Rev Bras Psiquiatr. 2012;34(Supl1):S104-S117



Revista Brasileira de Psiquiatria
RBPPsychiatry
Official Journal of the Brazilian Psychiatric Association
Volume 34 • Supplement 1 • June/2012



ARTICLE

Cannabidiol, a *Cannabis sativa* constituent, as an anxiolytic drug

Alexandre Rafael de Mello Schier,[1] Natalia Pinho de Oliveira Ribeiro,[1] Adriana Cardoso de Oliveira e Silva,[1,2,4] Jaime Eduardo Cecilio Hallak,[3,4] José Alexandre S. Crippa,[3,4] Antonio E. Nardi,[1,4] Antonio Waldo Zuardi[3,4]

[1] Laboratory of Panic and Respiration, Institute of Psychiatry (IPUB), Universidade Federal do Rio de Janeiro (UFRJ), Brazil
[2] Universidade Federal Fluminense, Brazil
[3] Department of Neuroscience and Behavioral Sciences, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo, Brazil
[4] Instituto Nacional de Ciência e Tecnologia Translacional em Medicina (National Institute for Translational Medicine; INCT-TM), Brazil

Received on March 2, 2011; accepted on December 18, 2011

DESCRIPTORS
Cannabidiol;
Cannabis sativa;
Anxiolytics;
Anxiety disorders.

Abstract
Objectives: To review and describe studies of the non-psychotomimetic constituent of *Cannabis sativa,* cannabidiol (CBD), as an anxiolytic drug and discuss its possible mechanisms of action. *Method:* The articles selected for the review were identified through searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO, combining the search terms "cannabidiol and anxiolytic", "cannabidiol and anxiolytic-like", and "cannabidiol and anxiety". The reference lists of the publications included, review articles, and book chapters were handsearched for additional references. Experimental animal and human studies were included, with no time restraints. *Results:* Studies using animal models of anxiety and involving healthy volunteers clearly suggest an anxiolytic-like effect of CBD. Moreover, CBD was shown to reduce anxiety in patients with social anxiety disorder. *Conclusion:* Future clinical trials involving patients with different anxiety disorders are warranted, especially of panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorders. The adequate therapeutic window of CBD and the precise mechanisms involved in its anxiolytic action remain to be determined.

Corresponding author: Alexandre Rafael de Mello Schier; E-mail: alexschier@hotmail.com

1516-4446 - ©2012 Elsevier Editora Ltda. All rights reserved.

Introduction

Cannabis sativa is the most used drug of abuse worldwide and around 20% of youth use it heavily and regularly around the globe.[1] The main psychoactive component of the plant is Δ9-tetrahydrocannabinol (Δ9-THC), one of the substances responsible for the psychoactive effects of Cannabis.[2-4]

Cannabidiol (CBD) is another abundant compound in *Cannabis sativa*, constituting around 40% of the plant's active substances.[5] The pharmacological effects of CBD are different and often opposite to those of Δ9-THC.[6] The number of publications on CBD has increased remarkably over the last years and support the view that CBD has a vast array of possible therapeutic effects. Among these possibilities, the anxiolytic and antipsychotic properties of CBD stand out.[7-10] CBD's anxiolytic effects are apparently similar to those of approved drugs to treat anxiety,[11] although its effective doses have not been clearly established and the mechanisms underlying these effects are not fully understood. The low affinity of CBD for cannabinoid neuroreceptors[12,13] and its agonist properties at 5-HT1A receptors[14,15] have been repeatedly demonstrated.

Most studies on CBD have been conducted with rodents, but studies with human samples have also provided promising results.[16,17] Therefore, the aim of this paper is to review the scientific literature on the anxiolytic properties of CBD in animal and in humans.

Method

The articles selected for this review were identified by searches in English, Portuguese, and Spanish in the electronic databases ISI Web of Knowledge, SciELO, PubMed, and PsycINFO combining the search terms "cannabidiol and anxiolytic", "cannabidiol and anxiolytic-like", and "cannabidiol and anxiety". In addition, the reference lists of the selected articles and relevant literature reviews and book chapters were handsearched for additional references. We included experimental studies with human and animal samples with no time limits. We sought to exclude studies that used smoked Cannabis, as it is not possible to establish the dose, composition, and proportion of the different cannabinoids in this case, besides the great individual variations in the samples enrolled. Finally, we did not include studies using extracts containing both THC and CBD in oral (Cannador®) or oromucosal spray (Sativex®) forms due to the difficulty to establish the effects of CBD alone (Table 1).

Animal studies

The two first articles about the effects of CBD on experimental anxiety were published in journals that were not indexed in the databases used for this review but were located through handsearch in the reference lists of relevant literature. These two investigations showed contradictory results. In one study, no significant effects of high doses of CBD (100 mg/kg) were seen in rats in the Geller-Seifter conflict test.[18] In the other, a low dose of CBD (10 mg/kg) had anxiolytic effects in rats submitted to the conditioned emotional response test.[19]

Later studies using the elevated plus maze (EPM) helped to elucidate this contradiction.[9] The EPM consists of two opposing open arms (50 x 10 cm) and two closed arms (50 x 10 x 40 cm) that intersect in their central portion. The arms are made of wood and stand 50 cm above the ground. In this study, mice injected with CBD, diazepam or vehicle (no active substances) were placed in the center of the maze facing the closed arms. The time spent and the numbers of entries in the open and closed arms were measured for 10 minutes. The frequency of entries in the open arms of animals receiving CBD presented an inverted U-shaped curve, with significantly higher rates than those observed in animals treated with vehicle, at the doses of 2.5, 5, and 10 mg/kg. The measures of mice treated with CBD 20 mg/kg did not differ from those of controls, suggesting that anxiolytic effects are only present at low doses, which explains the absence of effects with CBD 100 mg/kg reported in 1981.[18] The same inverted U-shaped dose-response curve was obtained with a wider range of doses of CBD in the EPM (Onaivi et al.).[20] Furthermore, the same pattern was observed with the direct infusion of CBD in the periaqueductal gray (PAG) of rats tested in the EPM,[15,21] confirming that anxiolytic effects should only be expected with low doses of CBD.

The mechanisms through which CBD acts to diminish anxiety have been studied in a number of animal models of anxiety using rodents. One of these studies used Vogel's conflict test,[22] in which the animal is water-deprived from and placed in a cage with an electrified grid at the bottom through which the animal receives a shock after licking water for a predetermined number of times. Three substances were tested in rats using the following procedure: CBD (2.5, 5 and 10 mg/kg), diazepam, and flumazenil (an antagonist of benzodiazepine receptors), in addition to vehicle (placebo). The tests showed that CBD produced effects consistent with those of diazepam by increasing the number of licks, even if they resulted in punishment. Flumazenil antagonized the anxiolytic effect of diazepam, but not that of CBD, suggesting that the effects of CBD are not mediated by the activation of benzodiazepine receptors.

There is strong evidence showing that the serotonergic system is involved in the anxiolytic action of CBD. The injection of the 5-HT1A receptor antagonist WAY-100635 (WAY) directly into the dorsolateral portion of the PAG (dlPAG) in rats antagonized the anxiolytic effects of CBD in the EPM and in Vogel's conflict test.[15] The participation of 5-HT1A receptors in the anxiolytic action of CBD was also derived from behavioral and cardiovascular responses to restraint stress in rats.[11] In this study, animals were intraperitoneally injected with vehicle or CBD (1, 10 and 20 mg/kg) and, after 30 minutes, they were restrained for 60 minutes. Immobilization increased blood pressure, heart rate, and anxiety responses in the EPM 24 hours later, and these effects were attenuated by CBD. Pretreatment with WAY blocked the anxiolytic action of CBD. The injection of CBD into the intra-dorsal PAG also blocked panic-like responses in the elevated T-maze (ETM) and flight responses to the electrical stimulation of this area.[23] The ETM has three arms with the same dimensions, two open and one closed, and allows the measure of entrance avoidance in the open arms when the animal is placed in the closed arm, as well as of escape when the animal is placed in the open arm. The panic-like response seen with CBD in the two procedures was antagonized by the previous intra-dlPAG administration of WAY.[22] Chronic oral administration of CBD also had anti-panic effects in the ETM that were neutralized

Table 1 Studies of the anxiolytic effect of cannabidiol in humans and animals

Study	Model	Route	Dose	Anxiolytic effect
Animals				
Silveira Filho et al.[18]	Conflict test	Intraperitoneal	100 mg/kg	–
Zuardi et al.[19]	Conditioned emotional response paradigm	Intraperitoneal	10 mg/kg	+
Onaivi et al.[20]	Elevated plus maze test	Intraperitoneal	0.01, 0.1, 0.5, 1.0, 2.5, 5.0, 10.0, 50.0 and 100.0 mg/kg	+
Guimarães et al.[9]	Elevated plus maze test	Intraperitoneal	2.5, 5.0, 10.0 and 20.0 mg/kg	+
Moreira et al.[22]	Vogel's conflict test	Intraperitoneal	2.5, 5.0 and 10.0 mg/kg	+
Resstel et al.[10]	Contextual fear conditioning	Intraperitoneal	10 mg/kg	+
Campos et al.[15]	Elevated plus maze test and Vogel's conflict test	Intra-dorsal periaqueductal gray		+
Bitencourt et al.[28]	Contextual fear conditioning	i.c.v.	2.0 microg/microl	+
Campos et al.[21]	Elevated plus maze test	Intra-dorsal periaqueductal gray	30 or 60 nmol	+
Resstel et al.[19]	Restraint stress	Intraperitoneal	1, 10 and 20 mg/kg	+
Soares et al.[23]	Elevated T maze	Intra-dorsal periaqueductal gray	15, 30 or 60 nmol	+
Lemos et al.[29]	Contextual fear conditioning	Intraperitoneal and direct microinjection into the PL prefrontal cortex	10 mg/kg (i.p.) and 30 nmol (microinjection into the PL prefrontal cortex)	+
Casarotto et al.[26]	Marble-burying test	Intraperitoneal	15, 30 and 60 mg/kg	+
Gomes et al.[30]	Vogel's conflict test	Intra bed nucleus of the stria terminalis	15, 30, and 60 nmol	+
Deiana et al.[27]	Marble-burying test	Intraperitoneal and oral	120 mg/kg	+
Uribe-Mariño et al.[31]	Prey-predator paradigm	Intraperitoneal	0.3, 3.0 and 30 mg/kg	+
Campos et al.[24]	Elevated T maze	Oral		+
Humans				
Zuardi et al.[7]	Decreased STAI scores elevation induced by THC (healthy volunteers)	Oral	1 mg/kg	+
Zuardi et al.[32]	Decreased VAS factor anxiety scores after public speaking (healthy volunteers)	Oral	300 mg	+
Crippa et al.[34]	Decreased VAS factor anxiety scores before SPECT procedure (healthy volunteers)	Oral	400 mg	+
Fusar-Poli et al.[35]	Decreased skin conductance fluctuation in task with fearful faces during a fMRI procedure (healthy volunteers)	Oral	600 mg	+
Crippa et al.[17]	Decreased VAS factor anxiety scores before SPECT procedure (social phobia patients)	Oral	400 mg	+
Bergamaschi et al.[33]	Decreased VAS factor anxiety scores after public speaking (social phobia patients)	Oral	600 mg	+

by intra-dlPAG injection of WAY. However, chronic administration of CBD did not change the extracellular concentration of serotonin in the dlPAG or the expression of 5-HT1A or 5-HT2C, indicating that CBD directly activates 5-HT1A receptors.[24] CBD was also found to activate the vanilloid receptor type 1 (TRPV1)[25] and there is evidence that this activation could explain the inverted U-shaped dose-response curve of CBD's anxiolytic effect seen in the EPM. TRPV1 receptors regulate the release of glutamate in the dlPAG and the increased activation of this system would result in increased anxiety. Thus, it has been suggested that elevated doses of CBD in the dlPAG could activate local TRPV1 receptors facilitating the glutamatergic neurotransmission and increasing anxiety.

To test this hypothesis, rats pre-treated with the TRPV1 antagonist capsazepine in the dlPAG were injected with CBD (30 and 60 mg/kg) in the same region and tested in the EPM. The dose of 60 mg/kg CBD, which had no anxiolytic action before, was able to reduce anxiety after pre-treatment with capsazepine, suggesting that the activation of TRPV1 receptors by the higher dose of CBD would counterbalance the anxiolytic effect of CBD produced by the activation of 5-HT1A receptors.[21]

Because serotonin has also been implicated in obsessive-compulsive disorder (OCD), the effects of CBD were tested in mice submitted to the marble-burying test (MBT), an animal model of compulsive behavior. CBD induced a significant reduction in the number of buried marbles at different doses (15, 30, and 60 mg/kg) compared to controls in a dose-dependent pattern. The same was found with the administration of the ISRS paroxetine (10 mg/kg) and diazepam (2.5 mg/kg). However, the effects of CBD 30 mg/kg persisted even after seven days of repeated daily administration, whereas the effects of diazepam disappeared. Pre-treatment with WAY (3 mg/kg) counteracted the effects of paroxetine, but did not affect the action of CBD, which was prevented by pre-treatment with the CB1 receptor antagonist AM251 (1 mg/kg).[26] This action of CBD in the MBT was recently replicated by another group using a higher dose (120 mg/kg).[27]

The participation of specific cannabinoid receptors (CB1) in the anxiolytic action of CBD has also been investigated using animal models. In the study with the EPM that reported the antagonism of the anxiolytic effect of intra-dlPAG CBD by WAY, the CB1 receptor antagonist AM251 was unable to avoid this effect.[15] However, this receptor system seems to be involved in another anxiolytic-like action of CBD, according to tests using a procedure known as contextual fear conditioning. In this procedure, animals are pre-conditioned to a hostile environment (foot shocks) and later exposed to the same environment, when they normally present freezing, the duration of which can be monitored as a measure of anxiety. Both CBD and diazepam are successful in attenuating freezing in rats, as well as the increased heart rate and blood pressure induced by re-exposure to the contextually feared environment.[10] This effect of CBD on contextual memory is also produced by the endocannabinoid reuptake inhibitor AM404, which increases the availability of cannabinoids in the synaptic cleft.[28] In this study, the two drugs were injected into the ventricles and their effects were counteracted by the CB1 receptor antagonist SR141716A, suggesting the involvement of the endocannabinoid system in the anxiolytic action of CBD in this model. The pre-limbic region of the prefrontal cortex appears to underlie this effect of CBD, as the reduction in contextual fear produced by systemic administration of CBD (10 mg/kg) is associated with reduced c-Fos expression in this area. In addition, the microinjection of CBD (30 nmol) in the pre-limbic region of the frontal cortex reduced freezing induced by re-exposure to the aversive context.[29] The effects of CBD on contextual fear indicate a possible therapeutic action of this cannabinoid in post-traumatic stress disorder.

Another area that is apparently involved in the anxiolytic-like effects of CBD is the bed nucleus of the stria terminalis (BNST). The intra-BNST injection of CBD (15, 30, and 60 nmol) increased the number of punished licks in Vogel's conflict test and the number of open arm entries in the EPM. These effects were blocked in rats pre-treated with WAY.[30]

CBD was also effective in an ethologic model that investigates behaviors induced by innate fear, the predator-prey paradigm.[31] This procedure was performed using a semi-transparent plexiglass box in the shape of a quadrangular arena (154x72x64 cm) with walls covered with a light-reflecting film and floor in transparent plexiglass over a board of stainless steel divided in 20 equal rectangles. One of the corners of the arena has a shelter box with black walls and a complex maze inside. Three days prior to the experiment, the mice were placed and kept in this arena, with free access to food and water until the day of the trial. The "no threat" group had its behaviors recorded for five minutes. Animals exposed to the predator (snake) were divided into four groups (n = 12/11 per group) and pre-treated with intraperitoneal injections of CBD (0.3, 3 and 30 mg/kg) or vehicle (control group). The group of animals that were not confronted with the predator presented no defensive behaviors. Animals pre-treated with CBD had significant reductions in explosive flight and defensive immobility, responses related to panic models. Risk assessment and defensive attention were unaltered in animals treated with CBD. These results suggest that CBD can be effective in the control of panic attacks.

Human studies

The first evidence of CBD's anxiolytic effects in humans, documented with assessment scales, was published in 1982 in a study on the interaction between CBD and THC.[7] The study sample consisted of eight volunteers with a mean age of 27 years, no health problems and who had not used *Cannabis sativa* in the previous 15 days. In a double-blind procedure, the volunteers received CBD, THC, THC + CBD, diazepam, and placebo in different sequences and days. The results showed that the increased anxiety following the administration of THC was significantly attenuated with the simultaneous administration of CBD (THC + CBD).

Based on this preliminary evidence, researchers decided to investigate a possible anxiolytic action of CBD in experimentally induced anxiety in healthy volunteers using the simulated public speaking (SPS) model.[32] The procedure consists of asking a subject to speak in front of a video camera for a few minutes, while subjective anxiety is measured with self-rated scales and physiological correlates of anxiety are recorded (heart rate, blood pressure, skin conductance). CBD (300 mg), as well as the anxiolytic drugs diazepam (10 mg) and ipsapirone (5 mg), administered in a double-blind design, significantly attenuated SPS-induced anxiety.

The SPS test may be regarded as a good model of anxiety and has apparent validity for social anxiety disorder (SAD), as the fear of speaking in public is considered a central feature in this condition. Therefore, the anxiolytic effect of CBD in healthy volunteers observed in this test led to the hypothesis that this cannabinoid could be effective to treat SAD. This hypothesis was recently tested in 24 patients with SAD who had their performance in the SPS test compared to that of a group of 12 healthy controls.[33] The patients with SAD were divided into two groups of 12, one of which received CBD 600 mg and the other placebo, in a double-blind procedure. The results showed that the levels of anxiety, somatic symptoms, and negative self-assessment were higher in patients who took placebo than in those of the CBD group who performed similarly to healthy controls in some measures.

In another study that investigated the effects of CBD on regional cerebral blood flow (rCBF) in healthy volunteers using single photon emission computed tomography (SPECT), SPS-induced anxiety was reduced in patients receiving CBD.[34] In that study, patients received either CBD (400 mg) or placebo, in a crossed double-blind design, in two experimental sessions with an interval of one week. CBD significantly reduced subjective anxiety as measured by rating scales, while brain activity was increased in the left parahippocampal gyrus and decreased in the left amygdala-hippocampus complex, including the fusiform gyrus. This pattern of SPECT results is compatible with an anxiolytic action.

SPECT was also used later to investigate the neural correlates of CBD's anxiolytic effects in a sample of patients with SAD.[17] A single dose of CBD 400 mg was able to reduce subjective anxiety measures and SPECT showed changes in the same regions previously identified in healthy volunteers.

Functional magnetic resonance imaging (fMRI), which allows the acquisition of larger series of images with better temporal and spatial resolution, was used to investigate the neural correlates of the anxiolytic effects of CBD in 15 healthy volunteers.[35] This experiment showed that CBD (600 mg) attenuated fMRI responses during the recognition of fearful facial expressions in the amygdala and the anterior cingulate, and that this attenuation pattern correlated with skin conductance responses to the stimuli. The same group also reported that the anxiolytic action of CBD occurs by altering the subcortical prefrontal connectivity via amygdala and anterior cingulated.[16]

Conclusion

Together, the results from laboratory animals, healthy volunteers, and patients with anxiety disorders support the proposition of CBD as a new drug with anxiolytic properties. Because it has no psychoactive effects and does not affect cognition; has an adequate safety profile, good tolerability, positive results in trials with humans, and a broad spectrum of pharmacological actions,[36] CBD appears to be the cannabinoid compound that is closer to have its preliminary findings in anxiety translated into clinical practice.[37] Future studies should test this possibility in clinical trials involving patients with different anxiety disorders, especially panic disorder, obsessive-compulsive disorder, social anxiety disorder, and post-traumatic stress disorder. In addition, because the actions of CBD are biphasic, the adequate therapeutic window for each anxiety disorder remains to be determined. Regarding the mechanism underlying the anxiolytic effects of CBD, the most consistent evidence points to the involvement of the serotonergic system, probably through direct action on 5-HT1A receptors, although other systems, as the endocannabinoid system itself, may also be implicated. Further investigation is warranted to clarify these issues, especially if we consider that CBD is a drug with a variety of effects in the nervous system.[38-40]

Disclosures

Alexandre Rafael de Mello Schier
Employment: *Universidade Federal do Rio de Janeiro (UFRJ), Brazil.* **Research grant:** *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq)*, Brazil.* **Other:** *Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ), Brazil.*

Natalia Pinho de Oliveira Ribeiro
Employment: *Universidade Federal do Rio de Janeiro (UFRJ), Brazil.* **Research grant:** *Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes)*, Brazil.* **Other:** *Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ), Brazil.*

Adriana Cardoso de Oliveira e Silva
Employment: *Universidade Federal Fluminense (UFF), Brazil.* **Other:** *Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ); National Institute for Translational Medicine (INCT-TM), Brazil.*

Jaime Eduardo Cecilio Hallak
Employment: *Faculdade de Medicina da Universidade São Paulo (FMRP-USP), Brazil.* **Research grant:** *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes); Fundação de Amparo à Pesquisa de São Paulo (FAPESP), Brazil.* **Other:** *THC-Pharm, Novartis, AstraZaneca; Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; National Institute for Translational Medicine (INCT-TM), Brazil.*

José Alexandre S. Crippa
Employment: *Faculdade de Medicina da Universidade São Paulo (FMRP-USP), Brazil.* **Research grant:** *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes); Fundação de Amparo à Pesquisa de São Paulo (FAPESP), Brazil.* **Other:** *THC-Pharm, Elli-Lilly, Servier; Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; National Institute for Translational Medicine (INCT-TM), Brazil.*

Antonio E. Nardi
Employment: *Universidade Federal do Rio de Janeiro (UFRJ), Brazil.* **Research grant:** *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq)**, Brazil.* **Speaker's honoraria:** *Glaxo-Smikline*, Roche.* **Consultant/ Advisory board:** *Aché*.* **Other:** *ArtMed*; Laboratory of Panic and Respiration, Institute of Psychiatry, Universidade Federal do Rio de Janeiro (UFRJ); National Institute for Translational Medicine (INCT-TM), Brazil.*

Antonio Waldo Zuardi
Employment: *Faculdade de Medicina da Universidade São Paulo (FMRP-USP), Brazil.* **Research grant:** *Conselho Nacional de Desenvolvimento Científico e Tecnológico (Brazilian Council for Scientific and Technological Development, CNPq); Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (Coordination for the Improvement of Higher Education Personnel, Capes); Fundação de Amparo à Pesquisa de São Paulo (FAPESP), Brazil.* **Other:** *THC-Pharm; Departamento de Neurociências e Ciências do Comportamento, Faculdade de Medicina de Ribeirão Preto, Universidade de São Paulo; National Institute for Translational Medicine (INCT-TM), Brazil.*

** 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.*

References

1. Diehl A, Cordeiro DC, Laranjeira R. [Cannabis abuse in patients with psychiatric disorders: an update to old evidence]. Rev Bras Psiquiatr. 2010;32(Suppl 1):S41-5.
2. Mechoulam R. Marihuana chemistry. Science. 1970;168:1159-66.
3. Mechoulam R, Shani A, Edery H, Grunfeld Y. Chemical basis of hashish activity. Science. 1970;169:611-2.
4. Ilan AB, Gevins A, Coleman M, ElSohly MA, de Wit H. Neurophysiologicaland subjective profile of marijuana with varying concentrationsof cannabinoids. Behav Pharmacol. 2005;16:487-96.
5. Crippa J, Zuardi A, Martin-Santos R, Bhattacharyya S, Atakan Z, McGuire P, Fusar-Poli, P. Cannabis and anxiety: a critical review of the evidence. Hum Psychopharmacol. 2009;24(7):515-23.
6. Mechoulam R, Petersa M, Murillo-Rodriguez E, Hanus LO. Cannabidiol – recent advances. Chem Biodivers. 2007;4:1678-92.
7. 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;76:245-50.
8. Zuardi AW, Crippa JA, Hallak JE, Moreira FA, Guimaraes FS. Cannabidiol, a Cannabis sativa constituent, as an antipsychotic drug. Braz J Med Biol Res. 2006;39(4):421-9.
9. Guimarães FS, Chiaretti TM, Graeff FG, Zuardi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. Psychopharmacology (Berl). 1990;100:558-9.
10. Resstel LB, Joca SR, Moreira FA, Correa FM, Guimarães FS. Effects of cannabidiol and diazepam on behavioral and cardiovascular responses induced by contextual conditioned fear in rats. Behav Brain Res. 2006;172(2):294-8.
11. Resstel, LB, Tavares RF, Lisboa SF. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioural and cardiovascular responses to acute restraint stress in ratscardiovascular responses to acute restraint stress in rats. Br J Pharmacol. 2009;156(1):181-8.
12. Petitet F, Jeantaud B, Reibaud M, Imperato A, Dubroeucq MC. Complex pharmacology of natural cannabinoids: evidence for partial agonist activity of delta9-tetrahydrocannabinol and antagonist activity of cannabidiol on rat brain cannabinoid receptors. Life Sci. 1998:63:PL1–PL6.
13. Thomas BF, Gilliam AF, Burch DF, Roche MJ, Seltzman HH.Comparative receptor binding analyses of cannabinoid agonists and antagonists. J Pharmacol Exp Ther. 1998;285:285-92.
14. Russo EB, Burnett A, Hall B, Parker KK. Agonistic properties of cannabidiol at 5-HT1a receptors. Neurochem Res. 2005;30(8):1037-43.
15. Campos AC, Guimaraes FS. Involvement of 5HT1A receptors in the anxiolytic-like effects of cannabidiol injected into the dorsolateral periaqueductal gray of rats. Psychopharmacology (Berl) 2008;199:223-30.
16. 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. Modulation of effective connectivity during emotional processing by Delta(9)-tetrahydrocannabinol and cannabidiol. Int J Neuropsychopharmacol. 2010;13(4):421-32.
17. Crippa JAS, Derenusson GN, Ferrari TB, Wichert-Ana L, Duran FL, Martin-Santos R, Simões MV, Bhattacharyya S, Fusar-Poli P, Atakan Z, Santos Filho A, Freitas-Ferrari MC, McGuire PK, Zuardi AW, Busatto GF, Hallak JE. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol. 2011;25(1):121-30.
18. 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.
19. Zuardi AW, Karniol IG. Changes in the conditioned emotional response of rats induced by Δ9-THC, CBD and mixture of the two cannabinoids. Arq Biol Tecnol. 1983;26:391-7.
20. Onaivi ES, Green MR, Martin BR. Pharmacological characterization of cannabinoids in the elevated plus maze. J Pharmacol Exp Ther. 1990;253(3):1002-9.
21. Campos AC, Guimaraes FS. Evidence for a potential role for TRPV1 receptors in the dorsolateral periaqueductal gray in the attenuation of the anxiolytic effects of cannabinoids. Prog Neuropsychopharmacol Biol Psychiatry. 2009;33(8):1517-21.
22. Moreira FA, Aguiar DC, Guimaraes FS. Anxiolytic-like effect of cannabidiol in the rat Vogel conflict test. Prog Neuropsychopharmacol Biol Psychiatry. 2006;30(8):1466-71.
23. Soares V de P, Campos AC, Bortoli VC, Zangrossi H Jr, Guimarães FS, Zuardi AW. Intra-dorsal periaqueductal gray administration of cannabidiol blocks panic-like response by activating 5-HT1A receptors. Behav Brain Res. 2010;213(2):225-9.
24. Campos AC, Soares Vde P, Carvalho MC, Ferreira FR, Vicente MA, Brandão ML, Zuardi AW, Zangrossi JR. H, Guimarães FS. Cannabidiol chronic treatment attenuates panic-like responses via direct modulation of 5HT1A receptors functions in the dorsal periaqueductal grey matter. Neuropsychopharmacology (submitted).
25. Bisogno T, Hanus L, De Petrocellis L, Tchilibon S, Ponde DE, 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.
26. Casarotto PC, Gomes FV, Resstel LB, Guimarães FS. Cannabidiol inhibitory effect on marble-burying behaviour: involvement of CB1 receptors. Behav Pharmacol. 2010;21(4):353-8.
27. Deiana S, Watanabe A, Yamasaki Y, Amada N, Arthur M, Fleming S, Woodcock H, Dorward P, Pigliacampo B, Close S, Platt B, Riedel G. 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. Psychopharmacology (Berl). 2012; 219(3):859-73.
28. Bitencourt RM, Pamplona FA, Takahashi RN. Facilitation of contextual fear memory extinction and anti-anxiogenic effects of AM404 and cannabidiol in conditioned rats. Eur Neuropsychopharmacol. 2008;18(12):849-859.
29. Lemos JI, Resstel LB, Guimaraes FS. Involvement of the prelimbic prefrontal cortex on cannabidiol-induced attenuation of contextual conditioned fear in rats. Behav Brain Res. 2010;207(1):105-11.
30. Gomes FV, Resstel LB, Guimarães FS. The anxiolytic-like effects of cannabidiol injected into the bed nucleus of the stria terminalis are mediated by 5-HT1A receptors. Psychopharmacology (Berl). 2011;213(2-3):465-73.
31. Uribe-Mariño A, Francisco A, Castiblanco-Urbina MA, Twardowschy A, Salgado-Rohner CJ, Crippa JA, Hallak JE, Zuardi AW, Coimbra NC. 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. Neuropsychopharmacol. 2012;37(2):412-21.
32. Zuardi AW, Cosme RA, Graeff FG, Guimarães FS. Effects of ipsapirone and cannabidiol on human experimental anxiety. J Psychopharmacol 1993;7:82-8.
33. Bergamaschi MM, Queiroz RH, Chagas MHN, de Oliveira DCG, De Martinis BS, Kapczinski F, Quevedo J, Roesler R, Schroder N, Nardi AE, Martin-Santos R, Hallak JEC, Zuardi AW, Crippa JAS. Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naïve Social Phobia Patients. Neuropsychopharmacol. 2011;36(6):1219-26.

34. 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. Neuropsychopharmacol. 2004;29(2):417-26.
35. Fusar-Poli P, Crippa JA, Bhattacharyya S, Borgwardt SJ, Allen P, Martin-Santos R, Seal M, Surguladze SA, O'Carrol C, Atakan Z, Zuardi AW, McGuire PK. Distinct effects of Δ9-tetrahydrocannabinol and cannabidiol on neural activation during emotional processing. Arch Gen Psychiatry. 2009;66(1):95-105.
36. Bergamaschi MM, Queiroz RH, Zuardi AW, Crippa JA. Safety and side effects of cannabidiol, a Cannabis sativa constituent. Curr Drug Saf. 2011;6(4):237-49.
37. Crippa JA, Zuardi AW, Hallak JE. [Therapeutical use of the cannabinoids in psychiatry]. Rev Bras Psiquiatr. 2010;32(Suppl1):S56-66.
38. Zuardi AW. Cannabidiol: from an inactive cannabinoid to a drug with wide spectrum of action. Rev Bras Psiquiatr. 2008;30(3):271-80.
39. Izzo AA, Borrelli F, Capasso R, Di Marzo V, Mechoulam R. Non-psychotropic plant cannabinoids: new therapeutic opportunities from an ancient herb. Trends Pharmacol Sci. 2009;30(10):515-27.
40. Crippa JA, Zuardi AW, Hallak JE Cannabis sativa: the plant that can induce unwanted effects and also treat them. Rev Bras Psiquiatr. 2010;32 Suppl 1:S51-52.