking ability improved, as to allow us to gradually decrease her barbiturate intake.

Along the same line, CBD was proposed to another patient, a 17 year-old boy with an equally drug-resistant Lennox-Gastaut syndrome: although he reached the dose of only 30 drops daily, he also exhibited a slight improvement of the crises and, first and foremost, a clear-cut attention-behavioural improvement, and even in his case a suspension of the barbiturate treatment was initiated.

During the last year, 16 more children were started on CBD, all of them affected with symptomatic drug-resistant EPILEPSY; however, only 9 out of these are currently on treatment, since the parents of the remaining

children, although appreciating the improvement of their offspring, not only concerning the fits but also the awareness and the muscular tone, preferred to discontinue due to the economic overcharge induced by the treatment (approximately 300 EURos per month).

Conclusions: So far obtained results in our open study appear encouraging for various reasons:

1) no side effects of such a severity were observed as to require CBD discontinuation;

2) in most of the treated children an improvement of the crises was obtained equal to, or higher than, 25% in spite of the low CBD doses administered;

3) in all CBD- treated children a clear improvement of consciousness and spasticity (whenever present) was observed.

All Conditions Benefited by Medical Marijuana

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Cannabidiol decreases bone resorption by inhibiting RANK/RANKL expression and pro-inflammatory cytokines during experimental periodontitis in rats

Napimoga MH, Benatti BB, Lima FO, Alves PM, Campos AC, Pena-Dos-Santos DR, Severino FP, Cunha FQ, Guimarães FS
Cannabidiol decreases bone resorption by inhibiting RANK/RANKL expression and pro-inflammatory cytokines during experimental periodontitis in rats. [Journal Article, Research Support, Non-U.S. Gov't]
Int Immunopharmacol 2009 Feb; 9(2):216-22.

Cannabidiol (CBD) is a cannabinoid component from Cannabis sativa that does not induce psychotomimetic effects and possess anti-inflammatory properties. In the present study we tested the effects of CBD in a periodontitis experimental model in rats. We also investigated possible mechanisms underlying these effects.

Periodontal disease was induced by a ligature placed around the mandible first molars of each animal.

Male Wistar rats were divided into 3 groups: control animals; ligature-induced animals treated with vehicle and ligature-induced animals treated with CBD (5 mg/kg, daily).

Thirty days after the induction of periodontal disease the animals were sacrificed and mandibles and gingival tissues removed for further analysis.

Morphometrical analysis of alveolar bone loss demonstrated that CBD-treated animals presented a decreased alveolar bone loss and a lower expression of the activator of nuclear factor-kappaB ligand RANKL/RANK. Moreover, gingival tissues from the CBD-treated group showed decreased neutrophil migration (MPO assay) associated with lower interleukin (IL)-1beta and tumor necrosis factor (TNF)-alpha production.

These results indicate that CBD may be useful to control bone resorption during progression of experimental periodontitis in rats.

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The nonpsychoactive cannabis constituent cannabidiol is a wake-inducing agent

Murillo-Rodríguez E, Millán-Aldaco D, Palomero-Rivero M, Mechoulam R, Drucker-Colín R
The nonpsychoactive cannabis constituent cannabidiol is a wake-inducing agent. [Journal Article]
Behav Neurosci 2008 Dec; 122(6):1378-82.

Cannabidiol (CBD) is a constituent of Cannabis sativa that induces nonpsychotropic effects, and some of its biological actions in sleep have been described by the authors' group.

Here, the authors report that when administered 10 or 20 microg/1 microl during the lights-on period directly into either lateral hypothalamus (LH) or dorsal raphe nuclei (DRN), which are wake-inducing brain areas, CBD enhanced wakefulness and decreased slow wave sleep and REM sleep.

Furthermore, CBD increased alpha and theta power spectra but diminished delta power spectra.

Additionally, CBD increased c-Fos expression in LH or DRN. These findings suggest that this cannabinoid is a wake-inducing compound that presumably activates neurons in LH and DRN. (PsycINFO Database Record (c) 2008 APA, all rights reserved).

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Cannabinoids Induce Cancer Cell Proliferation via Tumor Necrosis Factor {alpha}-Converting Enzyme (TACE/ADAM17)-Mediated Transactivation of the Epidermal Growth Factor Receptor

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2. Oliver M. Fischer
3. Axel Ullrich
4. Department of Molecular Biology, Max-Planck-Institute of Biochemistry,
5. Martinsried, Germany

Abstract

1. Cannabinoids, the active components of marijuana and their endogenous counterparts were reported as useful analgetic agents to accompany primary cancer treatment by preventing nausea, vomiting, and pain and by stimulating appetite. Moreover, they have been shown to inhibit cell growth and to induce apoptosis in tumor cells.

Here, we demonstrate that anandamide, Δ^9-tetrahydrocannabinol (THC), HU-210, and Win55,212-2 promote mitogenic kinase signaling in cancer cells. Treatment of the glioblastoma cell line U373-MG and the lung carcinoma cell line NCI-H292 with nanomolar concentrations of THC led to accelerated cell proliferation that was completely dependent on metalloprotease and epidermal growth factor receptor (EGFR) activity.

2. EGFR signal transactivation was identified as the mechanistic link between cannabinoid receptors and the activation of the mitogen-activated protein kinases extracellular signal-regulated kinase 1/2 as well as prosurvival protein kinase B (Akt/PKB) signaling. Depending on the cellular context, signal cross-communication was mediated by shedding of proAmphiregulin (proAR) and/or proHeparin-binding epidermal growth factor-like growth factor (proHB-EGF) by tumor necrosis factor α converting enzyme (TACE/ADAM17). Taken together, our data show that concentrations of THC comparable with those detected in the serum of patients after THC administration accelerate proliferation of cancer cells instead of apoptosis and thereby contribute to cancer progression in patients.

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Divergent effects of cannabidiol on the discriminative stimulus and place conditioning effects of Δ9-tetrahydrocannabinol

Robert E. Vann, Thomas F. Gamage, Jonathan A. Warner, Ericka M. Marshall, Nathan L. Taylor, Billy R. Martin, and Jenny L. Wiley

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The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: Δ9-tetrahydrocannabinol, cannabidiol and Δ9-tetrahydrocannabivarin

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Received June 22, 2007; Accepted August 7, 2007.

Abstract
Cannabis sativa is the source of a unique set of compounds known collectively as plant cannabinoids or phytocannabinoids. This review focuses on the manner with which three of these compounds, (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC), (−)-cannabidiol (CBD) and (−)-*trans*-Δ^9-tetrahydrocannabivarin (Δ^9-THCV), interact with cannabinoid CB_1 and CB_2 receptors. Δ^9-THC, the main psychotropic constituent of cannabis, is a CB_1 and CB_2 receptor partial agonist and in line with classical pharmacology, the responses it elicits appear to be strongly influenced both by the expression level and signalling efficiency of cannabinoid receptors and by ongoing endogenous cannabinoid release. CBD displays unexpectedly high potency as an antagonist of CB_1/CB_2 receptor agonists in CB_1- and CB_2-expressing cells or

tissues, the manner with which it interacts with CB_2 receptors providing a possible explanation for its ability to inhibit evoked immune cell migration. Δ^9-THCV behaves as a potent CB_2 receptor partial agonist *in vitro*. In contrast, it antagonizes cannabinoid receptor agonists in CB_1-expressing tissues. This it does with relatively high potency and in a manner that is both tissue and ligand dependent. Δ^9-THCV also interacts with CB_1 receptors when administered *in vivo*, behaving either as a CB_1 antagonist or, at higher doses, as a CB_1 receptor agonist. Brief mention is also made in this review, first of the production by Δ^9-THC of pharmacodynamic tolerance, second of current knowledge about the extent to which Δ^9-THC, CBD and Δ^9-THCV interact with pharmacological targets other than CB_1 or CB_2 receptors, and third of actual and potential therapeutic applications for each of these cannabinoids.

Keywords: cannabis, Δ^9-tetrahydrocannabinol, cannabidiol, Δ^9-tetrahydrocannabivarin, CB_1 receptors, CB_2 receptors, cannabinoid receptor agonism, cannabinoid receptor antagonism, clinical applications, endocannabinoid system

Introduction

It was research in the 1960s and early 1970s that led to the discovery that the psychotropic effects of cannabis are produced mainly by (−)-*trans*-Δ^9-tetrahydrocannabinol (Δ^9-THC; Figure 1), to the pharmacological characterization of this plant cannabinoid (phytocannabinoid) and to the development of synthetic cannabinoids (reviewed in Pertwee, 2006).

These advances led on to the introduction into the clinic in the 1980s of Δ^9-THC (dronabinol, Marinol, Solvay Pharmaceuticals, Brussels, Belgium) and of one of its synthetic analogues, nabilone (Cesamet, Valeant Pharmaceuticals, Aliso Viejo, CA, USA), for the suppression of nausea and vomiting produced by chemotherapy and, in 1992, of Marinol for the stimulation of appetite in AIDS patients (reviewed in Robson, 2005; Pertwee and Thomas, 2007).

Importantly, they also led on to the discovery that many of the effects produced by Δ^9-THC and its synthetic cousins depend on the ability of these ligands to target a new family of receptors (reviewed in Howlett *et al.*, 2002; Pertwee, 2005a, 2006). Two types of these cannabinoid receptors have so far been identified and both are members of the superfamily of G-protein-coupled receptors. These are the CB_1 receptor, first cloned in 1990 (Matsuda *et al.*, 1990), and the CB_2 receptor, cloned in 1993 (Munro *et al.*, 1993).

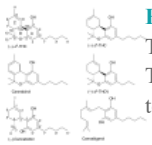

Figure 1

The structures of the phytocannabinoids, (−)-Δ^9-tetrahydrocannabinol (Δ^9-THC), (−)-Δ^8-tetrahydrocannabinol (Δ^8-THC), cannabinol, (−)-Δ^9-tetrahydrocannabivarin (Δ^9-THCV), (−)-cannabidiol (more ...)

The cloning of the CB_1 receptor was soon followed by the discovery that mammalian tissues can produce compounds that activate this receptor, and subsequently by the characterization of ligands such as Δ^9-THC, (6a*R*)-*trans*-3-(1,1-dimethylheptyl)-6a,7,10,10a-tetrahydro-1-hydroxy-6,6-dimethyl-6*H*-dibenzo[b,d]pyran-9-methanol (HU-210), (−)-*cis*-3-[2-hydroxy-4-(1,1-dimethylheptyl)phenyl]-*trans*-4-(3-hydroxypropyl)cyclohexanol (CP55940) and (*R*)-(+)-[2,3-dihydro-5-methyl-3-(4-morpholinylmethyl)pyrrolo-[1,2,3-de]-1,4-benzoxazin-6-yl]-1-naphthalenylmethanone (*R*-(+)-WIN55212) as mixed CB_1/CB_2 receptor agonists and by the development of CB_1- and CB_2-selective agonists and antagonists (reviewed in Howlett *et al.*, 2002; Pertwee, 2005a, 2006).

It also soon became clear that CB_1 receptors are located primarily in central and peripheral neurons and CB_2 receptors predominantly in immune cells. CB_1 receptors are also expressed by some non-neuronal cells, including immune cells, and CB_2 receptors by some neurons both within and outside the brain (Skaper *et al.*, 1996; Ross *et al.*, 2001; Van Sickle *et al.*, 2005; Wotherspoon *et al.*, 2005; Beltramo *et al.*, 2006; Gong *et al.*, 2006).

However, the role of neuronal CB_2 receptors is currently unknown. The first endogenous cannabinoid receptor agonists (endocannabinoids) to be identified were *N*-arachidonoylethanolamine (anandamide) and 2-arachidonoylglycerol (Devane *et al.*, 1992; Mechoulam *et al.*, 1995; Sugiura *et al.*, 1995), each of which can activate both CB_1 and CB_2 receptors and is synthesized on demand in response to elevations of intracellular calcium (Howlett *et al.*, 2002; Di Marzo *et al.*, 2005).

Together with their receptors, these and other more recently discovered endocannabinoids (Pertwee, 2005b) constitute what is now usually referred to as the ‘endocannabinoid system'.

There are several reasons for believing that one important role of the neuronal CB_1 component of the endocannabinoid system is to modulate neurotransmitter release in a manner that maintains homeostasis in health and disease by preventing the development of excessive neuronal activity in the central nervous system.

First, neuronal CB_1 receptors are found mainly at the terminals of central and peripheral neurons.

Second, there is good evidence that these receptors can mediate inhibition of ongoing release

of a number of different excitatory and inhibitory transmitters, for example acetylcholine, noradrenaline, dopamine, 5-hydroxytryptamine (5-HT), γ-aminobutyric acid (GABA), glutamate, D-aspartate and cholecystokinin (Howlett *et al.*, 2002; Pertwee and Ross, 2002; Szabo and Schlicker, 2005).

Finally, there is convincing evidence that endocannabinoids serve as retrograde synaptic messengers (Kreitzer, 2005; Vaughan and Christie, 2005). Thus, it is now generally accepted that postsynaptic increases in intracellular calcium induced by certain neurotransmitters can trigger the biosynthesis and release into the synapse of endocannabinoid molecules, which then act on presynaptic CB_1 receptors to inhibit the release of neurotransmitters such as glutamate and GABA. CB_2 receptor activation can also alter the release of chemical messengers, in this case the release of cytokines from immune cells and may, in addition, affect immune function by modulating immune cell migration both within and outside the central nervous system (reviewed in Walter and Stella, 2004; Cabral and Staab, 2005; Pertwee, 2005a).

This review focuses on the cannabinoid CB_1 and CB_2 receptor pharmacology of the phytocannabinoids Δ^9-THC, (−)-cannabidiol (CBD) and (−)-*trans*-Δ^9-tetrahydrocannabivarin (Δ^9-THCV) (Figure 1), all three of which interact with these receptors at reasonably low concentrations.

Whenever possible, previous review articles have been cited that provide more detailed information and list additional references.

The CB_1 and CB_2 receptor pharmacology of Δ^9-THC

(−)-*trans*-Δ^9-Tetrahydrocannabinol shares the ability of anandamide and 2-arachidonoylglycerol to activate both CB_1 and CB_2 receptors. More particularly, as discussed in greater detail elsewhere (Pertwee, 1997, 1999, 2005a; Howlett *et al.*, 2002; Childers, 2006), it binds to cannabinoid CB_1 and CB_2 receptors with K_i values in the low nanomolar range (Table 1) that indicate it to have higher affinity for these receptors than its corresponding (+)-*cis* (6a*S*, 10a*S*) enantiomer ((+)-Δ^9-THC), but lower CB_1 and CB_2 affinity than certain synthetic CB_1/CB_2 receptor agonists, for example HU-210, CP55940 and *R*-(+)-WIN55212. Δ^9-THC also exhibits lower CB_1 and CB_2 efficacy than these synthetic agonists, indicating it to be a partial agonist for both these receptor types. In contrast, the affinity of Δ^9-THC for CB_1 and CB_2 receptors does match or exceed that of the phytocannabinoids (−)-Δ^8-THC, Δ^9-THCV, CBD, cannabigerol and cannabinol (Table 1).

It has also been found that Δ^9-THC resembles anandamide in its CB_1 affinity, in behaving as a partial agonist at CB_1 receptors, albeit with less efficacy than anandamide, and in displaying even lower efficacy at CB_2 than at CB_1 receptors *in vitro*. Although 2-arachidonoylglycerol also possesses Δ^9-THC-like CB_1 affinity, it has been found in several investigations to display higher efficacy than anandamide and hence Δ^9-THC at both CB_1 and CB_2 receptors.

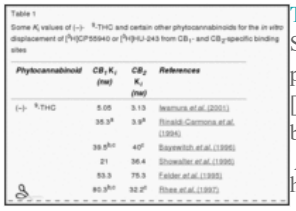

Table 1

Some K_i values of (−)-Δ^9-THC and certain other phytocannabinoids for the *in vitro* displacement of [^{3}H]CP55940 or [^{3}H]HU-243 from CB_1- and CB_2-specific binding sites

Among the effects that Δ^9-THC seems to produce *in vivo* in healthy animals by....read more

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Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption

Am J Physiol Heart Circ Physiol. Author manuscript; available in PMC 2008 February 4.
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Am J Physiol Heart Circ Physiol. 2007 July; 293(1): H610–H619.
Published online 2007 March 23. doi: 10.1152/ajpheart.00236.2007.
PMCID: PMC2228254
NIHMSID: NIHMS38117

Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption

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Abstract

A nonpsychoactive cannabinoid cannabidiol (CBD) has been shown to exert potent anti-inflammatory and antioxidant effects and has recently been reported to lower the incidence of diabetes in nonobese diabetic mice and to preserve the blood-retinal barrier in experimental diabetes.

In this study we have investigated the effects of CBD on high glucose (HG)-induced, mitochondrial superoxide generation, NF-κB activation, nitrotyrosine formation, inducible nitric oxide synthase (iNOS) and adhesion molecules ICAM-1 and VCAM-1 expression, monocyte-endothelial adhesion, transendothelial migration of monocytes, and disruption of endothelial barrier function in human coronary artery endothelial cells (HCAECs).

HG markedly increased mitochondrial superoxide generation (measured by flow cytometry using MitoSOX), NF-κB activation, nitrotyrosine formation, upregulation of iNOS and adhesion molecules ICAM-1 and VCAM-1, transendothelial migration of monocytes, and monocyte-endothelial adhesion in HCAECs. HG also decreased endothelial barrier function measured by increased permeability and diminished expression of vascular endothelial cadherin in HCAECs.

Remarkably, all the above mentioned effects of HG were attenuated by CBD pretreatment. Since a disruption of the endothelial function and integrity by HG is a crucial early event underlying the development of various diabetic complications, our results suggest that CBD, which has recently been approved for the treatment of inflammation, pain, and spasticity associated with multiple sclerosis in humans, may have significant therapeutic benefits against diabetic complications and atherosclerosis.....**read more**

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Cannabidiol in vivo blunts β-amyloid induced neuroinflammation by suppressing IL-1β and iNOS expression

PMCID: PMC2189818

Br J Pharmacol. 2
007 August; 151(8): 1272–1279.
Published online 2007 June 25. doi: 10.1038/sj.bjp.0707337.

Cannabidiol *in vivo* blunts β-amyloid induced neuroinflammation by suppressing IL-1β and iNOS expression
G Esposito C Scuderi, C Savani, L Steardo, Jr, D De Filippis, P Cottone, T Iuvone, V Cuomo, and L Steardo
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Received February 27, 2007; Revised April 4, 2007; Accepted April 27, 2007.

Abstract

Background and purpose:
Pharmacological inhibition of beta-amyloid (Aβ) induced reactive gliosis may represent a novel rationale to develop drugs able to blunt neuronal damage and slow the course of Alzheimer's disease (AD). Cannabidiol (CBD), the main non-psychotropic natural cannabinoid, exerts *in vitro* a combination of neuroprotective effects in different models of Aβ neurotoxicity.

The present study, performed in a mouse model of AD-related neuroinflammation, was aimed at confirming *in vivo* the previously reported antiinflammatory properties of CBD.

Experimental approach:

Mice were inoculated with human Aβ (1–42) peptide into the right dorsal hippocampus, and treated daily with vehicle or CBD (2.5 or 10 mg kg^{-1}, i.p.) for 7 days. mRNA for glial fibrillary acidic protein (GFAP) was assessed by *in situ* hybridization.

Protein expression of GFAP, inducible nitric oxide synthase (iNOS) and IL-1β was determined by immunofluorescence analysis. In addition, ELISA assay of IL-1β level and the measurement of NO were performed in dissected and homogenized ipsilateral hippocampi, derived from vehicle and Aβ inoculated mice, in the absence or presence of CBD.

Key results:
In contrast to vehicle, CBD dose-dependently and significantly inhibited GFAP mRNA and protein expression in Aβ injected animals. Moreover, under the same experimental conditions, CBD impaired iNOS and IL-1β protein expression, and the related NO and IL-1β release.

Conclusion and implications:
The results of the present study confirm *in vivo* anti-inflammatory actions of CBD, emphasizing the importance of this compound as a novel promising pharmacological tool capable of attenuating Aβ evoked neuroinflammatory responses.

....**read more...** Cannabidiol and (−)Δ9-tetrahydrocannabinol are neuroprotective antioxidants

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Cannabidiol has a cerebroprotective action

Hayakawa K, Mishima K, Nozako M, Hazekawa M, Irie K, Fujioka M, Orito K, Abe K, Hasebe N, Egashira N, Iwasaki K, Fujiwara M

Delayed treatment with cannabidiol has a cerebroprotective action via a cannabinoid receptor-independent myeloperoxidase-inhibiting mechanism. [Journal Article, Research Support, Non-U.S. Gov't]
J Neurochem 2007 Sep; 102(5):1488-96.

We examined the neuroprotective mechanism of cannabidiol, non-psychoactive component of marijuana, on the infarction in a 4 h mouse middle cerebral artery (MCA) occlusion model in comparison with Delta(9)-tetrahydrocannabinol (Delta(9)-THC).

Release of glutamate in the cortex was measured at 2 h after MCA occlusion. Myeloperoxidase (MPO) and cerebral blood flow were measured at 1 h after reperfusion. In addition, infarct size and MPO were determined at 24 and 72 h after MCA occlusion.

The neuroprotective effect of cannabidiol was not inhibited by either SR141716 or AM630. Both pre- and post-ischemic treatment with cannabidiol resulted in potent and long-lasting neuroprotection, whereas only pre-ischemic treatment with Delta(9)-THC reduced the infarction. Unlike Delta(9)-THC, cannabidiol did not affect the excess release of glutamate in the cortex after occlusion.

Cannabidiol suppressed the decrease in cerebral blood flow by the failure of cerebral microcirculation after reperfusion and inhibited MPO activity in neutrophils. Furthermore, the number of MPO-immunopositive cells was reduced in the ipsilateral hemisphere in cannabidiol-treated group.

Cannabidiol provides potent and long-lasting neuroprotection through an anti-inflammatory CB(1) receptor-independent mechanism, suggesting that cannabidiol will have a palliative action and open new therapeutic possibilities for treating cerebrovascular disorders.

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Cannabidiol-2',6'-Dimethyl Ether, a Cannabidiol Derivative, Is a Highly Potent and Selective 15-Lipoxygenase Inhibitor

Takeda S, Usami N, Yamamoto I, Watanabe K

[JOURNAL ARTICLE]
Drug Metab Dispos 2009 Apr 30.

The inhibitory effect of nordihydroguaiaretic acid (NDGA), a non-selective lipoxygenase (LOX) inhibitor, -mediated 15-LOX inhibition has been reported to be affected by modification of its catechol ring such as methylation of the hydroxyl group. Cannabidiol (CBD), one of the major components of marijuana, is known to inhibit LOX activity.

Based on the phenomenon observed in NDGA, we investigated whether or not methylation of CBD affects its inhibitory potential against 15-LOX, since CBD contains a resorcinol ring, which is an isomer of catechol. Although CBD inhibited 15-LOX activity with an IC50 value (50% inhibition concentration) of 2.56 microM, its mono-methylated and di-methylated derivatives, CBD-2'-monomethyl ether (CBDM) and CBD-2',6'-dimethyl ether (CBDD) inhibited 15-LOX activity more strongly than CBD.

The number of methyl groups in the resorcinol moiety of CBD (as a prototype) appears to be a key determinant for potency and selectivity in inhibition of 15-LOX. The IC50 value of 15-LOX inhibition by CBDD is 0.28 microM, and the inhibition selectivity for 15-LOX (i.e., the 5-LOX/15-LOX ratio of IC50 values) is more than 700.

Among LOX isoforms, 15-LOX is known to be able to oxygenate the cholesterol esters in the low density lipoprotein (LDL) particle (i.e., the formation of oxidized LDL).

Thus, 15-LOX is suggested to be involved in developing atherosclerosis, and CBDD may be a useful prototype for producing medicines for atherosclerosis.

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Beneficial effects of a Cannabis sativa extract treatment on diabetes-induced neuropathy and oxidative stress

Phytother Res 2009 May 13.

Comelli F, Bettoni I, Colleoni M, Giagnoni G, Costa B

Neuropathy is the most common complication of diabetes and it is still considered to be relatively refractory to most of the analgesics.

The aim of the present study was to explore the antinociceptive effect of a controlled cannabis extract (eCBD) in attenuating diabetic neuropathic pain.

Repeated treatment with cannabis extract significantly relieved mechanical allodynia and restored the physiological thermal pain perception in streptozotocin (STZ)-induced diabetic rats without affecting hyperglycemia.

In addition, the results showed that eCBD increased the reduced glutathione (GSH) content in the liver leading to a restoration of the defence mechanism and significantly decreased the liver lipid peroxidation suggesting that eCBD provides protection against oxidative damage in STZ-induced diabetes that also strongly contributes to the development of neuropathy.

Finally, the nerve growth factor content in the sciatic nerve of diabetic rats was restored to normal following the repeated treatment with eCBD, suggesting that the extract was able to prevent the nerve damage caused by the reduced support of this neurotrophin.

These findings highlighted the beneficial effects of cannabis extract treatment in attenuating diabetic neuropathic pain, possibly through a strong antioxidant activity and a specific action upon nerve growth factor.

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Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action

Zuardi AW Rev Bras Psiquiatr 2008 Sep; 30(3):271-80.

OBJECTIVE:

The aim of this review is to describe the historical development of research on cannabidiol.

METHOD:

This review was carried out on reports drawn from Medline, Web of Science and SciELO.

DISCUSSION:

After the elucidation of the chemical structure of cannabidiol in 1963, the initial studies showed that cannabidiol was unable to mimic the effects of Cannabis.

In the 1970's the number of publications on cannabidiol reached a first peak, having the research focused mainly on the interaction with delta9-THC and its antiepileptic and sedative effects.

The following two decades showed lower degree of interest, and the potential therapeutic properties of cannabidiol investigated were mainly the anxiolytic, antipsychotic and on motor diseases effects.

The last five years have shown a remarkable increase in publications on cannabidiol mainly stimulated by the discovery of its anti-inflammatory, anti-oxidative and neuroprotective effects. These studies have suggested a wide range of possible therapeutic effects of cannabidiol on several conditions, including Parkinson's disease, Alzheimer's disease, cerebral ischemia, diabetes, rheumatoid arthritis, other inflammatory diseases, nausea and cancer.

CONCLUSION:

In the last 45 years it has been possible to demonstrate that CBD has a wide range of pharmacological effects, many of which being of great therapeutic interest, but still waiting to be confirmed by clinical trials.

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Cannabidiol in medicine: a review of its therapeutic potential in CNS disorders

Scuderi C, Filippis DD, Iuvone T, Blasio A, Steardo A, Esposito G

Phytother Res 2008 Oct 9.

Cannabidiol (CBD) is the main non-psychotropic component of the glandular hairs of Cannabis sativa. It displays a plethora of actions including anticonvulsive, sedative, hypnotic, antipsychotic, antiinflammatory and neuroprotective properties.

However, it is well established that CBD produces its biological effects without exerting significant intrinsic activity upon cannabinoid receptors.

For this reason, CBD lacks the unwanted psychotropic effects characteristic of marijuana derivatives, so representing one of the bioactive constituents of Cannabis sativa with the highest potential for therapeutic use.

The present review reports the pharmacological profile of CBD and summarizes results from preclinical and clinical studies utilizing CBD, alone or in combination with other phytocannabinoids, for the treatment of a number of CNS disorders.

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Cannabidiol: a promising drug for neurodegenerative disorders?

Iuvone T, Esposito G, De Filippis D, Scuderi C, Steardo L

Cannabidiol: a promising drug for neurodegenerative disorders? [Journal Article, Research Support, Non-U.S. Gov't, Review]

CNS Neurosci Ther 2009; 15(1):65-75.

Neurodegenerative diseases represent, nowadays, one of the main causes of death in the industrialized country. They are characterized by a loss of neurons in particular regions of the nervous system. It is believed that this nerve cell loss underlies the subsequent decline in cognitive and motor function that patients experience in these diseases.

A range of mutant genes and environmental toxins have been implicated in the cause of neurodegenerative disorders but the mechanism remains largely unknown. At present, inflammation, a common denominator among the diverse list of neurodegenerative diseases, has been implicated as a critical mechanism that is responsible for the progressive nature of neurodegeneration.

Since, at present, there are few therapies for the wide range of neurodegenerative diseases, scientists are still in search of new therapeutic approaches to the problem. An early contribution of neuroprotective and antiinflammatory strategies for these disorders seems particularly desirable because isolated treatments cannot be effective.

In this contest, marijuana derivatives have attracted special interest, although these compounds have always raised several practical and ethical problems for their potential abuse.

Nevertheless, among Cannabis compounds, cannabidiol (CBD), which lacks any unwanted psychotropic effect, may represent a very promising agent with the highest prospect for therapeutic use.

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Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis

Borrelli F, Aviello G, Romano B, Orlando P, Capasso R, Maiello F, Guadagno F, Petrosino S, Capasso F, Di Marzo V, Izzo AA

Cannabidiol, a safe and non-psychotropic ingredient of the marijuana plant Cannabis sativa, is protective in a murine model of colitis. [Journal Article]
J Mol Med 2009 Nov; 87(11):1111-21.

Inflammatory bowel disease affects millions of individuals; nevertheless, pharmacological treatment is disappointingly unsatisfactory. Cannabidiol, a safe and non-psychotropic ingredient of marijuana, exerts pharmacological effects (e.g., antioxidant) and mechanisms (e.g., inhibition of endocannabinoids enzymatic degradation) potentially beneficial for the inflamed gut.

Thus, we investigated the effect of cannabidiol in a murine model of colitis. Colitis was induced in mice by intracolonic administration of dinitrobenzene sulfonic acid. Inflammation was assessed both macroscopically and histologically.

In the inflamed colon, cyclooxygenase-2 and inducible nitric oxide synthase (iNOS) were evaluated by Western blot, interleukin-1beta and interleukin-10 by ELISA, and

endocannabinoids by isotope dilution liquid chromatography-mass spectrometry.

Human colon adenocarcinoma (Caco-2) cells were used to evaluate the effect of cannabidiol on oxidative stress. Cannabidiol reduced colon injury, inducible iNOS (but not cyclooxygenase-2) expression, and interleukin-1beta, interleukin-10, and endocannabinoid changes associated with 2,4,6-dinitrobenzene sulfonic acid administration.
In Caco-2 cells, cannabidiol reduced reactive oxygen species production and lipid peroxidation. In conclusion, cannabidiol, a likely safe compound, prevents experimental colitis in mice.

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Cannabidiol ameliorates cognitive and motor impairments in mice with bile duct ligation

Magen I, Avraham Y, Ackerman Z, Vorobiev L, Mechoulam R, Berry EM
Cannabidiol ameliorates cognitive and motor impairments in mice with bile duct ligation.
[Journal Article, Research Support, Non-U.S. Gov't]
J Hepatol 2009 Sep; 51(3):528-34.

BACKGROUND/AIMS:

The endocannabinoid system in mice plays a role in models of human cirrhosis and hepatic encephalopathy (HE), induced by a hepatotoxin. We report now the therapeutic effects of cannabidiol (CBD), a non-psychoactive constituent of Cannabis sativa, on HE caused by bile duct ligation (BDL), a model of chronic liver disease.

METHODS:

CBD (5mg/kg; i.p.) was administered over 4weeks to mice that had undergone BDL.

RESULTS:

Cognitive function in the eight arm maze and the T-maze tests, as well as locomotor function in the open field test were impaired by the ligation and were improved by CBD. BDL raised hippocampal expression of the TNF-alpha-receptor 1 gene, which was reduced by CBD. However, BDL reduced expression of the brain-derived neurotrophic factor (BDNF) gene, which was increased by CBD. The effects of CBD on cognition, locomotion and on TNF-alpha receptor 1 expression were blocked by ZM241385, an A(2)A adenosine receptor antagonist. BDL lowers the expression of this receptor.

CONCLUSIONS: The effects of BDL apparently result in part from down-regulation of A(2)A adenosine receptor. CBD reverses these effects through activation of this receptor, leading to compensation of the ligation effect.

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Modulation of effective connectivity during emotional processing by Delta9-tetrahydrocannabinol and cannabidiol

Int J Neuropsychopharmacol. 2010 May;13(4):421-32. Epub 2009 Sep 24

Fusar-Poli P, Allen P, Bhattacharyya S, Crippa JA, Mechelli A, Borgwardt S, Martin-Santos R, Seal ML, O'Carrol C, Atakan Z, Zuardi AW, McGuire P.

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Abstract

Cannabis sativa, the most widely used illicit drug, has profound effects on levels of anxiety in animals and humans.

Although recent studies have helped provide a better understanding of the neurofunctional correlates of these effects, indicating the involvement of the amygdala and cingulate cortex, their reciprocal influence is still mostly unknown.

In this study dynamic causal modelling (DCM) and Bayesian model selection (BMS) were used to explore the effects of pure compounds of C. sativa [600 mg of cannabidiol (CBD) and 10 mg Delta 9-tetrahydrocannabinol (Delta 9-THC)] on prefrontal-subcortical effective connectivity in 15 healthy subjects who underwent a double-blind randomized, placebo-controlled fMRI paradigm while viewing faces which elicited different levels of anxiety.

In the placebo condition, BMS identified a model with driving inputs entering via the anterior cingulate and forward intrinsic connectivity between the amygdala and the anterior cingulate as the best fit. CBD but not Delta 9-THC disrupted forward connectivity between these regions during the neural response to fearful faces.

This is the first study to show that the disruption of prefrontal-subocritical connectivity by CBD may represent neurophysiological correlates of its anxiolytic properties.

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Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb

Trends Pharmacol Sci. 2009 Oct;30(10):515-27. Epub 2009 Sep 2.

Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R.

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Erratum in:

- Trends Pharmacol Sci. 2009 Dec;30(12):609.

Abstract

Delta(9)-tetrahydrocannabinol binds cannabinoid (CB(1) and CB(2)) receptors, which are activated by endogenous compounds (endocannabinoids) and are involved in a wide range of physiopathological processes (e.g. modulation of neurotransmitter release, regulation of pain perception, and of cardiovascular, gastrointestinal and liver functions).

The well-known psychotropic effects of Delta(9)-tetrahydrocannabinol, which are mediated by activation of brain CB(1) receptors, have greatly limited its clinical use. However, the plant Cannabis contains many cannabinoids with weak or no psychoactivity that, therapeutically, might be more promising than Delta(9)-tetrahydrocannabinol. Here, we provide an overview of the recent pharmacological advances, novel mechanisms of action, and potential therapeutic applications of such non-psychotropic plant-derived cannabinoids.

Special emphasis is given to cannabidiol, the possible applications of which have recently emerged in inflammation, diabetes, cancer, affective and neurodegenerative diseases, and to Delta(9)-tetrahydrocannabivarin, a novel CB(1) antagonist which exerts potentially useful actions in the treatment of epilepsy and obesity.

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Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT receptors

Title Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors.

Author(s) Zanelati TV, Biojone C, Moreira FA, Guimarães FS, Joca SR

Institution Department of Pharmacology, School of Medicine of Ribeirão Preto, University of São Paulo, Ribeirão Preto, SP, Brazil.

Source Br J Pharmacol 2010 Jan; 159(1):122-8.

Abstract

BACKGROUND AND PURPOSE: Cannabidiol (CBD) is a non-psychotomimetic compound from Cannabis sativa that induces anxiolytic- and antipsychotic-like effects in animal models. Effects of CBD may be mediated by the activation of 5-HT(1A) receptors. As 5-HT(1A) receptor activation may induce antidepressant-like effects, the aim of this work was to test the hypothesis that CBD would have antidepressant-like activity in mice as assessed by the forced swimming test.

We also investigated if these responses depended on the activation of 5-HT(1A) receptors and on hippocampal expression of brain-derived neurotrophic factor (BDNF). EXPERIMENTAL APPROACH: Male Swiss mice were given (i.p.) CBD (3, 10, 30, 100 mg*kg(-1)), imipramine (30 mg*kg(-1)) or vehicle and were submitted to the forced swimming test or to an open field arena, 30 min later.

An additional group received WAY100635 (0.1 mg*kg(-1), i.p.), a 5-HT(1A) receptor antagonist, before CBD (30 mg*kg(-1)) and assessment by the forced swimming test. BDNF protein levels were measured in the hippocampus of another group of mice treated with CBD (30 mg*kg(-1)) and submitted to the forced swimming test.

KEY RESULTS: CBD (30 mg*kg(-1)) treatment reduced immobility time in the forced swimming test, as did the prototype antidepressant imipramine, without changing exploratory behaviour in the open field arena. WAY100635 pretreatment blocked CBD-induced effect in the forced swimming test. CBD (30 mg*kg(-1)) treatment did not change hippocampal BDNF levels.

CONCLUSION AND IMPLICATIONS: CBD induces antidepressant-like effects comparable to those of imipramine. These effects of CBD were probably mediated by activation of 5-HT(1A) receptors.

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Pub Type(s) Comparative Study
Journal Article
Research Support, Non-U.S. Gov't

PubMed ID 20002102

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Effects of cannabidiol on amphetamine-induced oxidative stress generation in an animal model of mania

Title Effects of cannabidiol on amphetamine-induced oxidative stress generation in an animal model of mania.

Author(s) Valvassori SS, Elias G, de Souza B, Petronilho F, Dal-Pizzol F, Kapczinski F, Trzesniak C, Tumas V, Dursun S, Chagas MH, Hallak JE, Zuardi AW, Quevedo J, Crippa JA

Institution Laboratório de Neurociências, Programa de Pós-Graduação em Ciências da Saúde, Unidade Acadêmica de Ciências da Saúde, Universidade do Extremo Sul Catarinense.

Source J Psychopharmacol 2009 Nov 25.

Abstract Cannabidiol (CBD), a Cannabis sativa constituent, may present a pharmacological profile similar to mood stabilizing drugs, in addition to anti-oxidative and neuroprotective properties.

The present study aims to directly investigate the effects of CBD in an animal model of mania induced by D-amphetamine (D-AMPH).

In the first model (reversal treatment), rats received saline or D-AMPH (2 mg/kg) once daily intraperitoneal (i.p.) for 14 days, and from the 8th to the 14th day, they were treated with saline or CBD (15, 30 or 60 mg/kg) i.p. twice a day. In the second model (prevention treatment), rats were pretreated with saline or CBD (15, 30, or 60 mg/kg) regime i.p. twice a day, and from the 8th to the 14th day, they also received saline or D-AMPH i.p. once daily.

In the hippocampus CBD (15 mg/kg) reversed the D-AMPH-induced damage and increased (30 mg/kg) brain-derived neurotrophic factor (BDNF) expression. In the second experiment, CBD (30 or 60 mg/kg) prevented the D-AMPH-induced formation of carbonyl group in the prefrontal cortex. In the hippocampus and striatum the D-AMPH-induced damage was prevented by CBD (15, 30 or 60 mg/kg).

At both treatments CBD did not present any effect against D-AMPH-induced hyperactivity. In conclusion, we could not observe effects on locomotion, but CBD protect against D-AMPH-induced oxidative protein damage and increased BDNF levels in the reversal model and these effects vary depending on the brain regions evaluated and doses of CBD administered.

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Opposite Effects of Delta-9-Tetrahydrocannabinol and Cannabidiol on Human Brain Function and Psychopathology

Title Opposite effects of delta-9-tetrahydrocannabinol and cannabidiol on human brain function and psychopathology.

Author(s) Bhattacharyya S, Morrison PD, Fusar-Poli P, Martin-Santos R, Borgwardt S, Winton-Brown T, Nosarti C, O' Carroll CM, Seal M, Allen P, Mehta MA, Stone JM, Tunstall N, Giampietro V, Kapur S, Murray RM, Zuardi AW, Crippa JA, Atakan Z, McGuire PK

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Source Neuropsychopharmacology 2010 Feb; 35(3):764-74.

Abstract

Delta-9-tetrahydrocannabinol (Delta-9-THC) and Cannabidiol (CBD), the two main ingredients of the Cannabis sativa plant have distinct symptomatic and behavioral effects.

We used functional magnetic resonance imaging (fMRI) in healthy volunteers to examine whether Delta-9-THC and CBD had opposite effects on regional brain function. We then assessed whether pretreatment with CBD can prevent the acute psychotic symptoms induced by Delta-9-THC.

Fifteen healthy men with minimal earlier exposure to cannabis were scanned while performing a verbal memory task, a response inhibition task, a sensory processing task, and when viewing fearful faces.

Subjects were scanned on three occasions, each preceded by oral administration of Delta-9-THC, CBD, or placebo. BOLD responses were measured using fMRI. In a second experiment, six healthy volunteers were administered Delta-9-THC intravenously on two occasions, after placebo or CBD pretreatment to examine whether CBD could block the psychotic symptoms induced by Delta-9-THC.

Delta-9-THC and CBD had opposite effects on activation relative to placebo in the striatum during verbal recall, in the hippocampus during the response inhibition task, in the amygdala when subjects viewed fearful

faces, in the superior temporal cortex when subjects listened to speech,

and in the occipital cortex during visual processing.

In the second experiment, pretreatment with CBD prevented the acute induction of psychotic symptoms by Delta-9-tetrahydrocannabinol.

Delta-9-THC and CBD can have opposite effects on regional brain function, which may underlie their different symptomatic and behavioral effects, and CBD's ability to block the psychotogenic effects of Delta-9-THC.

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Brazilian Scientists Show How Marijuana Can Help in Treating Parkinson

Brazilian researchers from prestigious University of São Paulo (USP) have discovered that marijuana contains substances that can help ease the collateral effects of medicines prescribed to patients suffering from Parkinson disease.

Six patients with Parkinson were given during a whole month small doses of Cannabidiol (CBD) one of the 400 substances in marijuana, following which encouraging results were confirmed according to scientists from the Ribeirão Preto Medicine School from the SP University.

"Patients with Parkinson developed improvements in their sleeping alterations, in their psychotic symptoms and could even reduce their trembling," said psychiatrist Jose Alexander Crippa, Neuro-sciences Department professor.

The paper on the discovery was published last November and an additional paper with test results on the anxiolytic effects of Cannabidiol in patients with obsession and compulsion disorders will be released in 2010.

A group of voluntary patients with obsessive and compulsive conducts were medicated with the substance 70 minutes before facing situations that forced them into anxiety fits, and "improvements were evident."

Crippa underlined the significance of the research which scientifically establishes the positive effects of Cannabidiol but warned that "the non therapeutic use of marijuana was not recommended since it could only lead to worsen the psychotic symptoms and consequences of patients."

NewsHawk: Ganjarden: http://www.420magazine.com/
Source: Brazzil Mag
Contact: Brazzil Mag

Website: Brazilian Scientists Show How Marijuana Can Help in Treating Parkinson

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Cannabis by product helps reduce effects of Parkinson disease medication

Wednesday, December 30th 2009

Brazilian researchers have tested the positive effects of canabiodiol

Researchers from Brazil's prestigious University of Sao Paulo have discovered that marihuana contains substances which can help ease the collateral effects of medicines prescribed to patients suffering from Parkinson disease.

Six patients with Parkinson were given during a whole month small doses of "canabiodiol" one of the 400 substances in marihuana, following which encouraging results were confirmed according to scientists from the Riberao Preto Medicine School from the SP University.

"Patients with Parkinson developed improvements in their sleeping alterations, in their psychotic symptoms and could even reduce their trembling" said psychiatrist Jose Alexander Crippa, Neuro-sciences Department professor.

The paper on the discovery was published last November and next year an additional paper with test results on the anxiolytic effects of "canabiodiol" in patients with obsession and compulsion disorders will be released.

A group of voluntary patients with obsessive and compulsive conducts were medicated with the substance 70 minutes before facing situations that forced them into anxiety fits, and "improvements were evident".

Crippa underlined the significance of the research which scientifically establishes the positive effects of "canabiodiol" but warned that "the non therapeutic use of marihuana was not recommended since it could only lead to worsen the psychotic symptoms and consequences of patients".

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Cannabidiol and (−)Δ9-tetrahydrocannabinol are neuroprotective antioxidants

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Contributed by Julius Axelrod
Accepted April 27, 1998.
This article has been cited by other articles in PMC.

ABSTRACT
The neuroprotective actions of cannabidiol and other cannabinoids were examined in rat cortical neuron cultures exposed to toxic levels of the excitatory neurotransmitter glutamate. Glutamate toxicity was reduced by both cannabidiol, a nonpsychoactive constituent of marijuana, and the psychotropic cannabinoid (−)Δ^9-tetrahydrocannabinol (THC).

Cannabinoids protected equally well against neurotoxicity mediated by N-methyl-d-aspartate receptors, 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propionic acid receptors, or kainate receptors. N-methyl-d-aspartate receptor-induced toxicity has been shown to be calcium dependent; this study demonstrates that 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl)propionic acid/kainate receptor-type neurotoxicity is also calcium-dependent, partly mediated by voltage sensitive calcium channels.

The neuroprotection observed with cannabidiol and THC was unaffected by cannabinoid receptor antagonist, indicating it to be cannabinoid receptor independent. Previous studies have shown that glutamate toxicity may be prevented by antioxidants. Cannabidiol, THC and several synthetic cannabinoids all were demonstrated to be antioxidants by cyclic voltametry. Cannabidiol and THC also were shown to prevent hydroperoxide-induced oxidative damage as well as or better than other antioxidants in a chemical (Fenton reaction) system and neuronal cultures.

Cannabidiol was more protective against glutamate neurotoxicity than either ascorbate or α-tocopherol, indicating it to be a potent antioxidant.

These data also suggest that the naturally occurring, nonpsychotropic cannabinoid,

cannabidiol, may be a potentially useful therapeutic agent for the treatment of oxidative neurological disorders such as cerebral ischemia.....read more

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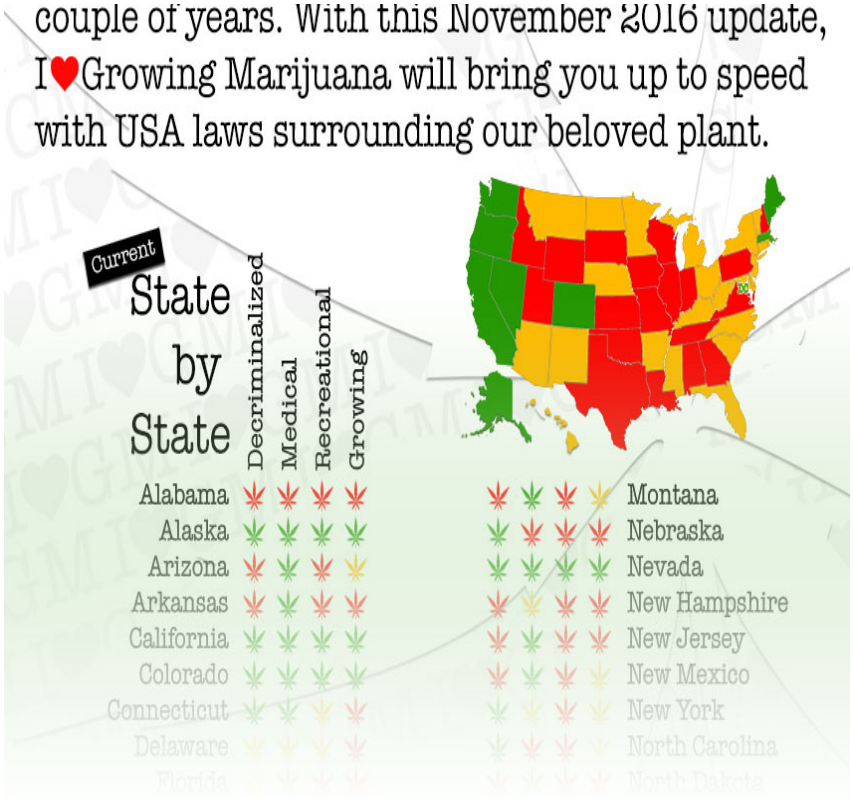

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