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Review Article

THE ROLE OF CANNABIDIOL IN THE INFLAMMATORY PROCESS AND ITS PROPERTIES AS AN ALTERNATIVE THERAPY – A REVIEW (META-ANALYSIS)

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ABSTRACT

The non-psychoactive compound of cannabis, cannabidiol (CBD), has stood out as promising in treating several disease with new mechanisms of action and a favorable side effect profile. The aim of the present study was to evaluate what has been published about CBD in the last 2 years (2019/2020) about anxiety, depression, panic attack and dementia, as well as side effects presented by this cannabidiol. The material analyzed consists of the cannabidiol (CBD) index in PubMed/Medline, and its relationship with metabolic activity, anxiety, depression, and dementia. The data were collected between 2019 and 2020, totaling 76 articles. Although most of the studies found are in the form of a review (55.3%), several clinical studies in humans have shown promising results with the use of CBD. The treatments for anxiety and stress with CBD were the most evident, corresponding to 37.8% of the total studies, as reported in Table 2. The relationship of CBD in metabolic processes as inflammatory markers was the second most evident item in Table 2, with 11.1%. Cognitive processes and depression appear in sequence, with 8.9% each. With 70.6% of favorable results in Table 3, CBD appears as a promising option in the treatment of anxiety, stress and similar behaviors. Regarding depression, the results were slightly lower. With 66.6% positive results, depression can also be treated with CBD as an alternative therapy option. We conclude that the findings in this meta-analysis need more studies that show us the use of CBD in behavioral pathologies, especially in the long term, and its interaction with other drugs, as well as its pharmacodynamics.

Keywords: Cannabidiol, Anxiety, Depression, Panic attack, Dementia.

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INTRODUCTION

Cannabis has been used as a medicinal plant for thousands of years in Asia [1]. Cannabis was known in the West by William O'Shaughnessy in 1838, who described remarkable results in the treatment of some diseases, among than epilepsy, rheumatic pain, and others, using this plant [2]. Numerous health benefits have been attributed to cannabis since its first reported use in 2600 BC in Chinese pharmacopeia [3]. The therapeutic potential of compounds derived from these plants has driven interest in the last few years [1]. The non-psychoactive compound of cannabis, cannabidiol (CBD), has stood out as promising in treating ellipsis as an anticonvulsant with new mechanisms of action and a favorable side effect profile [4].

There is interest among medical scientists in the gene-regulating properties of CBD [5]. Researchers at the California Pacific Medical Center have shown that CBD reduces brain cancer and breast cancer cell proliferation and metastasis by inhibiting the expression of the ID-1 gene. ID-1 expression is implicated in several kinds of aggressive cancer [6]. In 2012, Israeli scientists identified more than 1200 genes affected by CBD: 608 "gene transcripts" were upregulated by cannabidiol and 524 were downregulated by cannabidiol [7]. CBD also bears investigation in epilepsy and other neuropsychiatric disorders, including anxiety, schizophrenia, addiction, and neonatal hypoxic-ischemic encephalopathy [4]. Various *in vitro* and *in vivo* evidence also support CBD's role in degenerative inflammatory diseases [8]. CBD had a strong ability to inhibit the production of inflammatory cytokines, including interleukin (IL)-1β, IL-6, and interferon-β, in lipopolysaccharide-stimulated murine microglial cells [9,10]. On the other hand, recent studies have demonstrated that CBD-induced DNA damage in human liver cells when evaluated *in vitro* to administer different doses [11]. In this way, we seek to evaluate, through this present study, what has been published about CBD in the PubMed/Medline database in the past 2 years (2019/2020) concerning anxiety, depression, panic attack, and dementia, as well as therapeutic dosages, results with significant values, side effects, and others reported in the studies found. The results found in the present study may serve as a basis for further studies, as well as for treatments that require dose adjustment concerning CBD.

MATERIALS AND METHODS

The material analyzed consists of journal articles on the cannabidiol (CBD) index in PubMed/Medline, seeking this herb's relationship with metabolic activity, anxiety, depression, and dementia. The data were collected between 2019 and 2020, totaling 76 articles. The article's search was done through the keywords cannabidiol, anxiety, depression, panic attacks, and dementia.

RESULTS

The results were distribuited in Tables 1-4. In Table 1, we observed a predominance of review publications with 55,3%, followed the publications of clinical study in humans with 22.4%, and animal experiments with 17.1%. The significant proportion of 55.3% of reviews found in this study demonstrates a tremendous interest of the scientific community in recent years on the properties of CBD, their therapeutic applications, and the ratio of the dosage to use. However, in this present study, we see the presence of CBD as one of the cannabinoids supporting agents present in cannabis, being evaluated, in many cases, with other cannabinoids, mainly Δ9 tetrahydrocannabinol (THC). When searching for the word cannabidiol, there are many systematic reviews about CBD, but not all of them report the benefits and side effects of CBD alone. Understanding whether CBD is safe for treating psychiatric disorders is essential to empower psychiatrists and patients to make sound clinical decisions.

The treatments for anxiety and stress with CBD were the most evident in this present review. Studies in both humans (22.2%) and animals (15.6%) accounted for 37.8% of the total studies observed *in vivo* evaluations. The relationship of CBD in metabolic processes as inflammatory markers, the activator of specific nuclear receptors, and protein modulations was the

second most evident item in this present review, with 11,1%. Cognitive processes and depression appear in sequence, with 8.9% both.

The results of the significance values found in this study demonstrated a good acceptance in the treatment with CBD regarding anxiety and stress. With 70.6% of positive outcomes, CBD appears as a promising option in treating anxiety, stress, and similar behaviors. Regarding depression, the results were slightly lower. With 66.6% positive results, depression can also be treated with CBD as an alternative therapy option. In cognition, the process reversed. About 66.6% did not obtain significant developments in the observed surveys, demonstrating that CBD has better anxiety results than other behavioral methods.

In Table 4, the dosages for CBD administration are incredibly diverse. In the study by Shannon *et al*. (2019), 25 mg of CBD was used in most patients. However, if complaints of anxiety and insomnia predominated, patients received from 50 mg to up to 75 mg, depending on the case. The authors related that patients with a history of ezquisophrenia disorder received doses of up to 175 mg a day. In this study, CBD is used as a method to prevent or reduce psychiatric drugs.

DISCUSSION

Although most of the reviews presented in this study have shown promising results with the use of CBD, some studies have listed the possible side effect of using this cannabinoid. Khoury *et al*. (2019) reported, in their review, that after the analysis included six case reports and seven trials, comprising 201 subjects, most the study included six case reports and seven clinical trials, covering 201 subjects. Most of the published studies had several drawbacks and did not reach statistical significance reported by Khoury *et al*. lies published presented several drawbacks and did not reach statistical significance, stated the authors. The authors also have not found evidence regarding major depressive and bipolar disorders, revealing that CBD's efficacy and safety in psychiatry are still scarce [12].

On the other hand, CBD demonstrated satisfactory therapeutic effects in patients with Parkinson's disease (PD) in the review by Crippa *et al*. (2019). Seven preclinical models of PD found using CBD in this study, with six studies showing a CBD neuroprotective effect. Crippa *et al*. related that three studies involving CBD and PD also reported: An open study, a case series, and a randomized clinical trial (RCT). CBD well-tolerated and all three studies reported significant therapeutic effects on non-motor symptoms (psychosis, disturbed sleep behavior by rapid eye movements, daily activities, and stigma) [13]. However, the authors noted that the sample sizes were small, and treatment with CBD was short (up to 6 weeks). They related that further stated that large-scale RCTs are needed to replicate these results and assess the long-term safety of CBD [13].

CBD in psychiatry

The review of Galapai *et al*. (2019) on the use of CBD in psychiatry brought promising results. The authors conducted studies from 1970 to 2019 on the use of CBD in psychiatry with the keywords "psychiatry," "schizophrenia," "anxiety," "depression," "autism," "anxiolytic," "antidepressant," and "antipsychotic" were one by one added to the keyword "cannabidiol." [14]. In this review, articles published in revised scientific journals described CBD's preclinical effects in psychiatric use. Clinical studies conducted with patients affected by psychiatric illnesses were collected and discussed only cases of healthy individuals unaffected by psychiatric conditions included. The authors report that this review's results confirmed the vision of cannabinoids as a promising molecule, especially in psychiatry such as schizophrenia,

Table 1: Publication types

Years	2019	%	2020	%	Total	%
Review	39	51.3	3	4.0	42	55.3
In vitro	2	2.6	0	0	2	2,6
In vivo animal	12	15.8	1	1.3	13	17.1
In vivo human	14	18.4	3	4.0	17	22.4
Others	1	1.3	1	1.3	2	2.6
Total articles	68	89.4	8	10.6	76	100

Table 2: Proposal for evaluating the article *in vivo* treatment with CBD alone or with other cannabinoids

Disease and Synptoms	2019		%		2020		%		Total%	
	H	A	H	A	H	A	H	A	H	A
Anxiety and stress	8	7	20.0	17.5	2	-	40	-	22.2	15.6
Insomnia	2	-	5.0	-	-	-	-	-	4.5	-
Depression	1	2	2.5	5.0	1	-	20	-	4.5	4.4
Metabolism	4	1	10.0	2.5	-	-	-	-	8.9	2.2
Phobia and panic attack	1	1	2.5	2.5	-	-	-	-	2.2	2.2
Cognition	-	3	7/5	-	1	-	20	-	2.2	6.7
Dementia	1	-	2.5	-	-	-	-	-	2.2	-
Psychotic disorders	-	-	-	-	1	-	20	-	2.2	-
Autism	1	-	2.5	-	-	-	-	-	2.2	-
Post-traumatic stress disorder	2	-	5.0	-	-	-	-	-	4.5	-
Pain	2	1	5.0	2.5		-	-	-	4.5	2.2
Total	22	15	60	30	5	-	100	-	60.1	33.3

*H: Human, A: Animal

Table 3: The results with significance evaluated in human and animal

Significance Evaluated	2019	2019	2020	2020	Total%	Total%	Ratio
Results	Positive	Negative	Positive	Negative	Positive	Negative	p/n
Anxiety and stress	12	4	-	1	70.6	29.4	24/1
Insomnia	1	-	-	-	100	-	100/1
Depression	2	-	-	1	66.6	33,3	2/1
Metabolism	1	1	-	-	50	50	1/1
Phobia and panic attack	1	-	1	-	100	-	100/1
Cognition	1	1	-	1	33.3	66.6	1/2
Dementia	1	-	-	-	100	-	100/1
Autism	1	-	-	-	100	-	100/1
Pain	2	1	-	-	66.6	33.3	2/1

Table 4: Doses used in human studies

Articles	Clinical evaluation	Dosage/d
Perm J. 2019;23:18-041	Anxiety and sleep	25 mg–175 mg (Oral form for 12 weeks)
J Altern Complement Med. 2019 Apr;25(4):392-397	Stress disorder	25 mg caps 9 mg spray (for 8 weeks)
Braz J Psychiatry. 2019 Jan-Feb;41(1):9-14	Anxiety	150 mg (15) 300 mg (15) 600 mg (12) (During the speech)
BMC Psychiatry. 2019 Feb 13;19(1):69	Phobia and panic disorder	300 mg (for 8 weeks)
Front Pharmacol. 2019 Jan 9;9:1521	Autism symptoms	16 mg/Kg (max 600 mg) (for 66 days)
J Neurodev Disord. 2019 Aug 2;11(1):16	Behavioral symptoms associated with FXS	50–250 mg gel (Transdermal form) (for 12 weeks)
Am J Psychiatry. 2019 Nov 1;176(11):911-922	Anxiety in drug abstinence	400–800 mg (3 days consecutive)
Psychopharmacology (Berl). 2020 Jan 8	Anxiety and stress	600 mg (for 1 week)
J Psychopharmacol. 2020 Feb;34(2):189-196	Parkinson disease	300 mg (for 2 weeks)
Front Psychol. 2019 Nov 8;10:2466	Anxiety	300 mg (for 4 weeks)
Isr Med Assoc J. 2019 Nov;21(11):759-760	Dementia	60 mg (for 1 week)

anxiety, depression, and autism [14]. Still on this review, Calapai *et al*. concluded that although CBD has anti-inflammatory properties supported by the large number of experiments using experimental laboratory models, the evidence of CBD's therapeutic effects in the psychiatric field is restricted to some clinical studies investigating CBD in schizophrenic patients and individuals affected by anxiety. CBD has demonstrated a positive impact on some markers of neuroplasticity antidepressant effects, such as increased levels of brain-derived neurotrophic factor, restores impaired neuron proliferation caused by chronic stress in animals. CBD has also been shown to have anti-inflammatory, antioxidant, immunomodulators, and neuroprotectors, probably mediated by interaction with the receptor, and activated by a peroxisome proliferator stimulation of hippocampal neurogenesis [15]. The properties of CBD that reduces inflammation and oxidative stress associated with neurotoxicity, without psychoactive effects, make CBD a promising herbal medicine in the treatment of psychiatric disorders, say the authors [16].

Considering that modern life has been causing anxiety disorders in humans, the search for a natural anxiolytic is a fact. There are no evidence that popular and available anxiety levels can detect all or most types of anxiety disorder in primary care. Some levels, often used in research, measure specific types of anxiety, such as trait anxiety, or particular aspects of individual anxiety disorders, such as worry, social anxiety, and specific fears, whereas other scales aim to measure a common characteristic of most, as the general anxiety [17]. Usually, the anxiety process is linked to stress and can trigger insomnia, phobias, panic attacks, depression, and pain, in some specific cases [17-21]. CBD has been an alternative therapy for both disorders of the human psyche mentioned above, and with a good response in the articles observed in this present review. However, studies showing the central nervous system (CNS) by the CBD, also called attention in this current study.

CBD and liver DNA damage

A surprising result in Russo *et al*. regarding the use of CBD and DNA damage and chromosomal aberrations in human cells found in this present study [11]. The authors related that CBD and cannabidivarin (CBDV) cause the formation of comets (which reflect single and double-strand breaks and apurinic sites), oxidation of DNA bases, and induction of micronucleus (MN) (which formed because of structural and numerical chromosomal aberrations). The results of this study with liver enzyme homogenate suggested that drug-metabolizing enzymes (in particular, the CYPs that contained in the enzyme mixture) increase the genotoxic properties of CBD and CBDV. It documented that different CYPs (in specific CYP1A1, 1A2, and 3A4) catalyze the formation of CBD's hydroxyl derivatives, but the mutagenic properties of these metabolites have not yet investigated. The most relevant result of this investigation is detecting MN induction by CBD and CBDV in low physiologically relevant concentrations [11]. The authors still conclude that MNi formed as a consequence of chromosomal damage, and it documented that increased human lymphocyte rates indicate cancer risks.

CBD and cannabinoid and non-cannabinoid receptors

The mechanisms of action of cannabinoids are thought to be mediated cannabidiol receptors at the cell surface [22]. Two types of these cannabinoid receptors have so far identified, and both are members of the superfamily of G-protein-coupled receptors (GPCRs), CB1 and CB2 [22,23]. However, studies have shown that cannabidiol also has interactions in several other nuclear receptors, especially regarding CBD agonist properties in specific receptors, such as the serotonin receptor (5HT) and the peroxisome proliferator-activated receptor *gamma* (PPAR-γ) [24,25]. Several genes regulated by PPARs are involved in energy homeostasis, lipid uptake and metabolism, insulin sensitivity, and other metabolic functions [26]. In 2011, a research team reported that PPAR-γ activation degrades amyloid-beta plaque, a key molecule in developing Alzheimer's disease. PPAR-γ is a nuclear receptor of the PPAR family that plays a significant regulatory role in energy homeostasis and metabolic function in cells [27]. It is one reason why cannabidiol, a PPAR-γ agonist, may be a useful remedy for Alzheimer's patients [15]. In serotonergic receptors, the CBD agonist mechanism helps in the behavioral part, including anxiety and pain. Repeated treatment with a low dose of CBD induces analgesia predominantly through activation of transient receptor potential vanilloid type 1, reduces anxiety through activation of the 5-HT1A receptor, and rescues impaired 5-HT neurotransmission under conditions of neuropathic

pain [24]. However, the control of inflammation occurs through nuclear factor-kappa beta (NF-kB), a protein complex that controls DNA transcription, cytokine production, and cell survival [28].

The NF-κβ has attracted widespread attention among researchers in many fields. The central role in immunological processes and its apparent involvement in several diseases have been reported in several scientific studies [28]. The NF-κβ pathway has long been considered a prototypical pro-inflammatory signaling pathway, primarily based on the role of NF-κβ in the expression of pro-inflammatory genes [29]. NF-κβ may have decreased metabolic activity through the PPAR-γ. The PPAR-γ is ligand-activated receptors with distinct physiological functions in regulating lipid and glucose metabolism and inflammatory response [30]. PPAR-γ activation allows a coordinated up-regulation of numerous fatty acid oxidation (FAO) enzymes, resulting in significant PPAR-driven increases in mitochondrial FAO flux [30].

CBD, metabolism, inflammation, and behavior

There is a correlation between the metabolic part and the behavioral part concerning the CBD's mechanisms of action. Thus, the evidence from the studies found in this present work support that CBD has become a promising alternative regarding the treatment of anxiety, stress, depression, and diseases linked to behavioral disorders. In addition to CBD acting as an agonist of 5HT receptors, it also protects neurons when there are excesses of glutamate release in the CNS exhibiting therapeutic potential for various human diseases, including chronic neurodegenerative disorders, such as Alzheimer's and Parkinson's, ischemic stroke, epilepsy, and other convulsive syndromes, neuropsychiatric disorders, neuropathic allodynia, and certain types of cancer [31]. Medicinal herbs have been increasingly studied as a neuroprotective agent in this 21st century. Research has shown that natural herbs are increasingly on a promising path in the treatment of neurodegenerative diseases [32]. Although Roy and Awasthi (2017) mentioned several medicinal herbs with promising results, they did not say cannabidiol as an asset in their studies.

On the other hand, Rodrigues-Munhoz (2019) affirmed that CBD exhibits positive effects in situations in which glutamatergic signaling, mainly that mediated by N-methyl-D-aspartate acid receptor (NMDAR), plays a critical role. A recent study has revealed that the sigma-1 receptor (σ1R) antagonism prevents GPCRs from enhancing the function of NMDARs, thereby reducing the cellular impact of the excessive glutamatergic activity. CBD interacts as an σ1R antagonist. This demonstrated that CBD exhibits antioxidant properties and protects neurons from glutamate-induced death without cannabinoid receptor activation or NMDAR antagonism [31].

Another exciting factor about CBD regarding behavior is its interaction with an autism spectrum disorder. A recent study with CBD in autistic children showed a significant improvement in the patients using CBD [33]. This study supported the feasibility of CBD testing in children with autism. On the other hand, despite the growing interest in CBD as monotherapy or complementary treatment for the main symptoms and comorbidities of ASD [34], there are currently no convincing preclinical or clinical data to demonstrated the efficacy and safety of cannabinoid treatment in patients with ADS.

On the other hand, we observed a crucial neuroprotection mechanism associated with CBD in the main oxidative stress control enzyme, superoxide dismutase (SOD) [35]. The upregulation of the mRNA levels mediates the mechanism of neuroprotection and anti-inflammatory exerted by CBD for Cu–Zn SOD, an essential enzyme in endogenous defenses against oxidative stress, mainly in the production of superoxide (O-) due to cellular respiration [35]. This enzyme interacts in controlling the reactive oxygen species (ROS) produced in the mitochondria in the respiratory chain. ROS production triggers damage to DNA, RNA, and proteins in cells [36]. Thus, CBD's control of SOD expression may offer a promising future not only in the control of oxidative stress but also in inflammation. In a review of arthritis and medicinal plants, Paul *et al*. (2015) reported that cannabinoids act as potent immunosuppressive and anti-inflammatory agents in their respective CB1 and CB2 receptors and measure the beneficial effects in a wide range of immune-mediated diseases, such as multiple sclerosis, diabetes, septic shock, rheumatoid arthritis, and allergic asthma [37]. This review corroborates with other results found in this present study on the positive effects of cannabinoids on use in anti-inflammatory therapies.

CBD, anxiety, and sleep

In comparing the positive and negative results concerning anxiety, we can observe some differences between the studies. Shannon *et al*. (2019) related an interesting retrospective case series at a psychiatric clinic involving CBD's clinical application in both anxiety and sleep complaints as an adjunct to usual treatment. This retrospective chart review included monthly documentation of anxiety and sleep quality in 103 adult patients. In this study, the average age for patients with anxiety was 34 years (range = 18–70 years) and age 36.5 years for patients with sleep disorders (range = 18–72 years). Most patients with an anxiety diagnosis were men (59.6%, 28/47), whereas more sleep-disordered patients were women (64.0%, 16/25) [38]. The authors related that all 72 patients completed sleep and anxiety assessments at the onset of CBD treatment and at the 1st monthly follow-up. By the 2nd monthly follow-up, 41 patients (56.9%) remained on CBD treatment and completed assessments; 27 patients (37.5%) remained on CBD treatment at the 3rd monthly assessment. On average, anxiety and sleep improved for most patients, which sustained overtime [38]. Still the same study, at the 1st monthly assessment after the start of CBD treatment, 79.2% (57/72) and 66.7% (48/72) of all patients experienced an improvement in anxiety and sleep, respectively; 15.3% (11/72) and 25.0% (18/72) experienced worsening symptoms in stress and rest, respectively. Two months after the start of CBD treatment, 78.1% (32/41) and 56.1% (23/41) of patients reported improvement in anxiety and sleep, respectively, compared with the prior monthly visit; again, 19.5% (8/41) and 26.8% (11/41), respectively, reported worsening problems as compared with the preceding month, related the authors. The results of Shannon *et al*. (2019) demonstrated a more sustained response to anxiety than for sleepover time. Patient records displayed a more considerable decrease in anxiety scores than in sleep scores. The sleep scores demonstrated mild improvement. The anxiety scores decreased within the 1st month and then remained reduced during the study duration [38].

Similarly, Masataka proposed to investigate the possible effectiveness of CBD as at least an adjunct option for intervention in people with a social anxiety disorder (SAD) [39]. The author sought to systematically assess CBD's effectiveness in a total of 37 Japanese from 18 to 19 years of age with SAD, all naive to any form of treatment, measuring the level of SAD symptoms with both groups. The Negative Assessment Fear Questionnaire (FNE; Watson and Friend, 1969) and the Liebowitz Social Anxiety Scale (LSAS; Liebowitz, 1987) using a parallel, double-blind, experimental, exploratory, experimental paradigm. The results of this study provided evidence of the anxiolytic effects of repeated administration of CBD in adolescents with SAD. At the same time, however, the author recognizes several limitations of the present study. No CBD blood level test has been performed. According to the authors, a more detailed baseline sociodemographic assessment could have carried out to guarantee the pre-treatment similarity of the treatment groups [39]. They further stated that measurements need to take at additional times between the baseline and the end of the study. Such measures would be essential to show, for example, whether CBD could produce a rapid improvement in social anxiety (a putative advantage over paroxetine). Besides, possible side effects should be assessed systematically [39]. According to the authors, these are questions for future research that should also be long-term studies with the positive control (for example, paroxetine) to assess the potential usefulness of CBD in SAD therapy.

Interestingly, in a study by Linares *et al*. (2019), CBD was used to compare the acute effects of different doses of CBD itself and placebo

in healthy volunteers who perform a simulated public speaking test, a well-tested method anxiety induction. The authors used a total of 57 healthy male subjects who were prepared to receive oral CBD at doses of 150 mg (n=15), 300 mg (n=15), 600 mg (n=12) or placebo (n=15) in a double dose blind procedure. The results showed that pre-treatment with 300 mg of CBD significantly reduced anxiety during speech compared to placebo. No significant differences were observed in the Visual Analog Mood Scale [40].

Interestingly, in the study by Schleicher *et al*. (2019), CBD's behavioral profile was investigated with a battery of behavioral tests, including motor, anxiety, and memory tests after prolonged CBD treatment. Adult C57Bl/6J wild-type (WT) mice were daily intraperitoneally injected with 20 mg/kg CBD for 6 weeks starting at two different points of ages (3 months and 5 months) to compare the influence of prolonged CBD treatment with a washout period (former group) to the effects of long-term CBD treatment (current group) [41]. The results of this study showed that CBD treatment does not influence motor performance on an accelerating rotarod test, while it also results in a lower locomotor activity in the open field (OF). No CBD influence on spatial learning and long-term memory in the Morris water maze was observed. Memory in the novel object recognition test was unaffected by CBD treatment [41]. Two different anxiety tests revealed that CBD does not affect anxiety behavior in the dark-light box and OF test. However, anxiety is altered by current CBD treatment in the elevated plus maze.

Moreover, according to the authors, CBD-treated C57Bl/6J mice showed an unaltered acoustic startle response compared to vehicle-treated mice. However, current CBD treatment impairs pre-pulse inhibition (PPI), a test to analyze sensorimotor gating. The authors conclude that prolonged CBD treatment did not affect the hippocampal neuron number, and the results demonstrate that protracted CBD treatment has no adverse effect on the behavior of adult C57Bl/6J mice [41].

In a study by Appiah-Kusi (2019), the authors investigated CBD's effects on neuroendocrine responses to stress anxiety in high-risk clinical patients for patients with psychosis (CHR). Thirty-two CHR patients and 26 healthy controls (HC) took part in the trier social stress test, and their serum cortisol, anxiety, and stress associated with public speaking were estimated [42]. Half of the CHR participants were on 600 mg/day of CBD (CHR-CBD), and half were on placebo (CHR-P) for 1 week. The results of this study showed that a one-way analysis of variance (ANOVA) revealed a significant effect of group (HC, CHR-P, and CHR-CBD) ($p=0.005$) on cortisol reactivity as well as a significant ($p=0.003$) linear decrease [40]. According to the authors, the change in cortisol associated with experimental stress exposure was most notable in HC controls and least in CHR-P patients, with CHR-CBD patients exhibiting an intermediate response. Planned contrasts revealed that the cortisol reactivity was significantly different in HC compared with CHR-P ($p=0.003$) and in HC compared with CHR-CBD ($p=0.014$) but was not different between CHR-P and CHR-CBD ($p=0.70$) [42]. The related Thar across the participant groups (CHR-P, CHR-CBD, and HC), changes in anxiety, and experience of public speaking stress (all $p's<0.02$) were most significant in the CHR-P and least in the HC, with CHR-CBD participants demonstrating an intermediate level of change. Through the results obtained, the authors concluded that it is worth designing more successful studies that investigate whether CBD can be used to affect the response to cortisol at high clinical risk for patients with psychosis and any effect that this may have on symptoms [42].

Although the studies in this review have shown promising results regarding CBD's use in the behavioral part, more studies are needed to adjust doses, treatment time, and side effects, especially with long-term use. We have not had a longitudinal study using CBD to measure its benefits and possible adverse effects, only short-term studies. As the variety of papers published in this review is very heterogeneous, it is challenging to measure CBD safety, therapeutic doses, and drug interactions when used with other drugs. CBD is metabolized by cytochrome P450 (CYP450) [43], an enzyme that also participates in several other drug' metabolization. Therefore, much attention is needed when prescribing CBD with another medication to interact in the metabolization process. Most of the studies, by the way, place CBD as a therapeutic potential in behavioral treatments, such as anxiety, phobias, and pain. However, none of them safely points out the pharmacodynamics of this cannabinoid. There have been several studies where CBD has used with other cannabinoids, mainly THC, showing that both alone and other cannabinoids, the effects were most promising. However, at this moment, there is a need for further future studies to point out the anxiolytic potential of CBD.

CBD dosage

Therefore, the selection and dosage of CBD reflected the clinical preference individually [37]. Informed consent was obtained for each patient treated and considered for this study. Monthly visits included clinical assessment and documentation of patients' anxiety and sleep status using validated measures, said the authors. Still, in the same study, the authors related that CBD was added to the treatment, removed from the treatment, or refused according to the patient and the professional's individual preference, and it was used as a method to prevent or reduce psychiatric drugs. Therefore, the selection and dosage of CBD reflected the clinical preference individually. Informed consent was obtained for each patient treated and considered for this study [38]. Monthly visits included clinical assessment and documentation of patients' anxiety and sleep status using validated measures. CBD was added to the treatment, removed from the treatment, or refused according to the patient and the professional's individual preference. Therefore, the study of Shannon *et al*. (2019) was unable to provide us with a dosage standard since the doses were adequate individually and did not respect a sample for evaluation.

When comparing the studies presented in this table, we can observe that despite the difficulty of finding a dosage in the use of CBD, the versatility in the use of this cannabinoid is remarkable. In the study by Linares *et al*. (2019), patients received much higher doses of CBD to treat anxiety when these patients needed to speak in public in comparison of the study by Shannon *et al*. These doses were chosen based on previous evidence that acute anxiolytic effects have observed in healthy subjects given amounts ranging from 300 to 600 mg of CBD [40]. According to Shannon *et al*., the doses used in his study (25 mg/d to 175 mg/d) were much lower than those reported in some of the clinical literature, such as the Linares *et al*. study (300 mg/d to 600 mg/d). The authors attributed this to two distinct factors. First, lower doses seem to cause an adequate clinical response. Second, CBD's current retail cost would make the use of 600 mg/d prohibitive [40].

Interestingly, two other studies observed in the table above, Appiah-Kusi *et al*. and Masataka, treated their respective patients with dosages of 600 mg and 300 mg, respectively [39,42]. Appia-Kusi *et al*. used doses of 600 mg to treat patients with a high degree of anxiety, checking whether CBD would normalize neuroendocrine and stress anxiety responses in high-risk clinical patients for psychosis (CHR). At the same time, Masataka treated 37 young people with SAD with 300 mg of CBD a day. According to this author, in his study, it was reported that the previous studies showed that CBD reduces anticipatory anxiety, such as speaking in public, for example. Moreover, CBD was found to exert a significant effect on increased brain activity in the right posterior cingulated cortex that thought to be involved in the processing of emotional information [39].

Even higher doses of CBD were found in the study by Hurd *et al*. (2019). These authors investigated CBD's potential to reduce stimulus-induced desire and anxiety, two critical characteristics of addiction that often contribute to relapse and continued drug use in individuals abstaining from drugs with heroin use disorder [43,44]. As we can see, this treatment cannot be compared to the others due to the characteristics of patients abstaining from drugs with a disorder caused by heroin

use. These are different cases from those used in the table above and have different needs about the doses used and the time used. Acute CBD administration, in contrast to placebo, significantly reduced both craving and anxiety induced by the presentation of salient drug cues compared with neutral signals [44]. CBD also showed significant prolonged effects on these test 7 days after the final short-term (3-day) CBD exposure. Besides, Hurd *et al.* (2019) related that CBD reduced the drug cue-induced physiological measures of heart rate and salivary cortisol levels.

CONCLUSION

Analyzing the work in this review, we concluded that CBD is still a new asset in phytochemicals. Since its dosage, proposed treatment, side effects, contraindications, and mainly its pharmacodynamics, we are still in need of studies that show us the use of CBD in behavioral pathologies, primarily in the long term and its interaction with other drugs. Although all the results presented in this study are promising, we need more information to position ourselves on the efficiency of CBD in proposed treatments. A fact observed in earlier studies on CBD was the difference observed in the therapeutic curve concerning the isolated CBD and the full spectrum CBD, where the full spectrum tends to maintain the therapeutic effect for an indefinite period of use, while the isolate loses its action in continuous use.

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