SPECIAL ARTICLE

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

Canabidiol: de um canabinóide inativo a uma droga com amplo espectro de ação

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Abstract

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.*

Descriptors: *Cannabidiol; Cannabis; Cannabinoids; History; Therapeutic uses*

Resumo

Objetivo: *O objetivo desta revisão é descrever a evolução histórica das pesquisas sobre o canabidiol.* ***Método:*** *Esta revisão foi conduzida utilizando-se bases de dados eletrônicas (Medline*, Web of Science *e SciELO*). ***Discussão:*** *Após a elucidação de sua estrutura química, em 1963, os estudos iniciais do canabidiol demonstraram que ele não foi capaz de mimetizar os efeitos da maconha. Na década de 70, o número de publicações sobre o canabidiol atingiu um primeiro pico, com as investigações centrando-se principalmente na sua interação com o* delta9-THC e nos seus efeitos *antiepiléptico e sedativo. As duas décadas seguintes apresentaram um menor nível de interesse e as propriedades terapêuticas potenciais do canabidiol investigadas foram, principalmente, as ansiolíticas, antipsicóticas e seus efeitos sobre as doenças motoras. Os últimos cinco anos têm demonstrado um notável aumento de publicações sobre o canabidiol, principalmente estimulado pela descoberta dos seus efeitos anti-inflamatório, anti-oxidativo e neuroprotetor. Estes estudos têm sugerido uma vasta gama de possíveis efeitos terapêuticos da canabidiol em várias condições, incluindo doença de Parkinson, doença de Alzheimer, isquemia cerebral, diabetes, náusea, câncer, artrite reumatóide e outras doenças inflamatórias.* ***Conclusão:*** *Nos últimos 45 anos, foi possível demonstrar uma vasta gama de efeitos farmacológicos do canabidiol, muitos dos quais são de grande interesse terapêutico, que ainda necessitam ser confirmados por estudos clínicos.*

Descritores: *Canabidiol; Cannabis; Canabinóides; História; Usos terapêuticos*

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Introduction

In the tip of secreting hairs located mainly on female-plant flowers and, in a smaller amount, in the leaves of *cannabis* plant, there are resin glands that have a considerable amount of chemically related active compounds, called cannabinoids. In some varieties of *cannabis* the main cannabinoid is the psychoactive component of the plant, delta9-tetrahydrocannabinol (delta9-THC). *Cannabis* varieties typically bred for fiber are nearly always relatively low in delta9-THC, cannabidiol (CBD) being the predominant cannabinoid in these plants.[1]

Although CBD was isolated from marijuana extract in 1940 by Adams et al.,[2] for almost 25 years no further work has been reported, except for a few early works about its isolation. Only in 1963 its exact chemical structure was elucidated by Mechoulam and Shvo.[3] Over the following few years Mechoulam's group was responsible for the structure and stereochemistry determination of the main cannabinoids, which opened a new research field on pharmacological activity of *cannabis* constituents.[4,5]

The evolution of the number of publications on CBD since 1963, in comparison with publications on *cannabis* in general, is shown in Figure 1. Only a few pharmacological studies on CBD were reported before the early 1970's, showing that CBD had no *cannabis*-like activity.[6] The number of publications increased in this decade and reached a first peak around 1975. In this period, a Brazilian research group led by Carlini, gave an important contribution, especially about the interactions of delta9-THC with other cannabinoids, including CBD.[7] Then, the number of publications declined and remained stabilized until a few years ago. The interest in studies about *cannabis* was renewed in the early 1990's, by the description and cloning of specific receptors for the cannabinoids in the nervous system and the subsequent isolation of anandamide, an endogenous cannabinoid.[8] Afterwards, the number of publications about *cannabis* has been continuously growing, but the reports on CBD remained stable until the early 2000's. In the last five years there has been an explosive increase in publications on CBD, with the confirmation of a plethora of pharmacological effects, many of them with therapeutic potential.

There are some recent and very good reviews on CBD.[9-12] As historical aspects have so far not been yet emphasized, the aim of the present review is to describe the development of this research field which transformed our view about CBD from an inactive cannabinoid to a drug with multiple actions.

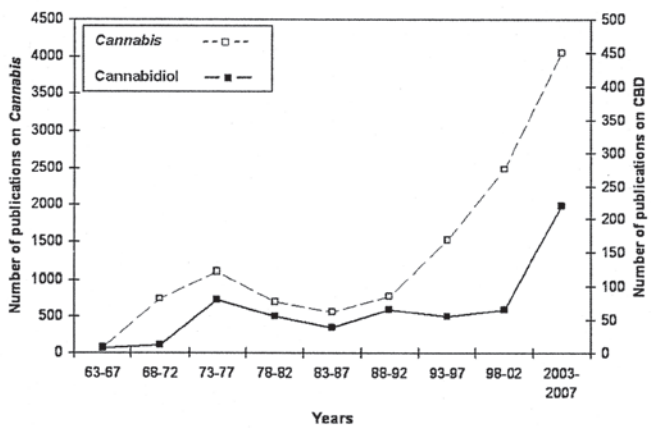

Figure 1 - Number of *cannabis* and cannabidiol-related publications in the last 45 years. The source used was the 'ISI Web of Knowledge' with the keywords: *Cannabis* and cannabidiol.

Inactive cannabinoid that interact with delta9-THC (1970's)

The early pharmacological tests on isolated cannabinoids had evidenced that except for delta9-THC, no other major psychotomimetically active compounds were present in *cannabis*.[13] During this period, several reports attested that CBD was unable to mimic the effects of *cannabis* both in animals[14] and in humans,[15,16] leading to the thought that it was an inactive cannabinoid.

This thought began to change with the observation that the activity in animals of several samples of *cannabis* differed widely, a fact which could not be attributed only to the different delta9-THC contents of the samples.[17,18] It was then hypothesized that other cannabinoids, among them CBD, could be interfering with the delta9-THC effects.

Many interactive studies between CBD and delta9-THC were accomplished by different groups, producing seemingly contradictory results both in animals,[19-21] and in humans.[22-24] Different schedules of drug administration used in these studies may help explain the contradictions. It seems that CBD administered before delta9-THC potentiates the effects of the latter compound. However, concomitant use of both compounds suggests that CBD antagonizes delta9-THC effects.[25-27] This difference could be explained by pharmacokinetic or pharmacodynamic interactions between the two cannabinoids.

CBD has been found to be a potent inhibitor of hepatic drug metabolism.[28,29] Pre-treatment of mice with high doses of CBD causes an increase in delta9-THC level in the brain.[30] Recently, evidence that CBD also inhibits the metabolic hydroxylation of delta9-THC in human volunteers[31] has been obtained. This pharmacokinetic interaction could explain the increased effects of delta9-THC by CBD pretreatment. On the other hand, CBD is not able to change delta9-THC blood level with co-administration of both compounds in rats[32] or humans volunteers.[33] Therefore, it has been suggested that CBD can antagonize delta9-THC effects pharmacodynamically.[34]

Early evidence (1970's) on CBD pharmacological activity

1. Antiepileptic action

The first pharmacological actions of CBD described were the antiepileptic and the sedative ones. In 1973, a Brazilian group reported that CBD was active in reducing or blocking convulsions produced in experimental animals by a variety of procedures,[35,36] which was confirmed by another group one year later.[37] At the end of that decade, the same Brazilian group has tested CBD as a treatment for intractable epilepsy in 16 grand- mal patients. Each patient received, in a double-blind procedure, 200 to 300 mg daily of CBD or placebo for as long as four and a half months. Throughout the experiment, the patients did not stop taking the antiepileptic drugs prescribed before the experiment (which had not eliminated their seizures). Only one of the eight patients getting CBD showed no improvement, while among the patients who received the placebo, 1 improved and 7 remained unchanged.[38] In a less successful study, no significant improvement in seizure frequency was observed among 12 epileptic patients who received 200-300 mg of cannabidiol per day, in addition to standard antiepileptic drugs.[39] No further clinical trials with CBD have been published since then. Therefore, the clinical efficacy of CBD on epilepsy is still uncertain.

2. Sedative action

In the early 1970's, suggestive evidence of a sedative action appeared, based on the observation that CBD reduced ambulation in

rats[40] and, with higher doses, operant behavior in rats and pigeons.[41] Few years later, Monti[42] reported sleep-inducing effects of CBD in rats, with an increase in total sleeping time, increment of slow-wave sleep (SWS) and decrease of SWS latency. In humans with insomnia, high doses of CBD (160 mg) increased sleep duration compared to placebo.[43] Sedative effect was also observed in healthy volunteers with high CBD dose (600 mg).[44] This effect of CBD may be biphasic, since in low doses (15 mg) the cannabinoid appears to have alerting properties in healthy volunteers, as it increases wakefulness during sleep and counteracts the residual sedative activity of 15 mg THC.[45] Previous reports of subjective feelings by healthy volunteers after CBD (1 mg/Kg) showed a significant increase in "clear minded" and "quick- witted" feelings, in contrast with THC (0.5 mg/Kg) that induced an increase in "muzzy"[46] feelings. In agreement with the two last observations, intracerebroventricular administration of CBD in rats during the lights-on period increased wakefulness (W) and decreased rapid eye movement sleep (REMS), probably through increased dopamine release.[47]

CBD effects on anxiety, psychoses and movement disorders (1980's and 1990's)

After the peak of reports on CBD in the 1970's, the next two decades the publication rate remained stabilized, indicating a lower degree of interest on the study of therapeutic actions of CBD. The reports in this field were maintained mainly by Brazilian researchers investigating the anxiolytic and antipsychotic properties of CBD and by a few studies about its effects in motor diseases conducted by Consroe et al.[48,49]

1. Anxiolytic action

In 1974, an interactive study between CBD and THC, *per os*, in healthy volunteers, gave the first clue that CBD could act as an anxiolytic drug.[22] This study showed that CBD (60 mg), added to delta9-THC (30 mg), changed the symptoms induced by delta9-THC alone in such a way that the subjects receiving the mixture showed less anxiety and more pleasurable effects. In 1982, a study with appropriate rating scales confirmed that CBD (1 mg/kg), co-administered with delta9-THC (0.5 mg/kg), significantly reduced anxiety indexes in healthy volunteers.[46]

The anxiolytic properties of CBD have been demonstrated by several pre-clinical studies that employed different paradigms such as the conditioned emotional response,[50] the Vogel conflict test[51] and the elevated plus-maze.[52,53] In the latter study,[53] 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. 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.[54] A recent study showed that the anxiolytic effect of CBD in the Vogel test was not mediated by benzodiazepine receptors.[55]

In order 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.[56] 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 itself can be interpreted as an anxiogenic situation, it allows the evaluation of anxiolytic drug action. CBD induced a clear anxiolytic effect and a pattern of cerebral activity compatible with an anxiolytic activity.[57] Another study, using functional magnetic resonance imaging (fMRI) to investigate the neurophysiologic basis of the effects of cannabis on human anxiety, showed that CBD affected activation when subjects were processing intensely fearful stimuli, attenuating responses in the amygdala and cingulate cortex. The suppression of the amygdalar response was correlated to the drug effect of reducing fluctuations of skin conductance.[58] Therefore, similar to the data obtained in animal models, results from studies in healthy volunteers strongly suggest an anxiolytic action of CBD.

2. Antipsychotic action

The first evidence that CBD could have antipsychotic effects was obtained in the interactive study of CBD and delta9-THC in healthy volunteers published in 1982.[46] This study demonstrated that CBD could inhibit THC-induced subjective changes that resembled symptoms of psychotic diseases such as: disconnected thought, perceptual disturbance, depersonalization and resistance to communication. 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.[59] These lines of evidence led to several investigations of a possible antipsychotic action of CBD.

As a first step to investigate antipsychotic-like properties of CBD in animal models, the drug was compared to haloperidol in rats.[60] Both drugs reduced the apomorphine-induced stereotyped behavior (such as sniffing and biting), in a dose-related manner. Even though these drugs also increased the plasma level of prolactine, CBD needs higher doses (120 and 240 mg/kg) to show such an effect. Moreover, contrary to haloperidol, CBD did not induce catalepsy, even at doses as high as 480 mg/kg. These results suggest that CBD may exhibit a profile similar to atypical antipsychotic drugs. Recently, a study tested CBD effects both in dopamine-based and glutamate-based models predictive of antipsychotic activity in mice.[61] In this study CBD was compared to haloperidol and clozapine, an atypical antipsychotic drug. CBD inhibited the hyperlocomotion induced by amphetamine in a dose-related manner, in agreement with the data obtained with another dopamine-based model, and also attenuated the hyperlocomotion induced by ketamine, extending its antipsychotic-like action to a glutamate-based model. As expected, while both haloperidol and clozapine inhibited hyperlocomotion, only haloperidol induced catalepsy within the dose range used. Therefore, similar to clozapine, CBD did not induce catalepsy with doses that inhibited hyperlocomotion. Strengthening these results, CBD reversed the disruption of prepulse inhibition (PPI) of the startle response in mice caused by MK-801, a glutamate receptor antagonist, as did clozapine, further supporting the idea that this compound may act as an atypical antipsychotic drug.[62] Consistent with the behavioral data, both CBD and clozapine, but not haloperidol, induced Fos immunoreactivity (Fos) in the prefrontal cortex, while only haloperidol increased Fos in the dorsal striatum.[63,64]

Even in human models of psychotic symptoms induced in healthy volunteers, the antipsychotic-like activity of CBD can be demonstrated. In the perception of binocular depth inversion, used to evaluate the antipsychotic effects of new drugs,[65] the impairment of

the perception of illusory image induced by nabilone was attenuated by CBD, suggesting an antipsychotic-like effect of this compound.[66] Another model used to evaluate antipsychotic-like activity of drugs in healthy volunteers is the administration of sub-anesthetic doses of ketamine that induce a psychotic reaction mimicking both positive and negative symptoms of schizophrenia.[67] A double-blind crossover procedure using this model was performed to compare the effects of CBD (600 mg) and placebo in nine healthy volunteers.[68] CBD attenuated the effects of ketamine on the depersonalization factor of a dissociative rating scale, further reinforcing the antipsychotic-like properties of CBD.

The therapeutic use of CBD in psychotic patients was tested for the first time in 1995. In a case study, a schizophrenic patient, who presented serious side effects after treatment with conventional antipsychotics, received oral doses of CBD (reaching 1500 mg/day) for 4 weeks.[69] A significant improvement was observed during CBD treatment, while a worsening was observed when the administration was interrupted. More recently, CBD was administered to three schizophrenic patients who had not responded to typical antipsychotic drugs.[70] A partial improvement was observed in one patient, but only slight or no improvement in the other two, thus suggesting that CBD has little effect in patients resistant to typical antipsychotics. Confirming the suggestion of case-studies, 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.[71] In conclusion, clinical studies suggest that CBD is an effective, safe and well-tolerated alternative treatment for schizophrenic patients.

3. Action on movement disorders

The possible therapeutic effect of CBD on movement disorders came from anecdotal accounts and preliminary reports of open trials, in the middle 1980's. CBD (100 to 600 mg/day) had antidystonic effects in humans when administered along with standard medication to five patients with dystonia, in an open study.[48] In Huntington's disease (HD), the effectiveness of CBD was investigated with a small number of patients (four) and a non-blinded design, showing some beneficial effects of CBD.[72] However, the latter finding was not confirmed by a study comparing the effects of oral CBD (10 mg/kg/day for 6 weeks) with placebo under a double-blind, randomized cross-over design. In this study, CBD at an average daily dose of about 700 mg/day was neither symptomatically effective nor toxic in neuroleptic-free patients with HD.[49]

Afterwards, this field of research was apparently abandoned until recently, when CBD's neuroprotective effects began to be reported in animal models of Parkinson's disease.

CBD as a drug with a wide spectrum of action (2000's)

The interest in studies about *cannabis* was renewed in the early 1990's, with the description and cloning of specific receptors for the cannabinoids (CB_1 and CB_2) in the nervous system and the subsequent isolation of anandamide, an endogenous cannabinoid.[73] After that, the number of publications about *cannabis* has been continuously growing, attesting the great interest in research involving the herb. However, the number of studies on CBD has increased only in the last five years (Figure 1), mainly stimulated by discoveries of the anti-inflammatory, anti-oxidative and neuroprotective actions of CBD.

1. Anti-oxidative and neuroprotective actions

In the late 1990's, it was demonstrated that CBD reduced glutamate toxicity mediated by N-methyl-D-aspartate receptors (NMDAr), 2-amino-3-(4-butyl-3-hydroxyisoxazol-5-yl) propionic acid receptors (AMPA) or kainate receptors. The neuroprotection observed with cannabidiol was not affected by a cannabinoid receptor antagonist, indicating it is cannabinoid-receptor independent.[74] Previous studies had shown that glutamate toxicity may be prevented by antioxidants. In line with this, it was demonstrated that CBD can reduce hydroperoxide-induced oxidative damage as well as or better than other antioxidants. CBD was more protective against glutamate neurotoxicity than either ascorbate or a-tocopherol, indicating that this drug is a potent antioxidant.[74]

The anti-oxidative action of CBD can be responsible for the neuroprotection reported in animal models of Parkinson's disease (PD). Daily administration of CBD during 2 weeks may produce a significant waning in the magnitude of toxic effects caused by a unilateral injection of 6-hydroxydopamine into the medial forebrain bundle,[75] probably due to receptor-independent actions. In this model of PD, CBD led to an up-regulation of mRNA levels of Cu/Zn-superoxide dismutase, a key enzyme in endogenous defense against oxidative stress. The conclusion was that the antioxidant properties of CBD can provide neuroprotection against the progressive degeneration of nigrostriatal dopaminergic neurons that occur in PD.[76] This is reinforced by the observation that CBD reduced the striatal atrophy caused by 3-nitropropionic acid, *in vivo*, through mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A_{2A} receptors.[77] The neuroprotective action of CBD in the human basal ganglia was suggested by the strong positive correlation of N-acetylaspartate/total creatine ratio and CBD in the putamen/globus pallidum found in recreational cannabis users. This could reflect an enhancement of neuronal and axonal integrity in these regions by CBD.[78] Considering the relevance of these preclinical data and the possible antipsychotic effect of CBD, a recently study evaluated, for the first time, the efficacy, tolerability and safety of CBD in PD patients with psychotic symptoms.[79] In an open-label pilot study, six consecutive outpatients with the diagnosis of PD and who also had psychosis for at least 3 months, have received a flexible-dose regimen of CBD administration (starting with an oral dose of 150 mg/day) for four weeks, in addition to their usual therapy. The psychotic symptoms significantly decreased along the CBD treatment, and the scale used to follow up the PD course exhibited a significant decrease of the total score. These preliminary data suggest that CBD may have a beneficial action in PD.[79]

The possible neuroprotective actions of CBD highlight the importance of studies on the therapeutic potential of this compound in Alzheimer's disease (AD). AD is widely associated with oxidative stress due in part, to the membrane action of beta-amyloid peptide (beta-A) aggregates. A marked reduction in the cell survival was observed following exposure of cultured rat pheochromocytoma PC12 cells to beta-A peptide. Treatment of the cells with CBD prior to beta-A exposure significantly elevated the cell survival, probably by a combination of neuroprotective, anti-oxidative and anti-apoptotic actions against beta-A toxicity. In addition, CBD inhibited caspase 3 generation from its inactive precursor, pro-caspase 3, an effect that is involved in the signaling pathway for this neuroprotection.[80] In the search for the molecular mechanism of this CBD-induced

neuroprotective action it was reported that CBD inhibits hyperphosphorylation of tau protein in beta-A-stimulated PC12 neuronal cells, which is one of the most representative hallmarks of AD.[81] A possible anti-inflammatory action may be involved in this CBD effect, since CBD inhibited both nitrite production and nitric oxide synthase (iNOS) protein expression induced by beta-A.[82] These results of *in vitro* studies were confirmed *in vivo* with a mouse model of AD-related neuroinflammation. Mice were inoculated with human beta-A into the right dorsal hippocampus, and treated daily with vehicle or CBD (2.5 or 10 mg kg, i.p.) for 7 days. In contrast to vehicle, CBD dose-dependent significantly inhibited mRNA for glial fibrillary acidic protein and the protein expression in beta-A injected animals. Moreover, under the same experimental conditions, CBD impaired iNOS and IL-1beta protein expression, and the related NO and IL-1beta release.[83] The possibility of CBD inhibiting beta-A-induced neurodegeneration is very promising to AD prevention.

Recently it has been suggested that CBD 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.[84] Prion diseases are transmissible neurodegenerative disorders characterized by the accumulation in the CNS of the protease-resistant prion protein, a structurally misfolded isoform of its physiological counterpart.[84]

2. Anti-inflammatory action

In 2000, a few previous reports showing that CBD can modulate tumor necrosis factor *in vitro* and suppress chemokine production by a human B cell,[85-87] motivated the study of CBD as a therapeutic agent in collagen-induced arthritis, a model for rheumatoid arthritis.[88] This model is based on immunizing mice with type-II collagen. CBD, administered i.p. or orally, has blocked the progression of arthritis. Dose-dependency was shown by a bell-shaped curve, with an optimal effect at 5 mg/kg per day (i.p.), or at 25 mg/kg per day (orally). In addition, CBD has suppressed T cell responses and has decreased the release of bioactive tumor necrosis factor (TNF) from synovial cells isolated from arthritic knee joints of treated mice. Data of this study suggest that the antiarthritic effect of CBD is due to a combination of immunosuppressive and anti-inflammatory actions.[10,12] A CBD anti-inflammatory effect was observed in acute inflammation induced by intraplantar injection of 0.1 ml carrageenan in rats.[89] Oral CBD (5-40 mg/kg) once a day for 3 days after the onset of acute inflammation had a beneficial action on edema and hyperalgesia. CBD also proved effective in chronic neuropathic (sciatic nerve chronic constriction) painful states in rats, reducing hyperalgesia to mechanical stimuli. This effect was prevented by the vanilloid antagonist capsazepine, but not by cannabinoid receptor antagonists.[90] In these models of inflammation, decreases in prostaglandin E2 (PGE2) plasma levels, tissue cyclooxygenase (COX) activity and production of nitric oxide (NO)[89,90] have been observed. The suppressive effects of CBD on cellular immune responses and on the production of pro-inflammatory mediators may indicate its usefulness in several inflammatory diseases.

3. Action on ischemia

The anti-oxidative and anti-inflammatory properties of CBD have led to the research of its possible activity in preventing damage caused by cerebral ischemia. CBD (1.25-20 mg/kg) was administered to freely-moving gerbils 5 min after bilateral carotid-artery occlusion for 10 minutes. Seven days after the ischemia, CBD antagonized electroencephalographic flattening, showing a dose-dependent bell-shaped curve. The best neuroprotective effect was observed at 5 mg/kg. Histological examination showed the complete survival of CA1 neurons in CBD-treated gerbils.[91] A similar effect has been reported by another research group in mice, after middle cerebral artery occlusion; the neuroprotective action of CBD being unaffected by CB_1 receptor blockade.[92] The same research group has verified that this effect was inhibited by WAY100135, a serotonin 5-hydroxytriptamine 1A ($5\text{-}HT_{1A}$) receptor antagonist, but not by capsazepine, a vanilloid receptor antagonist, suggesting that the neuroprotective effect of CBD may be due to the increase in cerebral blood flow mediated by the serotonergic $5\text{-}HT_{1A}$ receptor.[93] Experimental evidence has suggested that beyond this action on the $5\text{-}HT_{1A}$ receptor, the protective effect of CBD on ischemic injury is also secondary to its anti-inflammatory action.[94] In another study, the same research group reported that, while repeated treatment with delta9-THC leads to the development of tolerance for this neuroprotective effect, this phenomenon is not observed with CBD.[95]

CBD has been studied for ischemic heart diseases in rats.[96] The left anterior descending coronary artery was transiently obstructed 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 and showed preservation of shortening fraction in CBD-treated animals. Infarct size was reduced by 66% in CBD-treated animals and this effect was associated with reduction of myocardial inflammation and reduction of IL-6 levels. In isolated hearts, no significant difference was detected between rats that received CBD or vehicle regarding: infarct size, left ventricular developed pressures during ischemia and reperfusion, or coronary flow. This study shows that CBD induces a substantial cardioprotective effect, but only *in vivo*.

4. Action on diabetes

The potent anti-inflammatory effect of CBD, with reduction of cytokines production (IFN-γ and TNF-α) and inhibition of T cell proliferation observed in experimental arthritis,[88] led to investigation of the possible CBD effects on others autoimmune diseases.[12] Type 1 diabetes mellitus (insulin-dependent) is an autoimmune disease that results in the destruction of insulin-producing pancreatic β cells. The initial lesion of insulin-dependent diabetes mellitus is an inflammation of the islands of Langerhans, during which leukocytes, lymphocytes in particular, surround and infiltrate the islets. That way Mechoulam's group investigated CBD action on non-obese diabetic (NOD) mice. They found that CBD treatment of NOD mice before the development of the disease reduced its incidence from 86% in the non-treated control mice to 30% in CBD-treated mice. CBD treatment also resulted in significant reduction of plasma levels of the pro-inflammatory cytokines, IFN-γ and TNF-α. Histological examination of the pancreatic islets of CBD-treated mice revealed significant reduction of the inflammation.[97] It was also observed that administration of CBD to 11-14 week old female NOD mice, which were either in a latent diabetes stage or had initial symptoms of diabetes, ameliorated the manifestations of the disease. In addition, the level of the pro-inflammatory cytokine IL-12 produced by splenocytes was significantly reduced, whereas the level of the anti-inflammatory IL-10 was significantly elevated after CBD treatment.[98] This data have suggested that CBD can possibly be used as a therapeutic agent for the treatment of type 1 diabetes.

CBD has also been proven useful for possible complications of diabetes. The majority of diabetic complications are associated with pathophysiological alterations in the vasculature. Microvascular complications involve retinopathy and nephropathy while the atherosclerosis is the most common macrovascular complication of diabetes. The protective effects of CBD were studied in experimental diabetes induced by streptozotocin in rats. CBD treatment prevented retinal cell death and vascular hyperpermeability in the diabetic retina. In addition, it significantly reduced oxidative stress, decreased the levels of TNF-α, vascular endothelial growth factor, and intercellular adhesion-molecule.[99] It has also been suggested that CBD has significant therapeutic benefits against other diabetic complications and atherosclerosis, since it attenuated several effects of high glucose, including the disruption of the endothelial function.[100]

5. Antiemetic action

The treatment of nausea and vomiting associated with chemotherapy was one of the first therapeutic uses of cannabis and cannabinoids that has been evaluated with clinical trials. In the mid 1970's, a clinical trial indicated that delta9-THC was effective as an anti-nausea agent in patients receiving cancer chemotherapy.[101] In 1990, a survey of the members of the American Society of Clinical Oncology found that more than 44% of the respondents reported that they had already recommended the use of marijuana for the control of emesis to at least one cancer chemotherapy patient.[102]

Although the anti-emetic action has been associated to delta9-THC, many users claim that marijuana suppresses nausea more effectively than oral delta9-THC.[103] These observations led a Canadian group to investigate whether CBD can suppress nausea in the conditioned rejection model in rats. The association between a flavor and an emetic drug results in altered affective reactions, called conditioned rejection reactions, which reflect nausea.[10] In this model, rats were injected with a low dose (5 mg/kg i.p.) of CBD, a synthetic dimethylheptyl homolog of CBD, or vehicle 30 min prior to a pairing of saccharin solution and lithium chloride (20 ml/kg of 0.15 M LiCl) or saline. The rejection reactions (gapes, chin rubs and paw treads) that were elicited by lithium chloride and by a flavor paired with lithium chloride were suppressed by CBD and its synthetic dimethylheptyl homolog.[104] Since rats are incapable of vomiting, a better model for vomiting was found with a mouse species *(Suncus murinus)*, which both vomits and expresses nausea.[12] These animals were injected with vehicle or one of two cannabinoids, THC (1-20 mg/kg) or CBD (2.5-40 mg/kg), 10 min prior to an injection of LiCl (390 mg/kg of 0.15 M) and were then observed for 45 min. delta9-THC produced a dose-dependent suppression of Li-induced vomiting while CBD produced a biphasic effect, having lower doses produced suppression and higher doses produced enhancement of Li-induced vomiting. The suppression of Li-induced vomiting by delta9-THC, but not by CBD, was reversed by SR-141716, a CB_1 antagonist, suggesting that both cannabinoids are effective treatments for Li-induced vomiting, however, only delta9-THC acts through the CB_1 receptor.[105] CBD was effective also in the conditioned retching reaction, which is a model of anticipatory nausea. Following three pairings of a novel distinctive contextual cue with the emetic effects of an injection of lithium chloride, the context acquired the potential to elicit conditioned retching in the absence of the toxin. The expression of this conditioned retching reaction was completely suppressed by CBD and delta9-THC, but not by ondansetron, a 5-HT_3 antagonist that interferes with acute vomiting in this species.[106] A similar effect of CBD on anticipatory nausea was observed with a rat model of nausea (conditioned gaping).[107] These results support anecdotal claims that marijuana may suppress the expression of anticipatory nausea experienced by chemotherapy patients, resistant to current anti-nausea treatments.

6. Anticancer action

In the mid 1970's, several cannabinoids, including CBD, were studied in cancer cells and the results observed with CBD were not promising. However, these experiments were performed with extremely high doses (e.g., 200 mg/kg) and it is unlikely that these observations are relevant to the usual doses of CBD.[12]

In 2000, the interest in CBD as a potential anticancer drug was renewed with an investigation of its effect on glioma cells. In this study, CBD produced a modest reduction in the cell viability of C6 rat glioma cells, only evident after 6 days of incubation with the drug and only in a serum-free condition.[108] A further study has demonstrated that CBD, *in vitro*, caused a concentration-related inhibition of the human glioma cell viability that was already evident 24 h after the CBD exposure and significantly inhibited the growth of subcutaneously implanted human glioma cells in nude mice. The authors also showed for the first time that the antiproliferative effect of CBD was correlated to induction of apoptosis, as determined by cytofluorimetric analysis and single-strand DNA staining, which was not reverted by cannabinoid and vanilloid receptor antagonists.[109] CBD also caused apoptosis in human myeloblastic leukemia cells.[110] In addition, CBD inhibits the migration of U87 human glioma cells *in vitro* and this effect was also not antagonized by either selective CB_1 or CB_2 receptor antagonists.[111] A study of the effect of different cannabinoids on eight tumor cell lines, *in vitro*, has clearly indicated that, of the five natural compounds tested, CBD was the most potent inhibitor of cancer cell growth. In this study, two different tumor cell lines transplanted to hairless mice were half as big as those of the untreated group, and both breast- and lung-cancer cells injected to paws showed approximately three times less metastatic invasion.[112] An inhibitor of basic helix-loop-helix transcription factors (Id1) has recently been shown to be a key regulator of the metastatic potential of breast and additional cancers. CBD could down-regulate the Id-1 expression in aggressive human breast cancer cells, and the concentrations effective at inhibiting Id-1 expression correlated with those used to inhibit the proliferative and invasive phenotype of breast cancer cells.[113]

The precise mechanisms underlying CBD effects on apoptosis and tumor growth are not clear, and have recently been discussed in a review by Mechoulam.[12]

CBD: a drug with multiple mechanisms of action

The plethora of CBD effects described above can be explained by its multiple mechanisms of action. The description and cloning of specific receptors for the cannabinoids in the nervous system have been a great contribution to the understanding of the mechanism of actions of cannabinoids. However, in contrast to delta9-THC, CBD has little affinity to CB_1 and CB_2 receptors.[114]

1. Actions on the cannabinoid system

In spite of its low affinity for CB_1 and CB_2 receptors, experimental evidence has shown that CBD is capable of antagonizing $CB1_1$/CB_2 receptor agonists at reasonably low concentrations.[115] This unexpected effect of CBD raises the possibility that this antagonism is non-competitive in nature, a hypothesis that has been discussed

by Pertwee.[116] Recently, the cloning and protein sequence of the human, mouse and rat new cannabinoid receptor (GPR55) that can be activated by the established CB_1/CB_2 receptor agonists, such as delta9-THC and endogenous cannabinoids, has been described. The activation of the GPR55 receptor is antagonized by CBD at a concentration that is below any concentration at which it displaces agonists from CB_1 or CB_2 receptors.[117] Other actions of CBD on the cannabinoid system are the blockade of anandamide uptake and the inhibition of its enzymatic hydrolysis.[118]

2. Action on the vanilloid receptor type 1

CBD stimulated vanilloid receptors (VR1) with $EC_{50} = 3.2 \pm 3.5$ mM and with a maximal effect similar in efficacy to that of capsaicin, the natural agonists of this receptor.[118] Although VR1 is involved in inflammatory hyperalgesia, the stimulation of this receptor by capsaicin and some of its analogues leads to rapid desensitization, with subsequent paradoxical analgesic and anti-inflammatory effects. CBD desensitized VR1 to the action of capsaicin, thus opening the possibility that this cannabinoid exerts an anti-inflammatory action in part by desensitization of sensory nociceptors.[118]

3. Action on the5-HT_{1A} receptor

CBD displaces the agonist [3H]8-OHDPAT from the cloned human 5-HT_{1A} receptor in a concentration-dependent manner. In signal-transduction studies, CBD acts as an agonist at the human 5-HT_{1A} receptor.[119] This CBD action is probably involved in the protective effect of CBD on ischemia[93] and in its anxiolytic-like effects.[120]

4. Action on adenosine signaling

CBD decreases the uptake of [3H] adenosine in both murine microglia and macrophages, and binding studies show that CBD binds to the equilibrative nucleoside transporter.[121] The enhancement of adenosine signaling through inhibition of its uptake can provide a non-cannabinoid receptor mechanism by which CBD can decrease inflammation.

5. Anti-oxidant action

As mentioned above, CBD prevents hydroperoxide (H_2O_2)-induced oxidative damage equally well, or better than ascorbate (vitamin C) or tocopherol (vitamin E).[74] This action may be related to the neuroprotective effect of CBD.

6. Immunosuppressive and anti-inflammatory actions

The effects of CBD on pro-inflammatory cytokines and related compounds as well as its immunosuppressive effect have been reviewed above.

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. It is important to highlight that many effects of CBD draw a bell-shaped dose-response curve, suggesting that the dose is a pivotal factor in CBD research. The wide range of CBD effects can be explained by the multiple mechanisms through which CBD acts, although further research is needed to clarify the precise mechanisms that underlie some of the potentially beneficial effects of CBD.

Disclosures

Writting group member	Employment	Research grant[1]	Other research grant or medical continuous education[2]	Spekear's honoraria	Ownership interest	Consultant/ Advisory board	Other[3]
Antonio W. Zuardi	FMRP-USP	CNPq FAPESP	---	---	---	---	---

** Modest*
*** Significant*
**** Significant. Amounts given to the author's institution or to a colleague for research in which the author has participation, not directly to the author.*
Note: FMRP-USP = Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, CNPq = Conselho Nacional de Desenvolvimento Científico e Tecnológico; FAPESP = Fundação de Amparo à Pesquisa do Estado de São Paulo.
For more information, see Instructions for authors.

References

1. Clarke CR, Watson DP. Botany of natural Cannabis medicines. In: Grotenhermen F, Russo E, editors. *Cannabis and cannabinoids: pharmacology, toxicology and therapeutic potential.* New York: The Haword Interactive Healing Press; 2002. Chapter 1. p. 3-13.
2. Adams R, Hunt M, Clark JH. Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota wild hemp. *J Am Chem Soc.* 1940;62:196-200.
3. Mechoulam R, Shvo Y. Hashish. 1. Structure of Cannabidiol. *Tetrahedron.* 1963;19(12):2073-8.
4. Gaoni Y, Mechoulam R. Isolation, structure and partial synthesis of an active constituent of hashish. *J Am Chem Soc.* 1964;**86:**1646.
5. Mechoulam R, Gaoni Y. The absolute configuration of delta-1tetrahydrocannabinol, the major active constituent of hashish. *Tetrahedron Lett.* 1967:1109-11.
6. Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. *Science*. 1970;169(945):611-2.
7. Russo E. A tale of two cannabinoids: the therapeutic rationale for combining tetrahydrocannabinol and cannabidiol. *Med Hypotheses.* 2006;66(2):234-46.
8. Martin BR, Mechoulam R, Razdan RK. Discovery and characterization of endogenous cannabinoids. *Life Sci*. 1999;65(6-7):573-95.
9. Mechoulam R, Hanus L. Cann abidiol: an overview of some chemical and pharmacological aspects. Part I: chemical aspects. *Chem Phys Lipids.* 2002;121(1-2):35-43.
10. Mechoulam RE, Parker LA, Gallily R. Cannabidiol: an overview of some pharmacological aspects. *J Clin Pharmacol.* 2002;42(11 Suppl):11S-19S.
11. Long L, Malone DT, Taylor DA. The pharmacological action of cannabidiol. *Drug Future*. 2005;30(7):747-53.
12. Mechoulam R, Peters M, Murillo-Rodriguez E, Hanus LO. Cannabidiol--recent advances. *Chem Biodivers*. 2007;4(8):1678-92.
13. Mechoulam R, Carlini EA. Toward drugs derived from cannabis. *Naturwissenschaften*. 1978;65(4):174-9.
14. Kubena R, Barry H 3rd. Stimulus characteristics of marihuana components. *Nature*. 1072;235(5338):397-8.
15. Perez-Reyes M, Timmons MC, Dauls KH, Wall ME. A comparison of the pharmacological activity in man of the intravenously administered delta9 – tetrahydrocannabinol, cannabinol and cannabidiol. *Experientia*. 1973;29(11):1368-9.
16. Hollister LE. Cannabidiol and cannabinol in man. *Experientia.* 1973;29(7):825-6.
17. Carlini EA, Santos M, Claussen U, Bieniek D, Korte F. Structure activity relationship of four tetrahydrocannabinols and the

pharmacological activity of five semi-purified extracts of Cannabis sativa. *Psychopharmacologia*. 1970;18(1):82-93.
18. Karniol IG, Carlini EA. The content of (-) 9 -trans-tetrahydrocannabinol (9-thc) does not explain all biological activity of some Brazilian marihuana samples. *J Pharm Pharmacol.* 1972;24(10):833-4.
19. Karniol IG, Carlini EA. Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. *Psychopharmacologia.* 1973;33(1):53-70.
20. Borgen LA, Davis WM. Cannabidiol interaction with delta9-tetrahydrocannabinol. *Res Commun Chem Pathol Pharmacol.* 1974;7(4):663-70.
21. Fernandes M, Schabarek A, Coper H, Hill R. Modification of delta9-THC-actions by cannabinol and cannabidiol in the rat. *Psychopharmacologia.* 1974;38(4):329-38.
22. Karniol IG, Shirakawa I, Kasinski N, Pfeferman A, Carlini EA. Cannabidiol interferes with the effects of delta 9 - tetrahydrocannabinol in man. *Eur J Pharmacol.* 1974;28(1):172-7.
23. Hollister LE, Gillespie H. Interactions in man of delta-9-tetrahydrocannabinol. II. Cannabinol and cannabidiol. *Clin Pharmacol Ther*. 1975;18(1):80-3.
24. Dalton WS, Martz R, Lemberger L, Rodda BE, Forney RB. Influence of cannabidiol on delta-9-tetrahydrocannabinol effects. *Clin Pharmacol Ther*. 1976;19(3):300-9.
25. Zuardi AW, Finkelfarb E, Bueno OF, Musty RE, Karniol IG. Characteristics of the stimulus produced by the mixture of cannabidiol with delta 9-tetrahydrocannabinol. *Arch Int Pharmacodyn Ther.* 1981;249(1):137-46.
26. Zuardi AW, Karniol IG. Effects on variable-interval performance in rats of delta 9-tetrahydrocannabinol and cannabidiol, separately and in combination. *Braz J Med Biol Res.* 1983;16(2):141-6.
27. Zuardi AW, Teixeira NA, Karniol IC. Pharmacological interaction of the effects of delta 9-trans-tetrahydrocannabinol and cannabidiol on serum corticosterone levels in rats. *Arch Int Pharmacodyn Ther.* 1984;269(1):12-9.
28. Paton WD, Pertwee RG. Effect of cannabis and certain of its constituents on pentobarbitone sleeping time and phenazone metabolism. *Br J Pharmacol.* 1972;44(2):250-61.
29. Borys HK, Karler R. Cannabidiol and delta 9-tetrahydrocannabinol metabolism. In vitro comparison of mouse and rat liver crude microsome preparations. *Biochem Pharmacol.* 1979;28(9):1553-9.
30. Jones G, Pertwee RG. A metabolic interaction in vivo between cannabidiol and 1 -tetrahydrocannabinol. *Br J Pharmacol.* 1972;45(2):375-7.
31. Nadulski T, Pragst F, Weinberg G, Roser P, Schnelle M, Fronk E, Stadelmann AM. Randomized, double-blind, placebo-controlled study about the effects of cannabidiol (CBD) on the pharmacokinetics of delta 9-tetrahydrocannabinol (THC) after oral application of THC verses standardized cannabis extract. *Ther Drug Monit.* 2005;27(6):799-810.
32. Levy S, McCallum NK. Cannabidiol and its pharmacokinetic interaction with delta1-tetrahydrocannabinol. *Experientia.* 1975;31(11):1268-9.
33. Agurell S, Carlsson S, Lindgren JE, Ohlsson A, Gillespie H, Hollister L. Interactions of delta 1-tetrahydrocannabinol with cannabinol and cannabidiol following oral administration in man. Assay of cannabinol and cannabidiol by mass fragmentography. *Experientia.* 1981;37(10):1090-2.
34. Zuardi AW, Karniol IG. Interação farmacológica entre delta – 9 – THC e CBD, dos constituintes activos da cannabis sativa. *Ciência e Cultura.* 1984;36(3):386-94.
35. Carlini EA, Leite JR, Tanhauser M, Berardi AC. Cannabidiol and cannabis sativa extract protect mice and rats against convulsive agents. *J Pharm Pharmacol.* 1973;25(8):664-5.
36. Izquierdo I, Orsingher OA, Berardi AC. Effect of cannabidiol and other Cannabis sativa compounds on hippocampal seizures discharges. *Psychopharmacologia*. 1973;28(1):95-102.
37. Turkanis SA, Cely W, Olsen DM, Karler R. Anticonvulsant properties of cannabidiol. *Res Communic Chem Pathol Pharmacol.* 1974;8(2):231-46.
38. Cunha JM, Carlini EA, Pereira AE, Ramos OL, Pimentel G, Gagliardi R, Sanvito EL, Lander N, Mechoulam R. Chronic administration of cannabidiol to healthy volunteers and epileptic patients. *Pharmacology.* 1980;21(3):175-85.
39. Ames FR, Cridland S. Anticonvulsant effect of cannabidiol. *S Afr Med J*. 1986;69(1):14.
40. Karniol IG, Carlini EA. Pharmacological interaction between cannabidiol and delta 9-tetrahydrocannabinol. *Psychopharmacologia*. 1973;33(1):53-70.
41. Davis WM, Borgen LA. Effects of cannabidiol and delta-9-tetrahydrocannabinol on operant behavior. *Res Commun Chem Pathol Pharmacol.* 1974;9(3):453-62.
42. Monti JM. Hypnoticlike effects of cannabidiol in the rat. *Psychopharmacol* (Berl). 1977;55(3):263-5.
43. Carlini EA, Cunha JM. Hypnotic and antiepileptic effects of cannabidiol. *J Clin Pharmacol.* 1981;21(8-9 Suppl):417S-27S.
44. Zuardi AW, Guimarães FS, Moreira AC. Effect of cannabidiol on plasma prolactin, growth hormone and cortisol in human volunteers. *Braz J Med Biol Res.* 1993;26(2):213-7.
45. Nicholson AN, Turner C, Stone BM, Robson PJ. Effect of Delta-9-tetrahydrocannabinol and cannabidiol on nocturnal sleep and early-morning behavior in young adults. *J Clin Psychopharmacol.* 2004;24(3):305-13.
46. Zuardi AW, Shirakawa I, Finkelfarb E, Karniol IG. Action of cannabidiol on the anxiety and other effects produced by delta 9-THC in normal subjects. *Psychopharmacology (Berl).* 1982;76(3):245-50.
47. Murillo-Rodríguez E, Millán-Aldaco D, Palomero-Rivero M, Mechoulam R, Drucker-Colín R. Cannabidiol, a constituent of Cannabis sativa, modulates sleep in rats. *FEBS Lett.* 2006;580(18):4337-45.
48. Consroe P, Sandyk R, Snider SR. Open label evaluation of cannabidiol in dystonic movement disorders. *Int J Neurosci.* 1986;30(4):277-82.
49. Consroe P, Laguna J, Allender J, Snider S, Stern L, Sandyk R, Kennedy K, Schram K. Controlled clinical trial of cannabidiol in Huntington's disease. *Pharmacol Biochem Behav*. 1991;40(3):701-8.
50. Zuardi AW, Karniol IG. Changes in the conditioned emotional response of rats induced by Δ9-THC, CBD and mixture of the two cannabinoids. *Arquivos de Biologia e Tecnologia*. 1983;26:391-7.
51. Musty RE, Conti LH, Mechoulam R. Anxiolytic properties of cannabidiol. In: Harvey DJ, editor. *Marihuana '84. Proceedings of the Oxford Symposium on Cannabis.* Oxford, UK: IRL Press Limited; 1984. p. 713-9.
52. Onaivi ES, Green MR, Martin BR. Pharmacological characterization of cannabinoids in the elevated plus maze. *J Pharmacol Exp Ther.* 1990;253(3):1002-9.
53. Guimarães FS, Chiaretti TM, Graeff F, Zuardi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. *Psychopharmacology (Berl).* 1990;100(4):558-9.
54. Silveira Filho NG, Tufik S. Comparative effects between cannabidiol and diazepam on neophobia, food intake and conflict behavior. *Res Commun Psychol Psychiatry Behav*. 1981;6:25-6.
55. Moreira FA, Aguiar DC, Guimarães FS. Anxiolytic-like effect of cannabidiol in the rat Vogel conflict test. *Prog Neuropsychopharmacol Biol Psychiatry.* 2006;30(8):1466-71.
56. Zuardi AW, Cosme RA, Graeff FG et al. Effects of ipsapirone and cannabidiol on human experimental anxiety. *J Psychopharmacol.* 1993;7:82-8.
57. Crippa JA, Zuardi AW, Garrido GE, Wichert-Ana L, Guarnieri R, Ferrari L, Azevedo-Marques PM, Hallak JE,McGuire PK, Filho Busatto G. Effects of cannabidiol (CBD) on regional cerebral blood flow. *Neuropsychopharmacology*. 2004;29(2):417-26.
58. Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt S, Allen P, Martin-Santos R, Seal M, Surguladze SA, O'Carrol C, Atakan Z, Zuardi AW, McGuire P. Distinct efeects of Δ9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. *Arch Gen Psychiatry.* 2008. (In press).
59. Rottanburg D, Robins AH, Ben-Aire O, Teggin A, Elk R. Cannabis associated psychosis with hypomaniac feature. *Lancet.* 1982;2(8312):1364-6.
60. Zuardi AW, Rodrigues JA, Cunha JM. Effects of cannabidiol in animal models predictive of antipsychotic activity. *Psychopharmacology (Berl)*. 1991;104(2):260-4.
61. Moreira FA, Guimarães FS. Cannabidiol inhibits the hyperlocomotion induced by psychotomimetic drugs in mice. *Eur J Pharmacol.* 2005;512(2-3):199-205.
62. Long LE, Malone DT, Taylor DA. Cannabidiol reverses MK-801-induced

disruption of prepulse inhibition in mice. *Neuropsychopharmacology.* 2006;31(4):795-803.
63. Zuardi AW, Guimarães FS, Guimarães VM. Cannabidiol: possible therapeutic application. In: Grotenhermen F, Russo E, Varo RN, editors. *Cannabis and Cannabinoids: Pharmacology, Toxicology and Therapeutic Potential.* New York: The Haword Interactive Healing Press; 2002. p. 359-69.
64. Guimarães VM, Zuardi AW, Del Bel EA, Guimarães FS. Cannabidiol increases Fos expression in the nucleus accumbens but not in the dorsal striatum. *Life Sci*. 2004;75(5):633-8.
65. Schneider U, Borsutzky M, Seifert J, Leweke FM, Huber TJ, Rollnik JD, Emrich HM. Reduced binocular depth inversion in schizophrenic patients. *Schizophr Res*. 2002;53(1-2):101-8.
66. Leweke FM, Schneider U, Radwan M, Schmidt E, Emrich HM. Different effects of nabilone and cannabidiol on binocular depth inversion in man. *Pharmacol Biochem Behav.* 2000;66(1):175-81.
67. Krystal JH, Karper LP, Seibyl JP, Freeman GK, Delaney R, Bremner JD, Heninger GR, Bowers MB Jr, Charney DS. Subanesthetic effects of the noncompetitive NMDA antagonist, ketamine, in humans. Psychotomimetic, perceptual, cognitive, and neuroendocrine responses. *Arch Gen Psychiatry.* 1994;51(3):199-214.
68. Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimarães FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. *Braz J Med Biol Res*. 2006;39(4):421-9.
69. Zuardi AW, Morais SL, Guimarães FS, Mechoulam R. Antipsychotic effect of cannabidiol. *J Clin Psychiatry.* 1995;56(10):485-6.
70. Zuardi AW, Hallak JE, Dursun SM, Morais SL, Sanches RF, Musty RE, Crippa JA. Cannabidiol monotherapy for treatment-resistant schizophrenia. *J Psychopharmacol.* 2006;20(5):683-6.
71. Leweke F, Koethe D, Gerth CW, et al. Double blind, controlled clinical trial of cannabidiol monotherapy versus amisulpiride in the treatment of acutely psychotic schizophrenia patients. *Schizophr Bull.* 2007;33(2):310.
72. Sandyk R, Consroe P, Stern L, Snider SR, Bliklen D. Preliminary trial of cannabidiol in Hantington's disease. In: Chesher G, Consroe P, Musty R, editors. *Marijuana: an international research report. National campaign against drug monograph series nº 7.* Canberra: Australian Government Publishing Service; 1988. p.157-62.
73. Martin BR, Mechoulam RJ, Razdan RK. Discovery and characterization of endogenous cannabinoids. *Life Sci.* 1999;65(6-7):573-95.
74. Hampson AJ, Grimaldi M, Axelrod, Wink D. Cannabidiol and delta 9-tetrahydrocannabinol are neuroprotective antioxidants. *Proc Natl Acad Sci USA.* 1998;95(14):8268-73.
75. Lastres-Becker I, Molina-Holgado F, Ramos JA, Mechoulam R, Fernandez-Ruiz J. Cannabinoids provide neuroprotection against 6-hydroxydopamine toxicity in vivo and in vitro: relevance to Parkinson's disease. *Neurobiol Dis.* 2005;19(1-2):96-107.
76. Garcia-Arencibia M, Gonzalez S, de Lago E, Ramos JA, Mechoulam R, Fernandez-Ruiz J. Evaluation of the neuroprotective effect of cannabinoids in a rat model of Parkinson's disease: importance of antioxidant and cannabinoid receptor-independent properties. *Brain Res.* 2007;1134(1):162-70.
77. Sagredo O, Ramos JA, Decio A, Mechoulam R, Fernández-Ruiz J. Cannabidiol reduced the striatal atrophy caused 3-nitropropionic acid in vivo by mechanisms independent of the activation of cannabinoid, vanilloid TRPV1 and adenosine A2A receptors. *Eur J Neurosci.* 2007;26(4):843-51.
78. Hermann D, Sartorius A, Welzel H, Walter S, Skopp G, Ende G, Mann K. Dorsolateral prefrontal cortex N-acetylaspartate/total creatine (NAA/tCr) loss in male recreational cannabis users. *Biol Psychiatry.* 2007;61(11):1281-9.
79. Zuardi AW, Crippa JAS, Hallak JEC, Pinto JP, Nisihara MHC, Rodrigues GGR, Dursun SM, Tumas V. Cannabidiol for the treatment of psychosis in Parkinson's disease: possible mechanisms of actions. *J Psychopharmacology*. 2008 (in press).
80. Iuvone T, Esposito G, Esposito R, Santamaria R, Di Rosa M, Izzo AA. Neuroprotective effect of cannabidiol, a non-psychoactive component from Cannabis sativa, on beta-amyloid-induced toxicity in PC12 cells. *J Neurochem.* 2004;89(1):134-41.
81. Esposito G, De Filippis D, Carnuccio R, Izzo AA, Iuvone T. The marijuana component cannabidiol inhibits beta-amyloid-induced tau protein hyperphosphorylation through Wnt/beta-catenin pathway rescue in PC12 cells. *J Mol Med.* 2006;84(3):253-8.
82. Esposito G, De Filippis D, Maiuri MC, De Stefano D, Carnuccio R, Iuvone T. 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. *Neurosci Lett.* 2006;399(1-2):91-5.
83. Esposito G, Scuderi C, Savani C, Steardo L Jr, De Filippis D, Cottone P, Iuvone T, Cuomo V, Steardo L. Cannabidiol in vivo blunts beta-amyloid induced neuroinflammation by suppressing IL-1beta and iNOS expression. *Br J Pharmacol.* 2007;151(8):1272-9.
84. Dirikoc S, Priola SA, Marella M, Zsürger N, Chabry J. Nonpsychoactive cannabidiol prevents prion accumulation and protects neurons against prion toxicity. *J Neurosci.* 2007;27(36):9537-44.
85. Formukong EA, Evans AT, Evans FJ. Analgesic and anti-inflammatory activity of constituents of cannabis sativa L. *Inflammation.* 1998;12(4):361-71.
86. Watzl B, Scuderi P, Watson RR. Marijuana components stimulate human peripheral blood mononuclear cell secretion of interferon gamma and suppress interleukin-1 alpha in vitro. *Int J Immunopharmacol.* 1991;13(8):1091-7.
87. Srivastava MD, Srivastava BI, Brouhard B. Delta-9-tetrahydrocannabinol and cannabidiol alter cytokine production by human immune cells. *Immunopharmachology.* 1998;40(3):179-85.
88. Malfait AM, Gallily R, Sumariwalla PF, Malik AS, Andreakos E, Mechoulam R, Feldman M. The nonpsychoactive cannabis constituent cannabidiol is an oral anti-arthritic therapeutic in murine collagen-induced arthritis. *Proc Natl Acad Sci USA.* 2000;97(17):9561-6.
89. Costa B, Colleoni M, Conti S, Parolaro D, Franke C, Trovato AE, Giagnoni G. Oral anti-inflammatory activity of cannabidiol, a non-psychoactive constituent of cannabis, in acute carrageenan-induced inflammation in the rat paw. *Naunyn Schmiedebergs Arch Pharmacol.* 2004;369(3):294-9.
90. Costa B, Trovato AE, Comelli F, Giagnoni G, Colleoni M. The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *Eur J Pharmacol*. 2007;556(1-3):75-83.
91 Braida D, Pegorini S, Arcidiacono MV, Consalez GG, Croci L, Sala M. Post-ischemic treatment with cannabidiol prevents electroencephalographic flattening, hyperlocomotion and neuronal injury in gerbils. *Neurosci Lett.* 2003;346(1-2):61-4.
92 Hayakawa K, Mishima K, Abe K, Hasebe N, Takamatsu F, Yasuda H, Ikeda T, Inui K, Egashira N, Iwasaki K, Fujiwara M. Cannabidiol prevents infarction via the non-CB1 cannabinoid receptor mechanism. *Neuroreport.* 2004;15(15):2381-5.
93. Mishima K, Hayakawa K, Abe K, Ikeda T, Egashira N, Iwasaki K, Fujiwara M. Cannabidiol prevents cerebral infarction via a serotonergic 5-hydroxytryptamine1A receptor-dependent mechanism. *Stroke.* 2005;36(5):1077-82.
94. 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. *J Neurochem.* 2007;102(5):1488-96.
95. Hayakawa K, Mishima K, Nozako M, Ogata A, Hazekawa M, Liu AX, Fujioka M, Abe K, Hasebe N, Egashira N, Iwasaki K, Fujiwara M. Repeated treatment with cannabidiol but not Delta9-tetrahydrocannabinol has a neuroprotective effect without the development of tolerance. *Neuropharmacology.* 2007;52(4):1079-87.
96. Durst R, Danenberg H, Gallily R, Mechoulam R, Meir K, Grad E, Beeri R, Pugatsch T, Tarsish E, Lotan C. Cannabidiol, a nonpsychoactive Cannabis constituent, protects against myocardial ischemic reperfusion injury. *Am J Physiol Heart Circ Physiol*. 2007;293(6):H3602-7.
97. Weiss L, Zeira M, Reich S, Har-Noy M, Mechoulam R, Slavin S, Gallily R. Cannabidiol lowers incidence of diabetes in non-obese diabetic mice. *Autoimmunity.* 2006;39(2):143-51.
98. Weiss L, Zeira M, Reich S, Slavin S, Raz I, Mechoulam R, Gallily R. Cannabidiol arrests onset of autoimmune diabetes in NOD mice. *Neuropharmacology.* 2008;54(1):244-9.
99. El-Remessy AB, Al-Shabrawey M, Khalifa Y, Tsai NT, Caldwell RB, Liou GI. Neuroprotective and blood-retinal barrier-preserving effects of cannabidiol in experimental diabetes. *Am J Pathol.* 2006;168(1):235-44.

100. Rajesh M, Mukhopadhyay P, Bátkai S, Haskó G, Liaudet L, Drel VR, Obrosova IG, Pacher P. Cannabidiol attenuates high glucose-induced endothelial cell inflammatory response and barrier disruption. *Am J Physiol Heart Circ. Physiol.* 2007;293(1):H610-9.
101. Sallan SE, Zinberg NE, Frei E 3rd. Antiemetic effect of Delta-9-tetrahydrocannabinol in patients receiving cancer chemotherapy. *N Engl J Med.* 1975;293(16):795-7.
102. Doblin RE, Kleinman MA. Marijuana as antiemetic medicine: a survey of oncologists experiences and attitudes. *J Clin Oncol.* 1991;9(7):1314-9.
103. Grinspoon L, Bakalar JB. *Marihuana, the forbidden medicine.* New Haven, CT: Yale University Press; 1997.
104. Parker LA, Mechoulam R, Schlievert C. Cannabidiol, a non-psychoactive component of cannabis and its synthetic dimethylheptyl homolog suppress nausea in an experimental model with rats. *Neuroreport.* 2002;13(5):567-70.
105. Parker LA, Kwiatkowska M, Burton P, Mechoulam R. Effect of cannabinoids on lithium-induced vomiting in the Suncus murinus (house musk shrew). *Psychopharmacology* (Berl). 2004;171(2): 156-61.
106. Parker LA, Kwiatkowska M, Mechoulam R. Delta-9-tetrahydrocannabinol and cannabidiol, but not ondansetron, interfere with conditioned retching reactions elicited by a lithium-paired context in Suncus murinus: an animal model of anticipatory nausea and vomiting. *Physiol Behav.* 2006;87(1):66-71.
107. Rock EM, Limebeer CL, Mechoulam R, Piomelli D, Parker LA. The effect of cannabidiol and URB597 on conditioned gaping (a model of nausea) elicited by a lithium-paired context in the rat. *Psychopharmacology* (Berl). 2008;196(3):389-95.
108. Jacobsson SO, Rongård E, Stridh M, Tiger G, Fowler CJ. Serum-dependent effects of tamoxifen and cannabinoids upon C6 glioma cell viability. *Biochem Pharmacol.* 2000;60(12):1807-13.
109. Massi P, Vaccani A, Ceruti S, Colombo A, Abbracchio MP, Parolaro D. Antitumor effects of cannabidiol, a nonpsychoactive cannabinoid, on human glioma cell lines. *J Pharmacol Exp Ther.* 2004;308(3): 838-45.
110. 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;70(3):897-908.
111. Vaccani A, Massi P, Colombo A, Rubino T, Parolaro D. Cannabidiol inhibits human glioma cell migration through a cannabinoid receptor-independent mechanism. *Br J Pharmacol*. 2005;144(8):1032-6.
112. Ligresti A, Moriello AS, Starowicz K, Matias I, Pisanti S, De Petrocellis L, Laezza C, Portella G, Bifulco M, Di Marzo V. Antitumor activity of plant cannabinoids with emphasis on the effect of cannabidiol on human breast carcinoma. *J Pharmacol Exp Ther.* 2006;318(3):1375-87.
113. McAllister SD, Christian RT, Horowitz MP, Garcia A, Desprez PY. Cannabidiol as a novel inhibitor of Id-1 gene expression in aggressive breast cancer cells. *Mol Cancer Ther*. 2007;6(11):2921-7.
114. Pertwee RG. The pharmacology and therapeutic potential of cannabidiol. In: V Di Marzo, editor. *Cannabinoids*. Kluwer Academic/ Plenum Publishers; 2004. p. 32-83.
115. Thomas A, Baillie GL, Phillips AM, Razdan RK, Ross RA, Pertwee RG. Cannabidiol displays unexpectedly high potency as an antagonist of CB1 and CB2 receptor agonists in vitro. *Br J Pharmacol.* 2007;150(5):613-23.
116. Pertwee RG.The diverse CB1 and CB2 receptor pharmacology of three plant cannabinoids: delta9-tetrahydrocannabinol, cannabidiol and delta9-tetrahydrocannabivarin. *Br J Pharmacol*. 2008;153(2): 199-215.
117. Ryberg E, Larsson N, Sjögren S, Hjorth S, Hermansson N-O, Leonova J, Elebring T, Nilsson K, Drmota T,Greasley PJ. The orphan receptor GPR55 is a novel cannabinoid receptor. *Br J Pharmacol.* 2007;152(7):1092-101.
118. Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde D, Brandi I, Moriello AS, Davis JB, Mechoulam R, Di Marzo V. Molecular targets for cannabidiol and its synthetic analogues: effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *Br J Pharmacol.* 2001;134(4):845-52.
119. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. *Neurochem Res.* 2005;30(8): 1037-43.
120. Campos AC, Guimaraes FS. Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. *Psychopharmacology*. 2008; [Epub ahead of print].
121. Carrier EJ, Auchampach JA, Hillard CJ. Inhibition of an equilibrative nucleoside transporter by cannabidiol: a mechanism of cannabinoid immunosuppression. *Proc Natl Acad Sci U S A.* 2006;103(20): 7895-900.