Antidepressant-Like and Anxiolytic-Like Effects of Cannabidiol: A Chemical Compound of *Cannabis sativa*

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Abstract: Anxiety and depression are pathologies that affect human beings in many aspects of life, including social life, productivity and health. Cannabidiol (CBD) is a constituent non-psychotomimetic of *Cannabis sativa* with great psychiatric potential, including uses as an antidepressant-like and anxiolytic-like compound. The aim of this study is to review studies of animal models using CBD as an anxiolytic-like and antidepressant-like compound. Studies involving animal models, performing a variety of experiments on the above-mentioned disorders, such as the forced swimming test (FST), elevated plus maze (EPM) and Vogel conflict test (VCT), suggest that CBD exhibited an anti-anxiety and anti-depressant effects in animal models discussed. Experiments with CBD demonstrated non-activation of neuroreceptors CB1 and CB2. Most of the studies demonstrated a good interaction between CBD and the 5-HT1A neuro-receptor.

Keywords: Anxiety, anxiolytic-like, cannabis sativa, cannabidiol, CBD, major depression.

INTRODUCTION

Anxiety can be defined as a vague and unpleasant feeling that can be compared to fear or apprehension and that is usually caused by anticipation of a risk, danger or unknown situation [1, 2]. Anxiety and fear are considered pathological from the moment they become exaggerated, irrational and dysfunctional with regard to the stimulus, as well as when they begin to interfere in the daily activities of the subject, reducing their quality of life and performance in daily life activities [1]. Other factors differentiating between normal and pathological anxiety are the duration of the symptoms, voluntary restraint and whether anxiety occurs on the spur of the moment [3].

Anxiety disorders are clinical situations in which these symptoms appear in isolation and are not associated with any other secondary frame of reference or any other disease [3], although sometimes there is a difficulty in determining which is the primary symptom, because the patient presents with multiple concomitant and comorbid pathologies [4].

Depression can appear on several occasions: as a comorbid psychiatric condition [5] linked to substance abuse, to response to stress, or due to bereavement and clinical conditions, as has been pointed out in several studies [6-10]. It can also occur as a comorbid condition in chronic diseases and in diseases that cause pain, deformity, disability and even reductions in quality of life and life expectancy.

Depressed patients present symptoms such as mood changes, apathy, lack of ability to feel pleasure (anhedonia), increased levels of irritability, prostration, cognitive and psychomotor changes and changes in appetite and sleep regimen, among others. They can manifest themselves in different ways, but are often considered as a part of cyclothymia, as a characteristic of bipolar disorder types I and II, as major depressive disorder, as dysthymia and as melancholy [5].

Cannabis sativa is among the most commonly used drugs in the world, with approximately 20% of young people having used this drug [11]. It contains more than 400 different compounds, of which 66 are named phytocannabinoids [12]. Delta 9 tetrahydrocannabinol (THC) is the major active chemical component of this plant and the main ingredient responsible for the hallucinogenic effects of the consumed plant. Cannabidiol (CBD) is the second major active chemical compound [13] in the plant, and it has a large structure (Fig. **1**). This compound has been studied for more than three decades, and in this period, many findings were found in anxiety disorders, social phobia, schizophrenia, depression and other psychiatric conditions [14-17].

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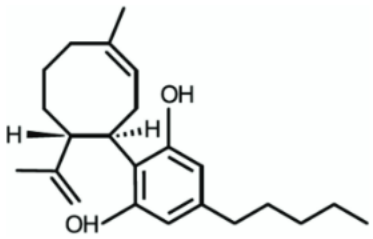

Fig. (1). CBD structure.

Research with animal models is an important step during the investigating process of a particular substance before making it marketable. This step consists in establishing the lethal dose, the half-life and effective and safe dosages. In addition, preclinical research is an important environment for guiding the substance usage.

CBD, different from the main constituent THC, is not hallucinogenic and can be isolated from the others constituents of the *Cannabis sativa* plant. It is a potential psychotherapeutic drug [18]. Thus, the aim of this study is to review studies of animal models using CBD as an anxiolytic-like and antidepressant-like compound.

METHODOLOGY

We identified articles using the major electronic database, including ISI Web of Knowledge, Scielo, PubMed and PsycINFO. As languages for this search, we used Portuguese and English. We combined the terms "Cannabidiol", "antidepressant-like" and "anxiolytic-like". Thirteen studies were found related to the term "antidepressant-like" on ISI Web of Knowledge, and in the other databases, we only found the same articles. We used five articles as main studies from this search. Using the term "anxiolytic-like", 19 articles in ISI Web of Knowledge, 21 papers in PubMed, two articles in SciELO and nothing in PsycINFO were found; excluding repeated articles among the electronic databases, we took 14 of these articles, which were animal studies of CBD and which met the other criteria described below (Fig. **2**), for this review. Also, five articles suggested by fellows were included.

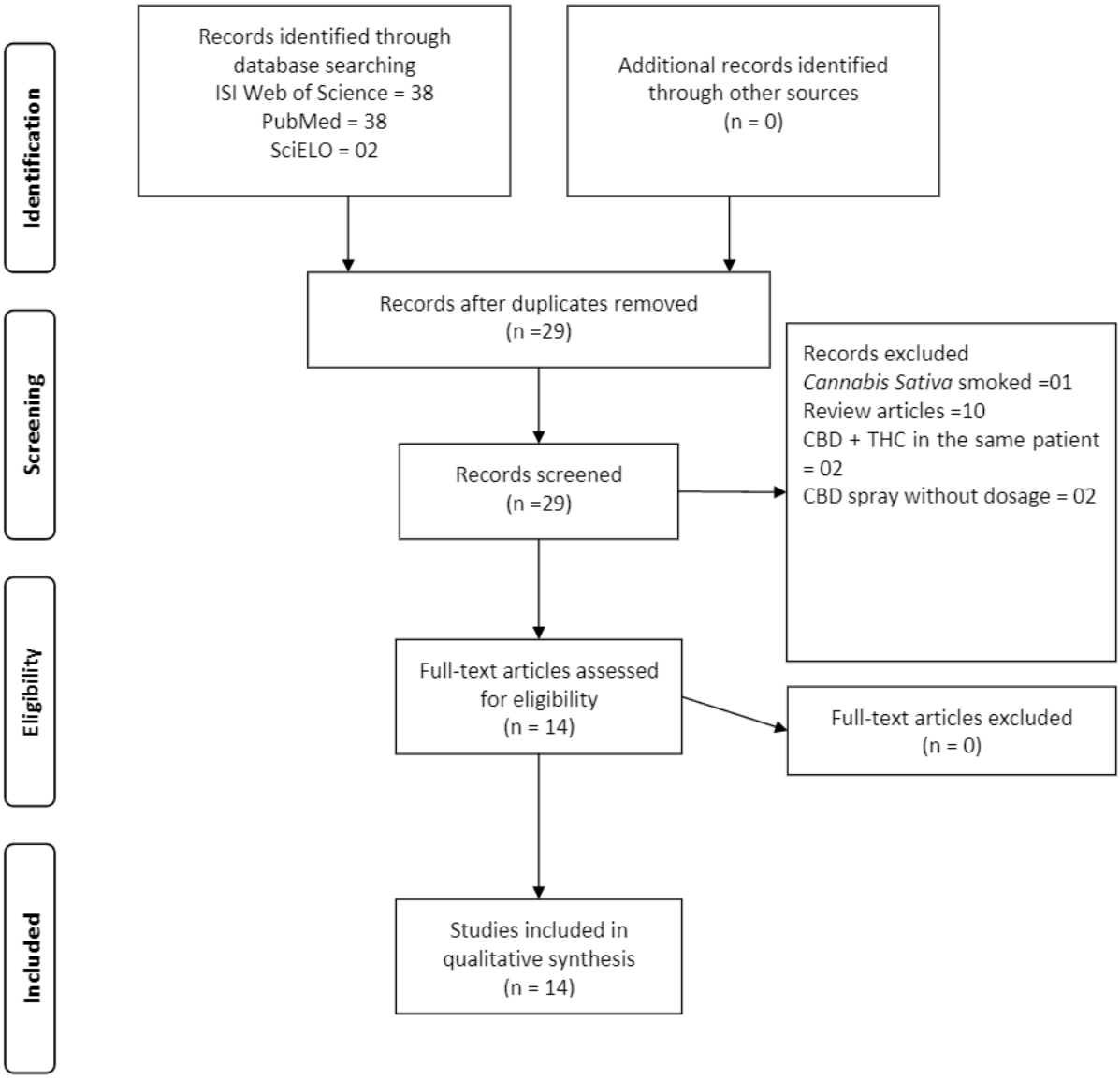

Fig. (2). Results of search strategy related to anxiolytic-like effects of cannabidiol.

This study included animal studies regarding depression or anxiety models, using CBD as an isolated substance. We excluded from this review articles using CBD concomitant with THC on the same animal or that involved smoking of *Cannabis sativa*, as it is impossible to define the dose compositions and proportions of the many different compounds in the plant. Table **1** describes all selected studies.

RESULTS

Antidepressant Effects of CBD

In 1977, Porsolt *et al*. [19] were the first to describe the forced swimming test (FST) as a useful tool in research. It consists of placing a rat in a cylinder full of water, where there is a stand hidden by the water but that is high enough for the rat to stay comfortable without the necessity to swim. In this test the rat is released into the water, and it must swim to stay alive and instinctively to find a way to leave the water. Exploring the cylinder surface, the rat can find the stand. In researches with depressed rats, they stay in the water without moving unlike normal rats, which usually try to find a place to stay.

In 2011 [20], rats were treated with CBD in different doses (15, 30 and 60 mg/kg), imipramine (30 mg/kg) or saline solution as placebo. This research showed that CBD in the 30 mg/kg dosage had similar effects to imipramine, with a larger number of rats climbing compared to rats treated with saline solution and slightly higher numbers of rats that received other dosages of CBD. The study also discussed brain-derived neurotrophic factor (BDNF), a biomarker also used to detect depression. In fact, decreased levels of BDNF have been shown in depressed animal and humans [21-23]. Conversely, administration of antidepressant treatments increases BDNF expression [24], and brain infusion of BDNF produces antidepressant-like actions in rats [22, 24]. Compatible with an antidepressant effect, an increase in BDNF was detected in animals treated with CBD, as well as in the animals treated with imipramine.

Other study on animal model [25] was performed using FST and found the same antidepressant-like effect in a dose-dependent manner, and also a non-hallucinogenic effect in rats, unlike the rats that received THC.

A study using an open field arena [26], with rats treated with CBD, showed interesting results regarding motor activity. Animals received injectable doses of CDB (i.e., 3, 10, 30 and 100 mg/kg) and placed in a circular open field arena (40 cm in diameter with a 50-cm-high Plexiglas wall), in which exploratory activity was videotaped for 6 min. Results showed decreased activity over the time of exposure, but it was not correlated with any dose of CBD, since the control animals behavior remained the same. The findings agree with the data of Guimarães *et al*. [27], indicating that CBD does not induce significant motor changes; the antidepressant-like effect of CDB is not secondary. In addition [27], authors also used FST adding the variable WAY 100635 (WAY), a 5-HT1A antagonist, and found similar results to other studies published previously. Rats were treated with WAY and received CBD (30 mg/kg^{-1}) or vehicle (placebo) 30 minutes later and then another dose 30 minutes after the first, subsequently to exposition to FST. These results were also compared with other group that received imipramine (30mg/kg^{-1}), and CBD was also effective in the FST, however, the BDNF levels were not modified.

In addition to the expected results related to FST (i.e., rats not treated with WAY), rats that received WAY spent more time only floating, like rats that received placebo (vehicle), clearly demonstrating a "non-effect" of CBD and leading researchers to conclude that the neuroreceptor 5-HT1A participates in the mechanism of action of CBD [26].

An experiment [28] used the Light-dark (LD) immersion model, a test based on the innate aversion of rodents to bright and illuminated areas and on the spontaneous exploratory behavior of the animals. Thus, there is a conflict between the tendency to explore and the initial tendency to avoid the unfamiliar. This test consists of two compartments, the first one is dark and the second one is illuminated. Differently from the results of [27], CBD failed on modifying the rats' responses to the test.

Anxiolytic Effects of CBD

Animal studies are an important way to test a substance before use it in human beings. CBD also has anxiolytic-like activities; therefore, we consider the most important studies that tested CBD in animal models. One way to undertake experiments with anxiety is to use the elevated plus-maze [28], which consists of a maze in a cross form, elevated approximately 50 cm above the floor. It has two arms with protections (walls) and two without walls. In the first experiment we found, mice that received CBD, diazepam or a vehicle (i.e., no active substance or placebo) and placed in the center of the maze, in front of the closed face. The flow rate and input into the arms were measured for 10 minutes.

The results showed that the increase in the frequency of open arm entries by animals that received CBD was statistically significant, compared to the frequency observed in animals that received only vehicle, regardless of the dose used (2.5, 5.0, and 10.0 mg/kg). Also, the use of 20.0 mg/kg of CBD was plotted on a graph in an inverted "U" shape. Low doses led to the rats to explore all of the arms of the maze, suggesting an anxiolytic effect, while higher doses caused a return to the baseline data.

Other experiment [29] using the EPM also resulted in a similar graph to the first study [28], an inverted "U" or bell-shaped curve. These results were obtained using CBD versus vehicle. Later, in other study by the same group [30], CBD administered inside the brain (i.e., right dorsolateral and ventral regions of the periaqueductal gray matter) also increased the percentage of entries into the open arms of the maze, but CBD did not affect the amount of time spent in the open arms. The parameters used were considered significant for measuring anxious behavior. However, these results are often not observed in this type of study.

With respect to the EMP experiments, Hsiao *et al*. [31] conducted an experiment evolving rats in a persistent stress conditioned task using open fields and EPM, with the sleep

Table 1. Main results of studies associated with antidepressant-like and anxiolytic-like effects of cannabidiol.

Ref.	Objective	Methodology	Results	Conclusion
[20]	The main objective of the present study was to evaluate behavioral and molecular effects induced by administration of CBD and imipramine in rats.	Rats treated for 14 days with saline, CBD (15, 30 and 60 mg/kg) or imipramine (30 mg/kg) and the animals behaviour was assessed in forced swimming and open-field tests. BDNF levels were also measured.	We observed that both acute and chronic treatments with imipramine at the dose of 30 mg/kg and CBD at the dose of 30 mg/kg reduced immobility time and increased swimming time. CBD at the dose of 15 mg/kg and imipramine at the dose of 30 mg/kg increased BDNF levels in the rat amygdala.	Results indicate that CBD has an antidepressant-like profile and could be a new pharmacological target for the treatment of major depression.
[25]	This study was conducted to assess the antidepressant-like activity of Cannabinoids.	Cannabinoids were initially evaluated in the mouse tetrad assay to determine doses that do not induce hypothermia or catalepsy. The automated mouse FST and TST tests were used to determine antidepressant action.	CBD exhibited significant effect at 20 and 200 mg/kg, respectively.	Δ9-THC and other cannabinoids exert antidepressant-like actions, and thus may contribute to the overall mood-elevating properties of cannabis.
[26]	The aim of this work was to test the hypothesis that CBD would have antidepressant-like activity in mice as assessed by the FST and investigated if these responses depended on the activation of 5-HT1A receptors and on hippocampal expression of BDNF.	Mice were given CBD (3, 10, 30, 100 mg·kg-1), imipramine (30 mg·kg-1) or vehicle and were submitted to the FST or to an open field arena, 30 min later. An additional group received WAY (0.1 mg·kg-1) a 5-HT1A receptor antagonist, before CBD (30 mg·kg-1).	CBD (30 mg·kg-1) treatment reduced immobility time in the FST. WAY pretreatment blocked CBD-induced effect in the forced swimming test.	CBD induces antidepressant-like effects comparable to those of imipramine. These effects of CBD were probably mediated by activation of 5-HT1A receptors.
[38]	The aim of this study was to further investigate the role of the bed nucleus of the stria terminalis on the anxiolytic effects of the CBD.	Male Wistar rats received injections of CBD (15, 30, or 60 nmol) into the BNST and were exposed to the EPM or to the VCT, two widely used animal models of anxiety.	CBD increased open arms exploration in the EPM as well as the number of punished licks in the VCT, suggesting an anxiolytic-like effect.	These results give further support to the proposal that BNST is involved in the anxiolytic-like effects of CBD observed after systemic administration, probably by facilitating local 5-HT1A receptor-mediated neurotransmission.
[34]	Test the hypothesis that CBD could also impair escape responses evoked by two proposed animal models of panic: the elevated T-maze (ETM) and electric stimulation of dPAG.	Three experiments using the CBD injected into the dPAG.	In the ETM microinjection of CBD into the dPAG impaired inhibitory avoidance acquisition, an anxiolytic-like effect, and inhibited escape response, a panicolytic-like effect. The drug also increased escape electrical threshold, an effect that was prevented by WAY.	Together, the results suggest that CBD causes panicolytic effects in the dPAG by activating 5-HT1A receptors.
[22]	To verify, using c-Fos immunocytochemistry, if the mPFC is involved in the attenuation of contextual fear induced by systemic administration of CBD and investigate if direct microinjections of CBD into mPFC regions would also attenuate contextual fear.	Five experiments involving fear c onditioning and injected CBD in the prelimbic or infralimbic prefrontal cortex.	Systemic administration of CBD decreased contextual fear.	These results suggest that the PL prefrontal cortex may be involved in the attenuation of contextual fear induced by systemic injection of CBD.
[36]	The aim of the present work was to test the hypothesis that CBD would attenuate the autonomic and behavioral consequences of restraint stress.	Rats received i.p. injections of vehicle or CBD and 30 min later were submitted to 60 min of restraint where their cardiovascular responses were recorded.	Exposure to RS increased blood pressure and heart rate and induced an anxiogenic response in the EPM 24h later.	The results suggest that CBD can attenuate acute autonomic responses to stress and its delayed emotional consequences by facilitating 5-HT1A receptor-mediated neurotransmission.
[30]	Test the hypothesis that, at high doses, cannabidiol and WIN 55,212-2 could activate TRPV1 receptors.	Rats with cannulae placed in dlPA G underwent three treatments, involving CBD and EPM.	CBD result showed ansiolitic and was compatible in respect to the expected placebo.	These results suggest that TRPV1 receptors in the dlPAG modulate anxiety.

(Table 1) contd…..

References	Objective	Methodology	Results	Conclusion
[37]	Investigate the central effects of the eCB uptake/metabolism inhibitor AM404 and the phytocannabinoid cannabidiol (CBD) on the extinction of contextual fear memories in rats.	Five experiments involving adult male Wistar rats. Drugs used: AM404, CBD. Capzazepine and diazepam. Tests conducted at EPM.	The result showed ansiolitic and was compatible with diazepam a common used ansiolitic.	CBD, a non-psychoactive phytocannabinoid could be an interesting pharmacological approach to reduce the anxiogenic effects of stress and promote the extinction of fear memories.
[29]	To investigate if the dlPAG could be a possible site of the anxiolytic effects induced by CBD and if these effects depend on CB1 or 5HT1A receptors.	Rats with cannulae aimed at the dlPAG were tested in the EPM and the VCT.	The anxiolytic effect of CBD was confirmed in the VCT. These effects were prevented by WAY.	These results suggest the CBD interacts with 5HT1A receptors to produce anxiolytic effects in the dlPAG.
[33]	The aim of the present study was to test the effects of CBD in the Vogel test, a widely used animal model of anxiety.	Rats were deprived of water for 2 4 hours and placed in the VCT, using CBD, flumazenil or diazepam.	CBD induced an anticonflict effect not mediated by benzodiazepine receptors.	These results reinforce the hypothesis that this cannabinoid has anxiolytic properties.
[35]	The aim of this work was to compare the behavioral and cardiovascular effects of CBD and diazepam in animals submitted to a contextual conditioned fear paradigm.	Rats were conditioned with fear and had their freezing behaviors monitored.	Conditioned rats submitted to the aversive context exhibited more freezing behavior and a larger increase in blood pressure and heart rate as compared to non-conditioned animals.	the results suggest that CBD has anxiolytic-like properties similar to those of diazepam in a rat model of conditioned fear to context.
[27]	Assess the presence of anxioliytic proprieties in CBD.	The drug was tested in rats using the elevated plus-maze.	The doses of CDB increased the number of entry in the EPM.	These results indicates that CBD causes selective anxiolytic effect in the EPM.
[39]	The aim of this study was to investigate the effects of cannabidiol on innate fear-related behaviors evoked by a prey *vs* predator paradigm.	Mice were submitted to habituation in an arena containing a burrow and subsequently pre-treated with intraperitoneal administrations of vehicle or cannabidiol. A constrictor snake was placed inside the arena, and defensive and non-defensive behaviors were recorded.	Cannabidiol caused a clear anti-aversive effect, decreasing explosive escape and defensive immobility behaviors outside and inside the burrow.	These results show that cannabidiol modulates defensive behaviors evoked by the presence of threatening stimuli, even in a potentially safe environment following a fear response, suggesting a panicolytic effect.

CBD: Cannabidiol; BDNF: Brain-derived neurotrophic factor; WAY: WAY 100635; TST: Tail suspension test; EPM: Elevated plus-maze; VCT: Voguel conflict test; FST: Forced swimming test; dlPAG: Dorsolateral periaqueductal gray; dPAG: Dorsal periaqueductal gray.

regulation context, showed that rats treated with CBD, reduced the number of entries on the field with protection and spent more time on the open arms and on the center. CBD blocked efficiently anxiety and induced rapid eyes movement (REM) sleep suppression, but had little effect on non-REM sleep.

A variation of EPM, i.e. the elevated "T" maze (ETM), was used in an experiment [32] to study the role of the serotoninergic neurotransmission in the DPAG, on response modulation of escapes. This showed that peripheral administration of CBD decreases the escape in the ETM, suggesting a panic lytic effect. Once the mentioned effects of CBD were prevented by the use of the 5-HT1A receptor agonist, researchers suggested that the repeated treatment with the substance may prevent panic like attacks.

In an experiment [33] using the Vogel Conflict Test (VCT), a test that places rats in a conflicted situation, a water-deprived animal is put in a cage with a floor grid and is offered water. However, after the rat laps the water a certain number of times predetermined by the researcher, rat receives a shock on the tongue. Thus, the rat experiences a conflict between the need for water and fear of punishment. Three substances were injected into the rats: CBD (multiple doses of 2.5, 5 and 10 mg/Kg), diazepam (i.e., a proven anxiolytic), and either flumazenil (i.e., a benzodiazepine receptor antagonist) or vehicle (i.e., no active drug or placebo). The tests showed that CBD had an effect consistent with diazepam effects, increasing the number of licks, including those that resulted in punishment. The administration of diazepam plus flumazenil resulted in a reduced anxiolytic effect, which did not occur as a result of a combination of CBD and flumazenil.

Moreover, two experiments [29, 34] involving the injection of WAY directly into the dorsolateral portion of the periaqueductal gray matter (dlPAG) of rats demonstrated that WAY has affinity with CBD. Authors found a similar conclusion in a study that administered WAY11 to mice in the EPM, but it was not injected directly into their dlPAG.

Other study [35] aimed to examine cardiovascular and behavioral responses in situations of contextual fear. Authors used the foot shock cage, which is made of Perspex walls and a grid formed by stainless steel rods (typically 25 cm x 22 cm x 22 cm). Mice have certain time to explore the cage, after this time, the grid delivers shocks to the foot of the animal at a time frequency and intensity determined by the controller. It is generally used to condition mice. This "fear conditioning" experiment used mice preconditioned to a hostile environment (foot shocks) and a control group, which interacted with a non-hostile environment. The drugs used in the experiment were CBD, diazepam, vehicle, and FG-7142, an inverse agonist of the benzodiazepine receptor.

The results showed that "freezing" behavior was very low in animals that were not conditioned to fear (i.e., less than 20% of the time of animals that received vehicle). For the conditioned mice, diazepam reduced freezing more than vehicle or FG-7142. In addition, not only the preconditioned mice but also the control groups (treated with FG-7142), produced a small but significant reduction in freezing behavior.

Regarding the impact of cardiovascular disease, there were small changes among the non-conditioned rats in either blood pressure or heart rate. However, in conditioned rats, the assessments of those animals treated only with vehicle or FG-7142 modified, and CBD and diazepam stabilized and even succeeded in reducing both the heart rate and blood pressure of the tested rats. Researchers concluded that the study's results were consistent with experiments using CBD plus diazepam.

A further demonstration of the anxiolytic effect of CBD on cardiovascular data [36] was obtained in a study that animals were exposed in the EPM to different doses of CBD and compared their activity to those that received vehicle (as a control) and the antagonist WAY, which works on 5-HT1A neuroreceptors. CBD reduced the tachycardia response to residual "stress", attenuating an increase in anxiety, although these effects were blocked by WAY.

Contextual fear was also used in experiments with CBD, together with substances tested for the inhibition of neural receptors (AM404, capsazepine [CPZ], and SR141716A [SR]) and with diazepam [37]. Rats were placed in boxes that, after three minutes, they received shocks lasting one second after being kept in place for 1 minute, until they returned to their cages. Freezing behavior was observed. This type of conditioning was also used in the EPM experiments.

The results once again demonstrated the effectiveness of CBD as an anxiolytic drug compared with diazepam. AM404 was also effective in diminishing the effects of fear preconditioning. Such responses were antagonized by the selective CB1 agonist SR, but they were not antagonized by the TRPV1 agonist CPZ. Regarding contextual fear conditioning, the prefrontal cortex (PFC), which received systematically CBD, has been shown to be involved in mitigating the effects of fear [27].

With the purpose of demonstrating that the TRPV1 receptors in the dlPAG matter mitigate the anxiolytic effects of cannabinoids, an experiment [24] with rats and EPM tested this hypothesis using CBD, analyzing the TRPV1 receptor antagonist CPZ and CB1 receptor agonist WIN 55.212-2 mesylate (WIN). The receptors were injected into dlPAG. Again, CBD increased the percentage of entries into the EPM, but the group that received only CPZ was not different from the group that received vehicle. With regard to the effects of WIN, higher doses (i.e., an intermediate dosage was the most effective) had opposite results to the effects of vehicle. Finally, compared with WIN, CPZ affected the number of entries into the open arms of the EPM; rare among rats previously treated with CBD, the percentage of entries into the open arms of the EPM increased when CBD was combined with CPZ.

Finally, a study published in 2011 linked anxiolytic effects to CBD that was injected into the "bed nucleus of the stria terminal" (BNST) [38]. Animals received various doses of CBD (15, 30, 60 n mol) intra-BNST and were exposed to the EPM or the VCT. Results demonstrated that the number of punishment-inducing licks in the VCT and the number of entries into the open arms of the EPM increased when CBD was used. However, the effects of CBD were blocked in rats pretreated with WAY.

In 2011, other experiment was performed on the anti-aversive effects of CBD on innate fear-induced behaviors [39]. Using mice and snakes, researchers put the mice in the arena three days before the experiment and maintained them there with free access to food or water until the day of the experiment.

The "no threat" group was removed from the arena, and their behaviors were recorded (one at a time) for 5 minutes. The remaining animals were exposed to the predator and divided into four groups (n=11-12 per group), which were pre-treated with intraperitoneal CBD (at doses of 0.3, 3, or 30 mg/kg), and a control group, which was administered vehicle.

The group of animals that was not exposed to a confrontation with a wild snake but only to the polygonal arena did not exhibit any defense-like behaviors. However, when exposed to the predator in the same context after 3 days of habituation, all of the mice exhibited defensive behaviors. Sometimes, threatened animals would run to the burrow during confrontation with the predator. Mice pretreated with CBD showed a significant and robust reduction in explosive escape and defensive immobility; these are responses that are considered panic-like behaviors. The response of active avoidance, in which mouse reacts with vigorous movement to avoid close contact with the predator, indicates reduced fear. Risk assessment and defensive attention were unchanged in the animals that received CBD. These findings suggest that CBD decreases the behavioral responses associated with settings of imminent danger, in which the aversive connotation of the stimulus, has been fully recognized.

DISCUSSION

Here, we aimed to review studies of animal models using CBD as an anxiolytic-like and antidepressant-like compound.

CBD has proved to be a useful and versatile substance, as well as being safe, with an effective dosage that is far from the lethal dose [40, 41]. According to the experiments, CBD did not affect the cognitive functioning or mobility of rats. In prey and predator experiments, animals treated with CBD froze fewer times when exposed to dangerous situations, allowing them to escape from the situation.

Other issue that demands attention deals with the neural receptors responsible for the effects of CBD. The findings of different experiments have yielded conflicting results; for example, one study [34] demonstrated no clear interaction between CBD and the 5-HT1A neuroreceptor, but other studies [29, 35, 38, 42] showed some interaction between them. Perhaps the use of several antagonist substances (e.g.,

WAY and flumazenil) was the major factor responsible for this discrepancy in results.

In addition to 5-HT1A [34, 43], changes in endocannabinoid mediated neurotransmission could also be involved in the effects of CBD chronic administration. Cannabinoids can modulate not only serotonergic neurotransmission, but also the expression of serotonin subtypes 1A and 2A/2C receptors in the brain.

Experiments with depressed rats and CBD showed an increase in rats' movements, an interesting result since authors only expected rats floating in the water, such as depressed rats do. BD also increased BDNF levels in experiments with rats, demonstrating antidepressant-like actions.

The experiment of Hsiao *et al*. [31], using the sleep regulation, demonstrated that CBD blocked the anxiety-induced REM sleep, probably blocking the anxiolytic effect less than the sleep regulation in fact.

Results [26] were also obtained in a dose dependent manner and had similar results compared with market antidepressants. However, the antidepressant failed to change the BDNF levels, and was not found to correlate between the BNDF levels and immobility on the animal. The study of Hsiao *et al*. [28], examined a very low dose of CBD in LD, and does not find the expected results. Previous findings demonstrated an inverse U shape on the effectiveness of CBD, i.e., low doses and high doses had poor results, which may have happened in that experiment.

CONCLUSION

In conclusion, more studies are necessary using CBD as an antidepressant-like drug to better understand its mechanisms of action. However, the results have been very promising, and we can conclude that CBD can become a new drug for the treatment of psychiatric disorders.

LIST OF ABBREVIATIONS

BDNF = Brain-derived neurotrophic factor

BNST = Bed nucleus of the stria terminal

CBD = Cannabidiol

CPZ = Capsazepine

dlPAG = Dorsolateral periaqueductal gray

dPAG = Dorsal periaqueductal gray

EPM = Elevated plus-maze

ETM = Elevated "T" Maze

FST = Forced swimming test

LD = Light-dark

PFC = Prefrontal cortex

REM = Rapid Eyes Movement

SR = SR141716A

THC = tetrahydrocannabinol

TST = Tail suspension test

VCT = Voguel conflict test

WAY = WAY 100635

CONFLICT OF INTEREST

The authors confirm that this article content has no conflict of interest.

ACKNOWLEDGEMENTS

Declared none.

REFERENCES

[1] Allen AJ, Leonard H, Swedo SE. Current knowledge of medications for the treatment of childhood anxiety disorders. J Am Acad Child Adolesc Psychiatry 1995; 34: 976-86.

[2] Swedo SE, Leonard HL, Allen AJ. New developments in childhood affective and anxiety disorders. Curr Probl Pediatr 1994; 24: 12-38.

[3] Castillo AR, Recondo R, Asbahr F, Manfro G. Transtornos de ansiedade. Rev Bras Psiquiatr 2000; 22(2): 20-23.

[4] Bernstein GA, Borchardt CM, Perwien, AR. Anxiety disorders in children and adolescents: a review of the past 10 years. J Am Acad Child Adolesc Psychiatry 1996; 35: 1110-9.

[5] Del Porto JA. Conceito e diagnóstico. Revista Brasileira de Psiquiatria 1999; 21(1): 6-11.

[6] Gilworth G, Chamberlain MA, Bhakta B, *et al*. Development of the BD-QoL: a quality of life measure specificto Behçet's disease. J Rheumatol 2004; 31: 931-7.

[7] Perin C, Ramos GZ, Oliveira RG, Tourinho TF. Artrite Reumatoide e depressão. Rev Bras Reumatol 2002; 42: 375-80.

[8] Duarte MB, Rego MAV. Comorbidade entre depressão e doenças clínicas em um ambulatório de geriatria. Cad Saúde Pública 2007; 23: 691-700.

[9] Borges NB, Angelotti GS. Ansiedade e Depressão em uma amostra de pacientes classificados como portando fatores psicológicos que afetam as condições médicas. Rev Estudos de Psicologia 2002; 19: 15-22.

[10]. Alexopulos GS, Buckwalter K, Olin J, *et al*. Comorbidity of late life depression: an opportunity for research on mechanisms and treatment. Biol Psychiatry 2002; 52: 543-58.

[11] Diehl A, Cordeiro DC, Laramjeira R. Cannabis abuse in patients with psychiatric disorders: an update to old evidence. Rev Bras Psiquiatr 2010; 32(1): S41-5.

[12] ElBatsh MM, Assareh N, Marsden CA, *et al*. Anxiogenic-like effects of chronic cannabidiol administration in rats. Psychopharmacology 2012; 221: 239-47

[13] Crippa JA, Zuardi AW, Martin-Santos R, *et al*. Cannabis and anxiety: a critical review of the evidence. Hum Psychopharmacol 2009; 24(7): 515-23.

[14] Bergamaschi MM, Costa QRH, Nisihara CMH, *et al*. Cannabidiol Reduces the Anxiety Induced by Simulated Public Speaking in Treatment-Naive Social Phobia Patients. Neuropsychopharmacology 2011; 35(6): 1219-26.

[15] Crippa JA, Derenusson GN, Ferrari TB, *et al*. Neural basis of anxiolytic effects of cannabidiol (CBD) in generalized social anxiety disorder: a preliminary report. J Psychopharmacol 2011; 25(1): 121-30.

[16] Deiana S. Medical use of cannabis. Cannabidiol: A new light for schizophrenia? Drug Test Anal 2013; 5(1): 46-51.

[17] Levin R, Almeida V, Peres FF, *et al*. Antipsychotic Profile of Cannabidiol and Rimonabant in an Animal Model of Emotional Context Processing in Schizophrenia. Curr Pharmaceut Des 2012; 32(18): 4650-5.

[18] Schier RMS, Ribeiro POR, Silva ACO, *et al*. Cannabidiol, a Cannabis sativa constituent, as an anxiolytic drug. Rev Bras Psiquiatr 2012; 34(1): S104-17.

[19] Calil CM, Bianchi FJ, Tanno AP, *et al*. Análise do significado do tempo de imobilidade em modelos experimentais de natação. Braz J Pharm Sci 2002; 38(4): 479-85.

[20] Réus GZ, Stringari RB, Ribeiro KF, *et al*. Administration of cannabidiol and imipramine induces antidepressant-like effects in the forced swimming test and increases brain-derived neurotrophic

factor levels in the rat amygdala. Acta Neuropsychiatr 2011; 23: 241-8.

[21] Nibuya M, Morinobu S, Duman RS. Regulation of BDNF and trkB mRNA in rat brain by chronic electroconvulsive seizure and antidepressant drug treatments. J Neurosci 1995; 15: 7539-47.

[22] Siuciak JA, Lewis DR, Wiegand SJ, Lindsay RM. Antidepressant-like effect of brain-derived neurotrophic factor(BDNF). Pharmacol Biochem Behav 1997; 56: 131-7.

[23] Nestler EJ, Barrot M, DiLeone RJ, *et al*. Neurobiology of depression. Neuron 2002; 34: 13-25.

[24] McArthur R, Borsini F. Animal models of depression in drug discovery: a historical perspective. Pharmacol Biochem Behav 2006; 84: 436-52.

[25] El-Alfy AT, Ivey K, Robinson K, *et al*. Antidepressant-like effect of Delta(9)-tetrahydrocannabinol and other cannabinoids isolated from Cannabis sativa L. Pharmacol Biochem Behav 2010; 95(4): 434-42.

[26] Zanelati TV, Biojone C, Moreira FA, *et al*. Antidepressant-like effects of cannabidiol in mice: possible involvement of 5-HT1A receptors. Br J Pharmacol 2010; 159(1): 122-8.

[27] Guimarães FS, Chiaretti TM, Graeff FG, Zuardi AW. Antianxiety effect of cannabidiol in the elevated plus-maze. Psychopharmacology 1990; 100: 558-9.

[28] Hsiao YT, Yi PL, Li CL, Chang FC. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. Neuropharmacology 2012; 62(1): 373-84.

[29] 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; 199: 223-230.

[30] 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.

[31] Hsiao YT, Yi PL, Li CL, Chang FC. Effect of cannabidiol on sleep disruption induced by the repeated combination tests consisting of open field and elevated plus-maze in rats. Neuropharmacology 2012; 62(1): 373-84.

[32] Campos AC, Soares VP, Carvalho MC, *et al*. Involvement of serotonin-mediated neurotransmission in the dorsal periaqueductal gray matter oncannabidiol chronic effects in panic-like responses in rats. Psychopharmacology 2013; 226(1): 13-24.

[33] 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.

[34] Soares VD, Campos AC, de Bortoli VC, *et al*. Intra-dorsal periaqueductal gray administration of cannabidiol blocks panic-like response by activating 5-HT1A receptors. Behav Brain Res 2010; 213(2): 225-9.

[35] 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.

[36] Resstel LB, Tavares RF, Lisboa SF. 5-HT1A receptors are involved in the cannabidiol-induced attenuation of behavioral and cardiovascular responses to acute restraint stress in ratscardiovascular responses to acute restraint stress in rats. Br J Pharmacol 2009; 156(1): 181-8.

[37] 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): 849-59.

[38] 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 2011; 213(2-3): 465-73.

[39] Uribe-Mariño A, Francisco A, Castiblanco-Urbina MA. 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. Neuropsychopharmacology 2012; 37(2): 412-21.

[40] Solomon D, Adams J, Graves N. Economic evaluation of St. John's wort (Hypericum perforatum) for the treatment of mild to moderate depression. J Affect Disord 2013; S0165-0327.

[41] Zuardi A, Crippa J, Dursun S, *et al*. Cannabidiol was ineffective for manic episode of bipolar affective disorder. J Psychopharmacol 2010; 24(1): 135-7.

[42] Campos AC, Ferreira FR, Guimarães FS. Cannabidiol blocks long-lasting behavioral consequences of predator threat stress: possible involvement of 5HT1A receptors. J Psychiatr Res 2012; 46(11): 1501-10.

[43] Campos AC, Ortega Z, Palazuelos J, *et al*. The anxiolytic effect of cannabidiol on chronically stressed mice depends on hippocampal neurogenesis: involvement of the endocannabinoid system. Int J Neuropsychopharmacol 2013; 9: 1-13.

Received: March 23, 2013 **Revised: April 18, 2013** **Accepted: April 24, 2013**