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Medicinal *Cannabis* and cannabinoids for the treatment of depression and anxiety: a literature review

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Genet. Mol. Res. 23 (1): gmr19167
Received June 26, 2023
Accepted December 12, 2023
Published February 14, 2024
DOI http://dx.doi.org/10.4238/gmr19167

ABSTRACT. About 350 million people worldwide are affected by depression, which is often accompanied by other comorbidities such as anxiety. Research on the use of cannabinoids for these debilitating mental illnesses has advanced. However, although *Cannabis* has putative therapeutic use for the treatment of both psychiatric and neurological diseases due to psychotropic and non-psychotropic effects of cannabinoid components of *Cannabis sativa* on the central nervous system, there is resistance in some countries due to regulations for the use of these substances. Given the diversity of different preparations characteristics, either containing natural phytocannabinoids or synthetic cannabinoids, successful

implementation of cannabis therapy will require considerable research. It has to be considered that the endocannabinoid system is complex; each neurological disease has its particular pathophysiology. Therefore, it is a challenge to obtain a pharmaceutical product with an adequate profile for each patient. This review examined the results of preclinical and clinical studies that focused on cannabinoid therapy for depression and anxiety disorders. Searches were carried out in international databases, including studies that presented consistent data on medical cannabis in depression and anxiety. Published studies provide weak scientific evidence concerning improvement of the symptoms of these mental disorders. More preclinical studies are needed that involve the various pathological conditions, as well as placebo controlled, double-blind and randomized clinical trials. We need robust data that can better evaluate dependence and other consequences of prolonged use of these compounds.

Key words: Depression and anxiety disorders; Medicinal *Cannabis*; Endocannabinoid system; Cannabinoids

INTRODUCTION

Depression and anxiety disorders affect approximately 300 to 350 million people worldwide (WHO, 2022). Studies have shown that physiological and behavioral effects observed in these mental illnesses are related to inadequate signaling of the endocannabinoid system both in humans and in laboratory animal models. On the other hand, anxiogenic and depressive symptoms are improved with adequate activation of this system; although it is known that in this context, other neural systems also participate, such as serotonergic, dopaminergic, adrenergic and opioid systems (Ahmed et al., 2022, Hasbi et al., 2023).

Cannabis sativa is popularly known as hemp, marijuana, cannabis, weed, among other names. Since the Neolithic period (12,000 years ago) humanity has used cannabis in a variety of ways, for recreational and medicinal purposes, including the production of fibers, seeds and the use of secondary metabolites called phytocannabinoids (Bonini et al., 2018).

Since the 1970s, publications have mentioned the use of cannabis for neurological diseases (Jain and Tarafder, 1970, Touw, 1981). Recently, these studies have become more common (Balant et al., 2021, Janecki et al., 2022, Ortiz et al., 2022). However, even if some therapeutic effect has been shown in neurodegenerative diseases, post-traumatic stress disorder, addiction, and cancer, the data are less convincing when compared to the effects of cannabinoids to reduce seizures, spasticity, pain, nausea and vomiting and appetite increasing (Legare et al, 2022; Sofrás and Desimone, 2022).

It is known that cannabis promotes the modulation of several pathophysiological phenomena due to the interaction between the various pharmacological preparations, containing natural phytocannabinoids or synthetic cannabinoids, and the endocannabinoid system (ES) (Bonini et al., 2018, Mastinu et al., 2018, Gilman et al., 2022, Zloto et al., 2022). However, even in the face of great advances in technologies and strategies for

obtaining medicinal cannabis, such as changes in the management and cultivation and plant breeding of cannabis and how they affect the ES, there is still a long way to go for the effective treatment of diseases affecting the central nervous system.

Unfortunately, the use of *C. sativa* derivatives is still highly associated with an increased risk of mental disorders, such as depression, substance abuse, suicide, and psychosis (Hall and Solowij, 1998, Wilson and Nicoll, 2002, Burggren et al., 2019; Tourjman et al., 2023). On the other hand, strong evidence points to an inverse association; namely, that depression can lead to initiation or increased frequency of cannabis use (Feingold and Weinstein, 2021).

Though studies have shown that interactions between the ES and cannabis are promising for the therapy of central nervous system (CNS) disorders, there is a need for studies on the neurobiology of cannabinoids in mental disorders and in neurological diseases. More investigation on psychobiology is needed to better understand the complex mechanisms of action of each pharmacological product containing cannabinoids. Thus, this review examined publications concerning the putative use of cannabis derivatives for the treatment of depression and anxiety disorders.

The endocannabinoid system and therapies for anxiety and depression disorders

The endocannabinoid system

Initially, the main endocannabinoid identified was N-arachidonylethanolamide (anandamide; AEA). However, other compounds were added to the group of endocannabinoids, such as 2-Arachidonoylglycerol (2-AG), O-arachidonoylethanolamine (virodamine), and N-arachidonoyldopamine (Devane et al., 1992, Sugiura et al., 1995, Porter et al., 2002, Walker et al., 2002, Walker and Huang, 2002). The endocannabinoids AEA and 2-AG are lipophilic in nature. Being derived from arachidonic acid, they are synthesized and metabolized by various pathways, acting as natural ligands of cannabinoid receptors coupled to G1 and G2 proteins, the CB1 and CB2 receptors, to elicit their biological activities (Basavarajappa et al, 2017).

With the advancement of studies, the ES has proven to be increasingly complex. The ES is known to be an expanded neural system that includes several mediators that are biochemically related to endocannabinoids and their receptors (CB1 and CB2) and metabolic enzymes (FAAH, NAPE-PLD, MAGL, DAGL, and DAGLβ). Hence, other receptors (PPARα, GPR118, GPR119, GPR55, TRPV1, PPARγ, T-type Ca^{2+} channels ($Ca_{v3.2}$), TRPM8, 5-HT_{1A}, and $GABA_A$), similar endocannabinoid mediators (N-acylethanolamines and 2- acylglycerols), other mediators such as primary amides, lipoamino acids and N-acyl neurotransmitters and specific enzymes exert a role in this expanded neural system. In this expanding system, targets of some of these molecules have been considered promiscuous and the identification of biosynthetic pathways is being investigated (Godlewski et al., 2009, Cristino et al., 2020). Cannabidiol is an example of a promiscuous cannabinoid, considering that there is evidence that it acts on 5-hydroxytryptamine (5-HT) 1A (5-HT_{1A}) receptor (Twardowschy et al., 2013) and, indirectly, on CB1 receptors (Khan et al., 2020; de Paula Rodrigues and Coimbra, 2022) in addition to the NLRP3 inflammasome pathway (Hartmann et al., 2023).

Therapeutic applications in diseases of the nervous system

Synthetic cannabinoids approved by the United States Food and Drug Administration (FDA) federal agency are already available. Nabilone, a synthetic analogue of THC, dronabinol, a synthetic enantiomer of THC, a buccal spray consisting of the compounds THC (27mg/ml), and CBD (25mg/ml) have been prescribed, in general for the treatment of spasticity due to multiple sclerosis. In addition, an oral solution whose predominant active ingredient is CBD (Ingram and Pearson, 2019, Legare et al., 2022) is also available. Several cannabis extracts have been tested, mainly in order to evaluate the entourage effect. On the other hand, the variability of prescription, over-the-counter, or illegally purchased cannabinoids makes it impossible to assess the impact and potential side effects of these drugs (Ingram and Pearson, 2019, Bilbao and Spanagel, 2022).

Depressive disorders

The involvement of the endocannabinoid system unbalance in the pathogenesis of depression and cannabinoids has been postulated to affect the treatment of mental disorders (Berardi et al., 2016; Poleszak et al., 2018, Hou et al., 2022), although there is no objective evidence supporting this hypothesis. Anxiolytic, anticonvulsant, and antipsychotic effects of cannabidiol in humans (Bergamaschi et al., 2011, Leweke et al., 2012) and in several animal models (Izzo et al., 2009, Campos and Guimarães, 2009, Twardowschy et al., 2013, Crippa et al., 2018) have been reported. Although its mechanism of action is not fully understood, its therapeutic effect seems to be related to several receptors, such as TRPV1, 5-HT_{1A}, CB1, PPARy, and GPR55 receptors (Zygmunt et al., 1999, Bouaboula et al., 2005, Russo et al., 2005, O'Sullivan, 2007, Ryberg et al., 2007).

Regarding treatment with cannabis-derived products, dronabinol, nabilone, CBD and nabiximols have been prescribed for the treatment of depression symptoms. There is some evidence that nabiximols modify depressive symptoms and that the use of CBD and nabilone are not able to alter these symptoms (Bilbao and Spanagel, 2022). On the other hand, important findings for understanding the CBD potential effect on depression have been published. Reduced levels of brain-derived neurotrophic factor (BDNF) have been related to the pathophysiology of depression (Lindholm and Castren, 2014; Caviedes et al., 2017). Acute antidepressant-like effects after CBD administration were associated with increased BDNF levels in the hippocampus and prefrontal cortex (Sartim et al., 2018, Sales et al., 2019, Xu et al., 2019). Furthermore, studies have suggested the involvement of 5-HT_{1A} receptors in the antidepressant-like effects induced by CBD (Zanelati et al., 2010; Linge et al., 2016, Sartim et al., 2018).

A recent report suggests the role of the ES in depression pathogenesis and putative effects of cannabinoids for the treatment of that mental disorder (Poleszak et al., 2018), although conflicting results have been reported. In the last decade, some studies using animal models (Table 1) have found evidence of the therapeutic effects of CBD in neuropsychiatric disorders (Crippa et al., 2018).

Table 1. Preclinical and clinical evidence using *Cannabis* derivatives in depressive disorder models.

Preclinical studies			
Model	**Treatment**	**Main findings**	**Reference**
Male Swiss mice assessed by the forced swimming test	Vehicle, CBD (3, 10, 30, 100 mg kg-1) or imipramine (30 mg kg-1) and exposure to either the forced swimming test or the open-field arena 30 min later.	CBD (30 mg kg^{-1}) induced antidepressant-like effects comparable to those of imipramine in the forced swim test with suggestions that these effects were mediated by activation of 5-HT_{1A} receptors. Additionally, it has not been shown to alter hippocampal BDNF levels.	Zanelati et al. (2010)
Olfactory bulbectomy mouse model of depression (male C57BL6 mice).	Vehicle or CBD (50 mg/kg/day for 3 days + 10 mg/kg/day until the end of treatment, ip) for 14 days.	CBD exerts rapid antidepressant-like effects, as evidenced by reversal of hyperactivity in mice induced by the olfactory bulbectomy model of depression immediately after the first injection. Acute administration of CBD promoted an elevation of marked glutamate, both in sham mice and in OBX	Linge et al. (2015)
Depressive-like Wistar-Kyoto (WKY) rat	Vehicle or CBD (15, 30, and 45 mg/kg per os).	CBD (30 mg/kg) had a prohedonic effect, caused an increase in exploration of new objects and locomotion (in a dose of 45 mg/kg), and increased locomotion (at 15 mg/kg), indicating an improvement in the low motivation in rats WKY,	Shoval et al. (2016)
Wistar rats submitted to the forced swim or open-field tests.	Vehicle or CBD (10, 30, 45, and 60 nmol/0.2 µl/side) or 8-OH-DPAT (5 and 10 nmol/0.2 µl/side) or WAY100635 (10 and 30 nmol/0.2 µl/side) or AEA (0.5 pmol/0.2 µl/side)	CBD in the prelimbic region of the ventromedial prefrontal cortex reduced the immobility time of rats during the test session at doses of 10, 30, or 60 nmol. Administration of CBD in the infralimbic region of the ventromedial CPF induced antidepressant-like effects at doses of 45 and 60 nmol.	Sartim et al. (2016))
Wistar–Kyoto and Flinders Sensitive Line adult male rats.	Vehicle or HU-580 (0.1, 1, or 5 mg/kg) orally ingested 2 h before the FST.	Acute oral intake of CBDA (HU-580) at a low dose (1 mg/kg) reduced depressive-like behavior in two different genetic animal models of depression.	Hen-Shoval et al. (2018)
Male Swiss mice submitted to the forced swim test	Cannabidiol (3, 7, and 10 mg/kg, fluoxetine (1, 5, and 10 mg/kg); desipramine hydrochloride (2.5 and 5 mg/kg); para-clorophenylalaninemethyl ester (100 mg/kg/day for 4 days); -N-(2-chloroethyl)-N-ethyl-2-bromobenzylamine (1 µg/µl).	CBD induces antidepressant-like effects on FST, suggesting that it is dependent on serotonin levels, and the reduction of serotonin, but not norepinephrine, cancels out the effects of CBD on FST. The combination of CBD with FLX induced an antidepressant-like effect in the forced swim test. On the other hand, the association of CBD with a tricyclic noradrenergic antidepressant (DES) did not demonstrate synergistic/additive effects.	Sales et al. (2018)
Male Swiss mice submitted to the forced swim test	Peripheral treatment with CBD (10 mg/kg) or microinjections in the hippocampus (10 nmol/0.2µl) and intrahippocampal injections of either Rapamycin (0.2 nmol/0.2 µl) or K252 (0.01 nmol/0.2 µl) before cannabidiol injection.	Administration of CBD into the dorsal hippocampus (dHPC) induced antidepressant-like effects in the forced swim test. Systemically administered CBD showed that blocking Trk in the hippocampus could not stop its effects. Only mTOR inhibition in dHPC using local administration of rapamycin abolished the effects induced by	Sartim et al. (2018)

		systemic administration of CBD. Thus, it was suggested that when the drug is administered locally, the hippocampal BDNF-TrkB-mTOR pathway is vital for the antidepressant effect induced by cannabidiol. Regarding the systemic administration of CBD, other brain regions may also be involved in the organizations of its antidepressant effect.	
Sprague-Dawley and Flinders Resistant or Flinders Sensitive	Vehicle or CBD (7, 10, and 30 mg kg^{-1}/ 50, 150, and 300 nmol/µl)	CBD produced an antidepressant-like effect in FSL/FRL mice. Acute administration of CBD (10 mg/kg^{-1}) rapidly increased BDNF levels in both the medial prefrontal cortex and the hippocampus, an effect that was not observed after 7 days. Activation of 5-HT_{1A} receptors in the medial prefrontal cortex induced an acute and sustained antidepressant-like effect, and the sustained effect induced by systemic injection of ketamine was attenuated by injection of the antagonist 5-HT_{1A} receptor (WAY100635) into the prefrontal cortex	Sales et al. (2019)
Wistar Kyoto and Flinders Sensitive Line rats.	Vehicle or CBD (30 mg/kg, po)	CBD has shown the potential to reduce depressive-like behavior, and it has been suggested that it may also have clinical value in other disorders with prominent symptoms of helplessness and/or anhedonia.	Shbiro et al. (2019)
Chronic mild stress mouse model	Vehicle or CBD (100 mg/kg, po or 10 mg/kg, iv)	Intravenous injection of low doses of CBD exhibited significant antidepressant-like activity by increasing BNDF expression and inhibiting microglial activation in the prefrontal cortex. There was an increase in BNDF mRNA expression in the prefrontal cortex. CBD can inhibit microglial activation caused by stress-induced depression.	Xu et al. (2019)
Adult male Wistar rats. Chronic unpredictable mild stress model of depression.	Vehicle or CBD (10 mg/kg, ip) for 28 days	Chronic treatment with CBD induced an increase in body weight gain. When given daily (10 mg/kg), it reduced body weight loss in an unpredictable moderate chronic stress model	Gáll et al. (2020)

5-HT_{1A} - serotoninergic receptors of the 5-HT_{1A} type, AEA – Anandamide, BDNF - Brain-derived neurotrophic factor; BDNF-TrkB-mTOR - Brain-derived neurotrophic factor/tropomyosin-receptor kinase B/mammalian target of rapamycin, CBD - Cannabidiol, CBDA - Cannabidiolic acid, CBDA (HU-580) - cannabidiolic acid methyl ester, DES - Desipramine hydrochloride, DSP-4 - N-2-chloroethyl -N-ethyl-2-bromobenzylamine, dHPC - Dorsal hippocampus, FRL - Flinders Resistant, FSL - Flinders Sensitive Line, FST - Forced swim test, FLX – Fluoxetine, OBX - Olfactory bulbectomy mouse model, PCPA - Para-Clorophenylalaninemethyl ester, SD - Sprague-Dawley, Trk - Tropomyosin receptor kinase, WKY - Wistar-Kyoto rat.

Recently, Hou et al. (2022) showed that treatment with CBD in a mouse model of stress prevents depressive-like behavior, a pharmacological mechanism that is partially regulated by the FoxO signaling pathway, which modulates differentiation into astrocytes of radial neural stem cells of the hippocampus. Although this study was limited in terms of elucidating the precise molecular mechanisms underlying the CBD effects, it strengthens the evidence for the therapeutic potential of CBD in depression.

In Figure 1, we provide a diagram showing a possible interaction of CBD, BDNF and the $5HT_{1A}$ receptor.

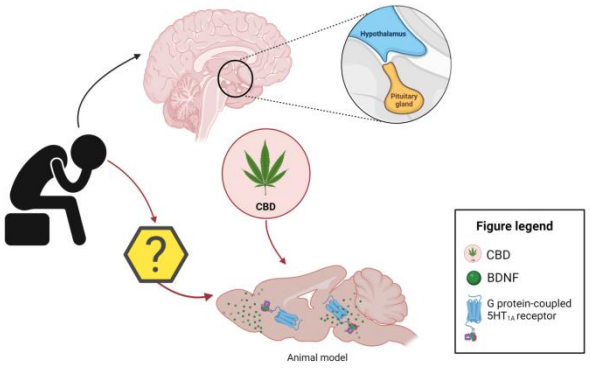

Figure 1. Possible interaction of CBD, BDNF and the $5HT_{1A}$ receptor. The diagram shows that abnormalities of the hypothalamic-pituitary-adrenal (HPA) axis are related to depressive disorders and that decreases in BNDF levels may be associated with the disease. CBD administration resulted in increased BDNF levels in the hippocampus and prefrontal cortex in an animal model, with possible involvement of the $5HT_{1A}$ receptor. 5-HT_{1A}, serotoninergic receptors of the 5-HT_{1A} type; BDNF, brain-derived neurotrophic factor; CBD, cannabidiol. (Created with BioRender.com).

Regarding the association between cannabis use and depression, a meta-analysis by Lev-Ran et al. (2014) reported that there is still no evidence of direct effects of cannabis use and increased risk of depression, as studies present large variability of effects due to non-expected additional drug associations. This includes the use of other substances such as alcohol and other drugs concomitantly with the use of Cannabis sativa-derived substances. There is a need for robust longitudinal studies to evaluate this aspect.

Anxiety disorders

Treating anxiety disorders consists of combining psychotherapy and/or medication. The latter are generally characterized by either the benzodiazepine class of medicines, facilitating GABAergic neurotransmission, or antidepressants, inhibiting serotonin reuptake. Studies have suggested an important role of the endocannabinoid system in mood modulation and, consequently, therapies with cannabinoids could be promising in reducing anxiety (Graczyk et al., 2021), especially regarding products with high CBD content (Kosiba et al., 2019, Schlag et al., 2021, Legare et al., 2022).

To investigate whether CBD exerts its effects on panic-like behavior by recruiting the 5-HT receptors, mice confronted by a wild snake were treated with CBD, and pretreatment with a 5-HT1A receptor selective antagonist; the CBD-induced panicolytic-like effect was impaired (Twardowschy et al., 2013). Additionally, dos Anjos-Garcia et al. (2017, 2019) demonstrated modulation exerted by ES on the defensive responses of animals treated with AEA, resulting in attenuation of panic-like responses in animals chemically stimulated or threatened by snakes. This beneficial association between anxiety and increased AEA levels has also been shown by other authors (Rutkowska et al., 2006, Legare et al., 2022).

Animals treated with CBD showed panicolytic-like effects, in addition to reduced fear-induced antinociception and these effects showed to be dependent of ventromedial hypothalamus CB1 receptor-signaling (Khan et al., 2020). CB1 cannabinoid and 5-HT_{1A} serotonergic receptors in the prelimbic cerebral cortex attenuated the antidepressive and analgesics effect of the CBD (Malvestio et al., 2021). These findings suggest that CBD is a putative medicine for the

treatment of depression and pain symptoms in patients with chronic neuropathic pain and depression comorbidity. Schleicher et al. (2019) showed that prolonged use of CBD in wildtype mice did not produce side effects related to anxiety behaviors, or memory and motor skills.

In the context of clinical research, Zuardi et al. (1993, 2017) reported an anxiolytic effect on acute cannabidiol treatment in volunteers undergoing a public speaking test. Furthermore, the anxiolytic effects of CBD mediated by limbic and paralimbic areas were observed through functional neuroimaging, as evidenced by Crippa et al. (2004). Interestingly, even when anxiety occurs as a secondary pathology, as demonstrated by Faria et al. (2020) in PD patients, CBD effectively reduced patient anxiety and tremor amplitudes.

Although therapy with some cannabinoids has shown good results in reducing anxiety, the association between THC and anxiety is unknown. In some cases, anxiety symptoms may be due to high THC content in cannabis (Onaivi et al., 1990, Moreira and Lutz, 2008, Crippa et al., 2009, Bhattacharyya et al., 2017; Botsford et al., 2020). Studies have shown this pattern of anxiolytic effect in CBD treatment in various anxiety disorders (Table 2).

Table 2. Preclinical and clinical evidence using Cannabis derivatives in anxiety disorders models and patients.

Preclinical studies			
Model	**Treatment**	**Main findings**	**Reference**
Male Swiss mice on instinctive fear-induced responses evoked by the presence of a wild snake were evaluated	Vehicle or CBD (3 mg/kg, ip) and pre-treatment with WAY-100635 (0.1, 0.3 and 0.9 mg/kg, ip)	CBD modulates defensive behaviors, and the effects are partially dependent on the 5-HT_{1A} receptors	Twardowschy et al. (2013)
Wistar rats in a state similar to a panic attack	Vehicle or Anandamide (AEA 0.5, 5, or 50 pmol) intra-VMHdm. followed by the intra-VMHdm injection of bicuculline (BIC 40 ng/0.2 µl)	AEA (5 pmol) modulates the proaversive effects of intra-VMHdm-bicuculline treatment, through CB1 cannabinoid receptors	dos Anjos-Garcia et al. (2017)
Adult Male C57BL/6NTac mice. confronted by snake (*Epicrates cenchria assisi*)	Vehicle or Anandamide (0.5, 5 or 50 pmol) intra-DMH and AM251 (at 100 pmol) and 6-I-CPS (at 3 nmol)	Anandamide exerts panicolytic-like effect in the DMH (CB1 receptors)	dos Anjos-Garcia; Coimbra (2019)
Adult C57Bl/6J wildtype (WT) mice	Vehicle or CBD (20 mg/kg, ip) for 6 weeks	Prolonged use of CBD did not affect anxiety behavior, did not influence motor performance, acoustic startle response, spatial learning and long-term memory as well as memory and recognition of new objects, reduced locomotor activity in the open field and did not affect the number of hippocampal neurons.	Schleicher et al. (2019)
Wistar rats in a state similar to a panic attack	Vehicle or CBD (25, 50, and 100 nmol) intra-VMH and NMDA (at 6 nmol) and AM251 (at 100 pmol)	CBD causes panicolytic-like effects and decreased unconditioned fear-induced antinociception	Khan et al. (2020)
Clinical studies			
Study features	**Treatment**	**Main findings**	**Reference**
Placebo-controlled double-blind study (n=40)	Placebo or CBD (300 mg), diazepam (10 mg) or ipsapirone (5 mg)	CBD attenuated anxiety after test. Ipsapirona and CBD causes anxiolytic effect in humans volunteers	Zuardi et al. (1993)
Randomized, placebo, double-blind study. (n=10)	Placebo or CBD (400 mg)	CBD decreased subjective anxiety and causes increased mental sedation. CBD has anxiolytic effect, mediated by limbic and paralimbic brains areas	Crippa et al. (2004)
Randomized, placebo, double-blind study. (n=60)	Placebo or CBD (100, 300, and 900 mg), clonazepam (1 mg)	The acute administration of CBD produced anxiolytic effects with 300 mg, but not other doses in the post-speech phase	Zuardi et al. (2017)
Randomized, double-blinded, placebo-controlled, crossover study. (n=24)	Placebo or CBD (400 mg)	CBD decreased anxiety and tremor amplitude in patients with PD	de Faria et al. (2020)

AEA – Anandamide; CBD – Cannabidiol, DMH - Dorsomedial hypothalamus, NMDA - N-methyl-D-aspartate, PD - Parkinson's disease, VHM - Ventromedial hypothalamus VMHdm - Dorsomedial division of the ventromedial hypothalamus.

Dronabinol, nabilone, CBD and nabiximols attenuate anxiety levels, but these results are considered weak or very weak evidence, according to the meta-analysis by Bilbao and Spanagel (2022). However, there is information about the mechanisms of action of cannabinoids, especially CBD, in anxiety disorders (Schier et al., 2012, Black et al., 2019, Elsaid et al., 2019, Larsen and Shahinas, 2020, Sarris et al., 2020, Skelley et al., 2020). Its therapeutic effect seems to be related to several receptors signaling, such as $TRPV_1$, PPARy, $5\text{-}HT_{1A}$, CB1 and GPR55 receptors (Zygmunt et al., 1999, Bouaboula et al., 2005, Russo et al., 2005, O'Sullivan, 2007, Ryberg et al., 2007, Silva-Cardoso et al., 2021). Figure 2 shows the potential of CBD for modulating panic-like responses.

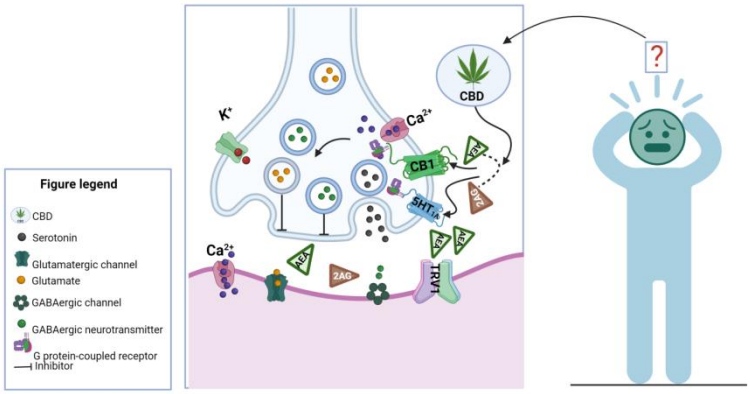

Figure 2. Potential of CBD for modulating panic-like responses. Diagram showing the potential of CBD in mitigating panic-like behaviors. These effects may be partially dependent on the recruitment of $5\text{-}HT_{1A}$ receptors. Furthermore, AEA has been associated with endocannabinoid system modulation in the attenuation of panic-like responses modulated by TRPV1 and CB1 receptors. With the activation of CB1 receptors, there is a reduction in calcium influx and inhibition of neurotransmitter release. 2-AG, 2-arachidonoyl-glycerol; $5\text{-}HT_{1A,}$ serotoninergic receptors of the $5\text{-}HT_{1A}$ type; AEA, anandamide; CB1, cannabinoid receptor 1; CBD, cannabidiol; TRPV1, transient receptor potential vanilloid 1 (Created with BioRender.com).

Perspectives: medical cannabis in depression and anxiety

Cannabis sativa is traded and consumed for a variety of purposes, depending on local culture and regulations (Bonini et al. 2018). In this review, the therapeutic potential in depressive and anxiety disorders was examined.

In this context, the highlights have been the cannabinoids, THC and CBD. Several strategies involving preclinical and clinical research have reinforced the role of CBD in anxiolytic and antipsychotic activities, as well neuroinflammation, neuroprotection and anti-apoptotic, antiepileptic, anxiolytic, antipsychotic effects. However, there is a need for studies on the molecular, cellular and behavioral mechanisms resulting from the interaction with a complex expanded endocannabinoid system.

The role of CBD as a CB2 receptor inverse agonist, AEA reuptake inhibitor and non-competitive negative allosteric modulator of the CB1 receptor is known (dos Santos et al., 2021). A possible action of CBD in neutralizing the effects of THC has been discussed and it is expected that such interaction mechanisms will be addressed in future studies.

In addition to CBD and THC, the cannabis plant produces a multitude of molecules, including various phytocannabinoids and additional compounds such as terpenoids and flavonoids. Studies seek to test hypotheses regarding the use of the whole plant extract because of a possible entourage effect, instead of using pure cannabinoids, which are more standardized and reproducible (Chacon et al., 2022).

Much research still needs to be done, requiring preclinical studies that mimic the pathological conditions and double-blind, randomized, placebo-controlled clinical trials so that robust data allow conclusions based on scientific evidence.

AUTHOR'S CONTRIBUTIONS

Maria de Fátima dos Santos Sampaio: writing, reviewing and figures design. Yara Bezerra de Paiva, Lucas Emmanuel Lopes e Santos, Frederico Velasco Costa Sanguedo and Fernanda da Silva Neves: writing. Messias Gonzaga Pereira and Norberto Cysne Coimbra: writing, revised and supervised. All authors have read and approved the final version of the manuscript.

ACKNOWLEDGMENTS

This work was supported by the Fundação de Amparo à Pesquisa do Estado de São Paulo (FAPESP) (Research Grant 2020/15050-7), Fundação de Apoio ao Ensino, Pesquisa e Assistência do Hospital das Clínicas da Faculdade de Medicina de Ribeirão Preto da Universidade de São Paulo (FAEPA) (Research Grant 374/2022), and Pro-Rectory of the University of São Paulo (USP) Research Grant (NAP-USP-NuPNE; process IaPq2012-156-USP-12.1.25440.01.6). M. de Fátima dos Santos Sampaio is a postdoctoral researcher supported by CNPq (PDJ grant 155489/2018-6). N.C. Coimbra is a researcher from CNPq (PQ1A-level grants 301905/2010-0 and 301341/2015-0; PQ2-level grant 302605/2021-5). Each organization had no role in the study design; the collection, analysis, and interpretation of the data; the writing of the report; or the decision to submit the paper for publication. All figures in the manuscript were created with BioRender.com.

CONFLICTS OF INTEREST

The authors declare no conflict of interest.

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