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REVIEW ARTICLE

Anxiolytic and antidepressant effects of cannabidiol: a systematic review

Efeitos ansiolíticos e antidepressivos do canabidiol: uma revisão sistemática

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Abstract

Objetctive: Realize a systematic review on articles about cannabidiol (CBD) as an anxiolytic and antidepressant drug. **Methodology**: A systematic review in PubMed, Science Direct and PsycINFO databases taking into consideration articles published in English and Portuguese from 2008 to 2018 with animal experimentation. **Results**: Eleven articles with experimental studies on animals were included. All studies exhibited anxiolytic and antidepressant activities after CBD use. **Conclusion**: It was proven by several experiments the anxiolytic and antidepressant activity of CBD, however there is still a need of more preclinicals and clinicals studies to elucidate its mechanisms.

Keywords: Cannabis. Cannabidiol. Anxiolytic. Antidepressant.

Resumo

Objetivo: Realizar uma revisão sistemática de artigos sobre o canabidiol (CBD) como ansiolítico e antidepressivo. **Metodos**: Revisão sistemática nas bases de dados PubMed, Science Direct e PsycINFO considerando artigos publicados em inglês e português de 2008 a 2018 com experimentação animal. **Resultados**: Onze artigos com estudos experimentais em animais foram incluídos. Todos os estudos exibiram atividades ansiolíticas e antidepressivas após o uso de CBD. **Conclusão**: Foi comprovada por diversos experimentos a atividade ansiolítica e antidepressiva do CBD, porém ainda há necessidade de mais estudos pré-clínicos e clínicos para elucidar seus mecanismos.

Palavras-chave: Cannabis. Canabidiol. Ansiolítico. Antidepressivo.

INTRODUCTION

Well known for its psychotropic activity, Cannabis sativa is the target of intense scientific research and debate[1]. Cannabis Sativa is a plant that in Brazil is known as marijuana, historically this term was first used by Angolans, which ended up being acquired by slaves in Brazil[2]. Marijuana has been recognized for at least 5,000 years as having therapeutic and psychotropic effects[3]. There are three different species of Cannabis: Cannabis sativa, C. indica and C. ruderalis, which are differentiated by their growth habits, morphological aspects and the amount of active ingredients obtained in the plant[4].

Medical cannabis sativa was known and widely used since ancient times, becoming one of the most important components of the pharmaceutical industry until the mid-1930s. After a smear campaign, its medicinal use ended up being prohibited, gaining the status of a proscribed substance worldwide[5].

This plant contains more than 400 different compounds, 66 of which are called phytocannabinoids[6]. Delta-9 tetrahydrocannabinol (THC) and cannabidiol (CBD) are the main active chemical components of this plant, THC is the compound of highest concentration in the extract and is responsible for the psychotropic effects of the plant. CBD is the main non-psychotropic compound, which constitutes up to 40% of the plant's extracts[7].

Medical cannabis is currently allowed in some American states and in countries like Holland and Belgium to alleviate symptoms related to the treatment of cancer, AIDS, multiple sclerosis and Tourette's syndrome, and epilepsy[8].

According to the Federal Council of Medicine "In Brazil, through CFM Resolution No. 2,113/2014, published in the Official Gazette of the Union of December 16, 2014, section I, p. 183, approved the compassionate use of cannabidiol for the treatment of epilepsies in children and adolescents resistant to conventional treatments." It was included in ANVISA's list of medicinal plants by RESOLUTION No. 156, OF MAY 5, 2017.

Cannabidiol (CBD) is part of the cannabinoid components

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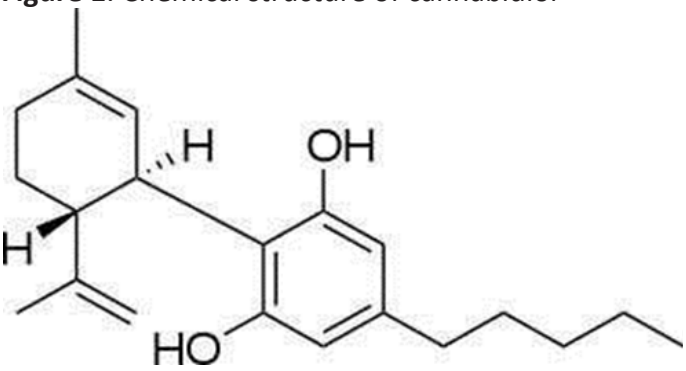
present in Cannabis sativa. It is a non-psychotomimetic compound that induces anxiolytic and antipsychotic effects, i.e., inducing sedative and psychomotor effects[7]. CBD (C21H30O2) with a molecular weight of 314.469 g/mol is a cyclohexane that is insoluble in water, but is soluble in organic solvents such as pentane. At room temperature, it is a colorless, crystalline solid. Regarding its stereoisomery, cannabidiol (CBD) has the two forms (-)CBD which is natural and (+)CBD which is synthetic. The (+)CBD has received little attention as it has been shown to have modest affinity for CB1 and CB2 receptors unlike (-) CBD, while both compounds inhibited anandamide hydrolysis and were agonists of the type 1 vanilloid receptor (VR1) where capsaicin acts. The (+)CBD isomer was more active than (-)CBD as an anticonvulsant agent in rat seizure models. However, to date, there is no substantial evidence showing whether (+)-CBD can cause psychoactive effects similar to THC[9].

Figure 1. Chemical structure of cannabidiol



Source: Fonseca et al., 2013[10]

In 1973, studies by Carlini et al. reported the first pharmacological actions of CBD in reducing or blocking convulsions in animal models, proving the antiepileptic effect of the cannabinoid. Besides, CBD is involved in the regulation of other brain receptor neurotransmitters, besides having an anti-inflammatory and antioxidant effect[11].

Studies show that cannabinoids have their main effect by interacting with specific receptors, of the endocannabinoid system, on cells in the brain and body: The CB1 receptor, found primarily on the presynaptic terminals of neurons and responsible for most of the neurobehavioral effects of cannabinoids, and the CB2 receptor, on the other hand, is found mainly on cells of the immune system, but can also express on neurons especially during inflammatory processes[7].

Even though the mechanism of action of CBD is not completely understood, it is likely that it interacts with specific receptors, just like THC7. CBD has the function of facilitating endocannabinoid signaling by blocking anandamide reuptake, increasing its bioavailability, generating a relaxing effect, regulating the cardiovascular system, and improving cognitive functions[12,13]. Also, as a way to explain its mechanism, according to studies by Gomes et al. 2011[14], Zanelati et al. 2010[15], Castillo et al. 2010[16] there is evidence that CBD potentiates the activation of serotonin receptors (5HT1A).

According to the World Health Organization (2016) "Depression is the leading cause of ill health and disability worldwide. According to the latest estimates, more than 300 million people live with depression, an increase of more than 18% between 2005 and 2015. The WHO has identified strong links between depression and other non-communicable diseases and disorders. Depression increases the risk of substance use disorders and diseases such as diabetes and heart disease. The opposite is also true, meaning that people with these other conditions have a higher risk of depression. It is also a major risk factor for suicide, which ends hundreds of thousands of lives each year.

The symptoms of depression are persistent sadness, anhedonia (loss of interest or pleasure), altered appetite and sleep pattern (increased or decreased), difficulty concentrating and making decisions, feelings of guilt and worthlessness, hopelessness, negative thoughts, and suicidal ideas, for at least a two-week period[17].

There are attempts to explain the cause of depression, where most involve the role of some monoamine neurotransmitters 5HT, NE and DA such as serotonin, norepinephrine and dopamine[18].

One of the antidepressants used for the treatment of depression is Sertraline Hydrochloride, a selective serotonin reuptake inhibitor, i.e., it inhibits its reuptake by the presynaptic neuron, increasing the level of serotonin available to bind to the postsynaptic receptor, resulting in increased duration of serotonin activity. Leaving the patient with a sense of well-being and happiness, contrary to what depression causes[19].

Also, benzodiazepines that produce anxiolytic effects may be useful as adjuvants in the treatment of anxiety or agitation associated with psychiatric disorders such as depression. To treat such pathologies, especially those related to affective disorders and depression, alternative treatments using antidepressants and anxiolytics are proposed in order to reduce the intensity of the symptoms. Thus, they reduce the tendency to suicide and accelerate the speed of normalization of the subject[20].

The purpose of this article is to review and describe studies from the past 10 years using cannabidiol as an anxiolytic and antidepressant compound.

METHODS

This paper is characterized as a systematic review using the PubMed, Science Direct, and PsycINFO databases taking into consideration articles published in English and Portuguese from 2008 to 2018 with animal experimentation.

The keywords "cannabidiol" and "anxiety" or "anxiolytic" or

"fear" or "stress" or "anxiety disorder" or "generalized anxiety disorder" were combined, also "cannabidiol" and "depression" or "antidepressant" or "depressive disorder" in the cited databases, chosen based on the technical-scientific terms MeSH (Medical Subjective Heading) and DeHS (Descriptors in Health Sciences).

This review was prepared according to the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) protocol[21]. They were selected by the authors following three steps: screening by title, by abstract, and by reading the entire article. A total of 11 articles of pre-clinical studies using CBD were extracted without repetition, and data related to the anxiolytic and antidepressant effects of this compound were extracted from each article. Exclusion criteria were: bibliographic reviews, clinical studies, or studies that did not have objectives compatible with those of this review. A total of 18 articles were excluded.

RESULTS AND DISCUSSION

The databases where the articles were extracted were PubMed (9 articles), Science Direct (2 articles), and PsycINFO, where no article was found in their data. All 11 articles included were experimental studies separated by author(s), year of publication, database where they were extracted, animal species that were used, sex of these animals, and sampling number, as presented in table 01.

Table 1. Characteristics of pre-clinical studies

Author	Year	Database	Species	Sex	Sampling
Campos[22]	2008	Pubmed	Wistar rat	Males	Non cited
Resstel[23]	2009	Pubmed	Wistar rat	Males	Non cited
Zanelati[15]	2010	Pubmed	Swiss mice	Males	Non cited
Soares[24]	2010	Pubmed	Wistar rat	Males	Non cited
Réus[25]	2011	Pubmed	Wistar rat	Males	Non cited
El-alfy[26]	2011	Science Direct	Camundongo swiss	Males	Non cited
Gomes[14]	2011	Pubmed	Wistar rat	Males	Non cited
Campos[27]	2013	Pubmed	Wistar rat	Males	Non cited
Fogaça[28]	2014	Science Direct	Wistar rat	Males	Non cited
Shoval[29]	2016	Pubmed	Wistar rat and WKY rat	Males	106 animals
Rock[30]	2017	Pubmed	Wistar rat	Males	Non cited

All the studies analyzed were published in English, and without exception used male animals. It is believed that the choice of male animals is due to the lesser hormonal and physiological influence that could serve as biases to the results. During the estrous cycle of the female, there is a cyclic variation of sex hormones that may intervene in her responses to the drugs used and thus alter the results[31]

Of the papers analyzed, 81.8%(n=9) used Wistar rats which is one of the most widely used in laboratory research worldwide and 18.18%(n=2) used swiss mice and only in 1 study used Wistar Kyoto rats (WKY). This strain, Wistar Kyoto, was established with a genetic animal model where they demonstrate hormonal and behavioral abnormalities that mimic many of those found in symptomatic depressive patients[32].

In the study by Shoval et al., 2016[29] they showed a large antidepressant effect of CBD at doses of 15, 30 and 45 mg/kg in WKY rats compared to Wistar rats, classified as "healthy" or without any genetic intervention, in the sucrose preference and object exploration tests, indicating an improvement in the characteristically low pleasure and exploration motivation in WKY rats.

In only one article[29] sampling was presented, which is the number of animals used in the experiment. The presentation of sampling in the methodology of the studied experiments would be important for the delimitation of the number of animals used, following the principles of the scientific community of reduction (Reduction), refinement (Refinement) and replacement (Replacement) in order to reduce the number of animals used in research, improving the genetic, sanitary and environmental quality of these animals. Enabling a lower dispersion of the results obtaine[33, 34].

The studies were divided for better understanding of their experiments, separating the type of effect studied: anxiolytic or antidepressant, the CBD dosages used, CBD vehicle or dissolving drug, treatment route, the behavioral tests, and biochemical tests used as presented in table 02.

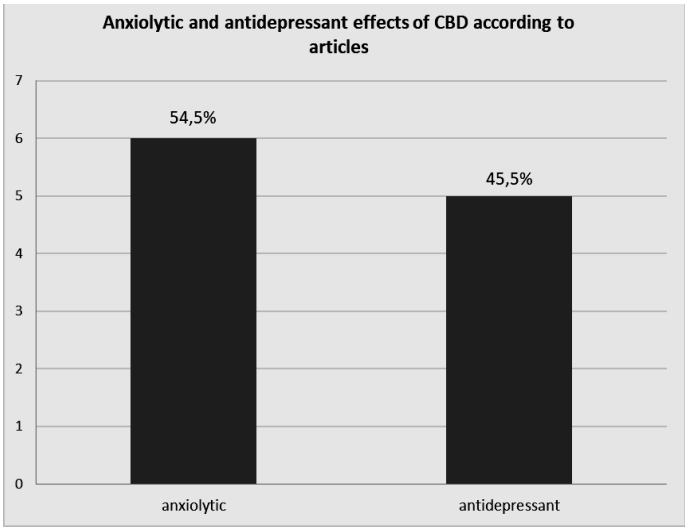
Of the 11 articles in this review, 54.4% (n=6) proved anxiolytic effect of CBD use and 45.4% (n=5) proved its antidepressant effect (Figure 2).

The doses of cannabidiol used ranged from 1-60mg/kg CBD. It is believed from the older studies by Onaivi et al., 1990 that the most relevant doses would be around 20 mg/kg where the best effects for anxiolytic and antidepressant activities would appear. So the most common doses used in the 11 articles were 15 and 30 mg/kg.

Table 2. Characteristics of pre-clinical experiments

Author	Year	Effect	Dosage	Drug Vehicle	Via	Behavior Test	Biochemical Test
Campos	2008	Anxiolytic	15 and 60 nmol	Grape seed oil	Intratecal	High Cross Labyrinth Vogel Conflict	Didn't do it
Resstel	2009	Anxiolytic	1, 10 or 20 mg/ kg	Tween 80 20%	Intraperitoneal	High Cross Labyrinth	Didn't do it
Zanelati	2010	Antidepressant	3, 10, 30, 100 mg/Kg	Salina	Intraperitoneal	Forced swim	BDNF (ELISA)
Soares	2010	Anxiolytic	15, 30 and 60 nmol	Grape seed oil	Intratecal	High Cross Labyrinth Electrical stimulation	Didn't do it
Réus	2011	Antidepressant	15, 30 and 60 mg / kg	Tween 80 20%	Intraperitoneal	Open field Forced swim	BDNF (ELISA)
El-Alfy	2011	Antidepressant	20 and 200 mg/kg	Salina	Intraperitoneal	Suspension of syrup	Didn't do it
Gomes	2011	Antidepressant	15,30,60 nmol	Grape seed oil	Intratecal	High cross labyrinth Conflict of Vorgel Suspension of syrup	Didn't do it
Campos	2013	Anxiolytic	5 and 20mg/kg	Tween 80 20%	Intratecal	High cross labyrinth	Didn't do it
Fogaça	2014	Anxiolytic	15,30 and 60 nmol	Grape seed oil	Intraperitoneal	Contextual conditioning of fear High cross labyrinth Containment stress	Didn't do it
Shoval	2016	Antidepressant	15, 30 and 45 mg/ kg	Ethyl alcohol	Oral	Preference to sucrose Labyrinth on high cross holding object.	Didn't do it
Rock	2017	Anxiolytic	5mg/kg	Salina	Intraperitoneal	Dark Light Test	Didn't do it

Figure 2. Anxiolytic and antidepressant effects of CBD.



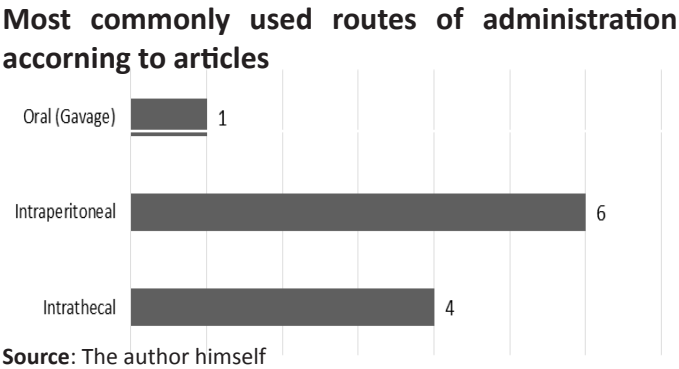
Source: The author himself

Regarding the vehicle drug or how the dissolution of the CBD was performed to be administered to the animals, we found no relevance in the literature and no explanation in the articles that addressed a methodology for this.

Regarding behavioral tests, the elevated cross maze stands out as one of the most used models in anxiety and depression studies[35]. When animals are treated with anxiolytic compounds the total time of permanence in the open arms tends to increase in comparison to animals that have not received any type of treatment[36].

Of the papers analyzed, 55% (n=6) used the intraperitoneal route of administration where the substance is injected into the peritoneal cavity between the abdominal organs due to the ease of administration compared to other parenteral methods (Figure 3).

Figure 3. Main CBD Administration Routes.



Source: The author himself

The intrathecal route was used in 36% (n=4) of the experiments. This route is used when local and rapid effects on the meninges or the cerebrospinal axis are desired. In this case, CBD was injected directly into the spinal subarachnoid space. In the articles that used this route it was seen that CBD activates sertoninergic receptors of the 5-HT1A type, however, the studies reported that there is a need for further studies to understand this action. The results that proved anxiolytic and antidepressant effects of cannabidiol were separated and reported in table form (Table 03).

In the study by Campos et al, 2008[22] to investigate the involvement of CBD to the serotoninergic system using the

5-HT1A receptor antagonist, WAY-100635, directly in the dorsolateral periaqueductal gray matter of rats, antagonized the anxiolytic effects of CBD in the elevated cross-maze behavior and in the punished drinking test or Vogel's conflict test, in which water-deprived rats are given access to drink water, but their drinking behavior is punished with a mild electric shock, both tests assessing anxiolytic activity. In that same study the 60nmol dose of CBD intrathecally was ineffective, it was analyzed by a bell-shaped dose-response curve.

At least 2 articles performed neurochemical tests - Brain-derived neurotrophic factor (BDNF) dosage[37], but were inconclusive. In the study by Reeves et al. 2011 evaluated a positive effect at a dose of 15 mg/kg measuring BDNF in the cerebellar amygdala a system related to behavioral emotions. It is believed that a high level of BDNF may be related to better brain health.

On the other hand, a decrease in BDNF may be related to different nervous system alterations such as depression, schizophrenia, Parkinson's disease, etc(38). In the study by ZANELATI et al. 2010, the dose of 30 mg/kg did not alter BDNF levels in the hippocampus, an organ mainly associated with memory.

Table 3. Results of the articles after CBD administration on the anxiolytic and antidepressant activity of CBD.

Author	Year	Results after CBD administration
Campos	2008	Elevated cross labyrinth: Increased permanence in the open arms. Vogel Conflict: Increase in the number of licks in water. Tail Suspension: An antinociception was seen (reduced ability to perceive pain).
Resstel	2009	Elevated cross labyrinth: 10mg/kg showed a better response to the test.
Zanelati	2010	Forced swim: 30 mg / kg CBD reduced immobility time compared to imipramine Evaluation of BDNF levels: 30 mg / kg CBD did not alter hippocampal BDNF levels.
Soares	2010	Elevated cross labyrinth: 60nmol exhibited better response to the test. Electrical stimulation: 30 and 60nmol showed better results.
Réus	2011	Forced swim: 30 mg / kg CBD reduced the immobility time and increased the swimming time of the rats, compared to positive controls of imipramine. Evaluation of BDNF levels: 15mg / kg increased BDNF levels in the cerebellar tonsils.
El-Alfy	2011	Sucrose Preference: 200m / kg CBD revealed a significant decrease in immobility time.
Gomes	2011	Elevated cross labyrinth: increased permanence in the open arms. Vogel Conflict: Increased numbers of licks in water.
Campos	2013	Elevated cross labyrinth: 5 and 20 mg / kg revealed increased permanence in the open arms.
Fogaça	2014	Contextual conditioning of fear: 30nmol resulted in a decrease in total freezing time compared to control animals.
Shoval	2016	Test sucrose preference: Positive effect in WKY dose of 30 mg / kg CBD; Object exploration: 15 mg / kg demonstrated increased locomotion and 45 mg / kg CBD increased the exploration for the new object in WKY.
Rock	2017	5 mg / kg CBD prevented ansiogenic response after foot shock 24 hours before treatment.

CONCLUSION

With this work we conclude that the use of the compound CBD, extracted from the Cannabis sativa plant has many positive effects regarding a possible therapeutic treatment for psychiatric disorders, that is, Cannabis is not only a recreational drug, it can have compounds extracted and be very useful for the treatment of various diseases, when used for therapeutic purposes.

It has been proven, within several experiments, that CBD presents an anxiolytic and antidepressant activity, however there is still the need for more pre-clinical studies to elucidate its mechanisms and neurochemical targets, determine the ideal doses, and discover possible positive or negative interactions with other drugs, because although there are researches on CBD, they are still restricted to the treatment of epilepsy and schizophrenia. Only from these studies, and the next ones, will we be able to answer whether CBD can generate a new medicine with fewer side effects for the treatment of depression and anxiety.

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