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Phyto Cannabinoids and Terpenoids for Treating Anxiety as an Alternative to Other Anxiolytics

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Abstract

Introduction: Anxiety disorders are clinical conditions marked by fear, uncertainty and worry. Cannabinoids are compounds derived from the Cannabis sativa plant which are recently decriminalized for the treatment of health conditions, which brought important therapeutic potential for these anxiety disorders. The objective was to synthesize the most recent data regarding the treatment of anxiety disorders with cannabinoids.

Material & Methods: It is a literature review based on the PRISMA method with a search for articles performed in the PubMed database, using the descriptors cannabidiol, terpenes and anxiety disorders. As eligibility criteria for articles, meta-analyses, observational studies, systematic reviews and randomized clinical trials with adult patients who had a diagnosis of anxiety were selected. No language restrictions were imposed.

Results: Although the mechanism by which cannabidiol exerts this effect remains unclear, it was seen that the activation of CB1 receptors in the amygdala can prevent the consolidation of negative memories and the activation in the prefrontal cortex elevates serotonin levels. As clinical results it was seen that: THC could be used as a therapeutic option for PTSD (Reduction activity amygdala related threat; Average reduction of nightmares; Reduction answer in conductance of skin for one stimulus conditioned previously extinct.); Galphimia glauca showed better results than other non-benzodiazepine anxiolytics such as tricyclic antidepressants and buspirones and there is no statistical difference in the therapeutic success between Galphimia and Alprazolam, but some adverse effects present in the treatment with Benzodiazepines were not reported in the therapy with Galphimia.

Conclusion: Despite the promising results found in this research, the true efficacy of terpenoids and cannabinoids in anxiety cannot yet be affirmed due to major methodological limitations in the present studies, which points to the need for further studies in this field.

Keywords: Anxiety; Anxiety disorders; Cannabidiol; Cannabinoids; Dronabinol; Terpenes

Introduction

Anxiety disorders are clinical conditions marked by fear, uncertainty and worry, which can start before or after adulthood. Social factors like drug use and socioeconomic conditions can contribute to the onset of the clinical presentation. In addition, they are often associated with comorbidities such as hypothyroidism, cardiovascular disease, and depression [1]. The exact pathophysiology of these conditions is unknown. However, neuroimaging studies show that its genesis is related to specific areas of the brain, which constitute the limbic system. Besides, there is a key role for some neurotransmitters, such as serotonin, gamma-aminobutyric acid, norepinephrine and dopamine, which can often be targeted by pharmacological therapies [2]. The latest edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-5-TR) classifies Generalized Anxiety Disorder (GAD), panic disorder (PD), Social Anxiety Disorder (SAD), Specific Phobia (SP), and Separation Anxiety Disorder (SEPAD)

as anxiety disorders. Post-traumatic stress disorder (PTSD) and obsessive-compulsive disorder (OCD) are found in specific chapters, but they share characteristic symptoms of an anxiety exacerbation. The recent decriminalization of cannabinoid-based compounds for the treatment of health conditions, associated with the growing publication of scientific papers and research, has brought important therapeutic potential for these anxiety disorders. It is also possible to notice that the recreational use has made many people believe that these components have undeniable therapeutic properties [3]. Cannabinoids, like many other substances, are compounds derived from the Cannabis sativa plant. More than 400 known substances originate from it, among which 140 cannabinoids have been studied [4,5]. It is also important to report the increase in the production of synthetic cannabinoids with standardized content and dosages of tetrahydro cannabidiol, cannabidiol, purified oils and derivatives of other synthetic cannabinoids [6]. In addition, a wide variety of terpenes, which are volatile organic compounds derived from plants, can cause a range of physiological effects [7]. Data from clinical and preclinical studies already show the therapeutic potential of these substances, which have demonstrated, in vitro and in animal models, anticonvulsant, anti-inflammatory, antioxidant, antiemetic, analgesic, antiarthritic and anxiolytic activity [8,9]. The objective was to synthesize the most recent data regarding the treatment of anxiety disorders with cannabinoids, to raise discussions about the therapeutic potential of these substances and the difficulties of their implementation in the world scenario.

Material & Methods

Search Strategy

A search for articles was performed in the PubMed database, using the descriptors cannabidiol, terpenes and anxiety disorders, they were combined by the Boolean operators “and” and “not”, in such a way that it was possible to find studies that associated anxiety disorders exclusively with cannabidiol or with terpenes and studies that associated them with both substances**.**

Screening and eligibility of studies

The reading of the title and abstract was performed by 5 authors and the articles that passed through this filter were selected for reading in full text. Any uncertainties were discussed and reviewed by the lead author. As eligibility criteria for articles, meta-analyses, observational studies, systematic reviews and randomized clinical trials with adult patients (18-60 years) and who had a diagnosis of anxiety were selected. Studies dealing with different types of cannabinoids were also considered, including cannabidiol and delta-9-tetrahydrocannabidiol, as well as solutions containing substances derived from terpenes and terpenoids. No language restrictions were imposed. Those studies that did not address a relationship between terpenes and/or cannabidiol for the treatment of anxiety disorders were eliminated. Still, the PRISMA method was used for the textual and methodological construction of the article.

Results

Flowchart of included studies

A total of 96 articles were found in the PubMed database. With these studies, the title and abstract were read, considering the eligibility criteria. Therefore, 61 articles were excluded. After this step, the full text reading of the filtered articles began and another 15 articles were eliminated. Therefore, 20 studies were used for the present review (Figure 1). 96 studies were found in the PubMed database. After the elimination step from reading the title and abstract and full text, 20 studies were selected.

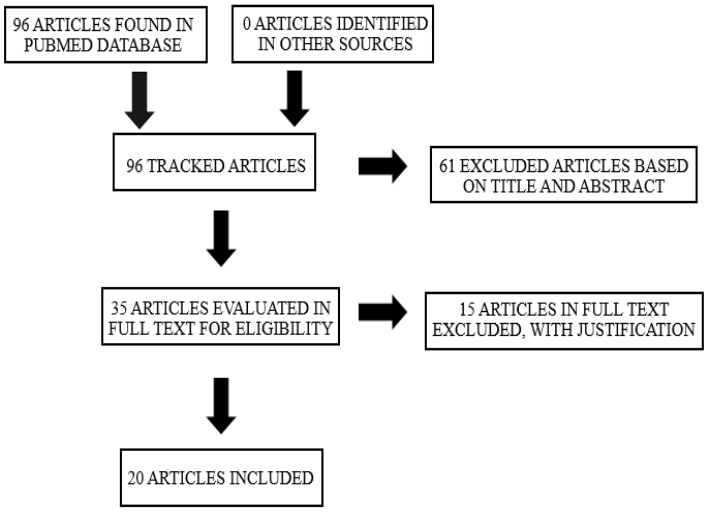

Figure 1: *Flow diagram of study selection.*

Neural basis of cannabinoid treatment

The mechanism of action behind the treatment of anxiety disorders with cannabinoids is not yet fully understood, due to the plurality of compounds based on synthetic and natural cannabinoids and their different interactions with the endocannabinoid system, with cytochrome P450 and other receptors in the Central Nervous System (CNS). Recent studies point to an anxiolytic action of cannabinoids, which is why they have a therapeutic potential for psychiatric diseases. However, the mechanism by which cannabidiol exerts this effect remains unclear. In tests with an animal model, it was found that this compound does not interact with benzodiazepine receptors, but with CB1 and CB2 receptors, which are part of the endocannabinoid system [10]. This interaction can also occur with other substances derived from cannabis - such as THC - and with endocannabinoids. Activation of these CB1 receptors in the amygdala can prevent the consolidation of memories that produce

feelings of fear and anxiety. Furthermore, this activation in the prefrontal cortex elevates serotonin levels, thus being a therapeutic potential for depression [11]. In an experimental study with 10 young adults aged between 20 and 33 years, diagnosed with GAD, it is suggested that the central action of CBD in the treatment of GAD aims its action in limbic and paralimbic pathways. These results were evidenced by monitoring cerebral blood flow after oral administration of CBD (400mg) and it was observed that there was an increase in specific brain areas such as the right posterior cingulate gyrus. In a review conducted by Rosolino, this limbic and paralimbic stimulation was found to reduce the state of hypervigilance and hyperarousal in important mood modulating canters such as the amygdala and hypothalamus However, it should be noted that CBD has low affinity for CB1 and CB2 receptors when compared to THC. Studies show that at low doses, CBD has antagonistic action on these receptors. In addition, it exerts a negative allosteric modulating effect on the CB1 receptor, which affects the binding of other molecules to it (Δ9-THC and 2-arachidonoylglycerol). Finally, it can also affect the endocannabinoid system by increasing the availability of anandamide, by inhibiting Fatty Acid Amide Hydrolase (FAAH) [12].

Clinical Results

THC as a treatment for PTSD

The pooled analysis of 3 clinical trials addressing cannabinoid treatment for trauma-exposed individuals with or without PTSD reveals a promising therapeutic potential in THC - in synthetic formulations - for the reduction of nightmares and threat-related amygdala reactivity, in addition to stimulating the memory of extinction associated with fear. In a double-blind, placebo-controlled RCT, Rabbinic demonstrated that THC administration in trauma-exposed patients increased the functional connectivity of the medial prefrontal cortex and the anterior cingulate cortex with the bilateral superficial subdivision of the amygdala, under conditions of non-threatening stimuli, when compared to placebo (PBO) (Table 1) [13]. However, there was no difference in this activation between THC and PBO in threatening conditions - stimulation by the visualization of faces and figures. Furthermore, THC decreased bilateral amygdala activation in non-trauma and exposed subjects with or without PTSD when compared to PBO. These findings are in line with data suggesting that reaction time to threatening conditions is faster in individuals allocated to the group that ingested THC. Similar results are presented in another double-blind RCT, in which subjects with treatment-refractory PTSD received formulations of Nabilone - a synthetic cannabinoid - titrated to a maximum of 3.0 mg and were compared with a PBO group. The final outcome was assessed by the mean reduction in nightmares and the Clinical Global Impression of Change scale. This study demonstrated significant symptom relief [14]. However, further studies with larger samples are needed to expand the level of evidence, since this was carried out with 10 participants. Furthermore, data presented by Rabbinic suggest that the action of THC on CB1 receptors may facilitate fear extinction memory in humans, as already seen in animal models [15].

Table 1: *RTCs with THC formulations for PTSD treatment.*

Reference	Outline	Dosage and formulation	Outcome
Rabinak et al (2020) [a]	Double-blind RCT and controlled by placebo.	Dronabinol at 7,5 mg.	Reduction activity amygdala related threat.
Jetly et al (2015)[b]	Double-blind RCT and controlled by placebo.	Nabilone at 0.5 mg and titrated to an effective dose or maximum dose of 3.0 mg.	Average reduction of nightmares.
Rabinak et al (2013)[c]	Double-blind RCT and controlled by placebo.	Marinol at 7,5 mg	Reduction answer in conductance of skin for one stimulus conditioned previously extinct.
RTCs, Randomized clinical trails; THC, tetrahydrocannabidiol; PTSD, Post traumatic stress disorder.			

In this study, patients underwent 15 presentations on computer screens for fear acquisition. After stimulus withdrawal, for memory extinction, patients were allocated to therapy with synthetic formulations of THC or PBO. It was noticed that the THC group had lower rates of spontaneous recovery of fear memory after previously extinguished conditioning stimuli, unlike the PBO group, which showed spontaneous recovery.71 participants were included in final analyses' A sample of 10 men with a mean age of 43.6 years ± 8.2 (median 44) was used. At screening, all had an initial global impression of PTSD severity of

3.3 ± 0.9 (4 = extreme).c Twenty-nine healthy volunteers participated in this study and were randomly assigned to the THC (n = 14) or placebo (n = 15) condition.

Terpenoids *vs* Benzodiazepines in the treatment of GAD

Two studies (Table 2) evaluated the effectiveness of formulations based on Gallophilia (GP), a compound isolated from Gallophilia glauca, compared to drugs of the benzodiazepine class. The results found in the RCT with 10 weeks of therapy reveal that there is no statistical difference in the therapeutic success between both substances, with Alprazolam as control [16]. In the RCT with 15 weeks of therapy, it was noted better anxiolytic activity of the experimental drug compared to Lorazepam (control group), with high percentages of safety and tolerability [17]. Still, it is necessary to consider that some adverse effects (AE) present in the treatment with Benzodiazepines were not reported in the therapy with Galphimia. The intensity of these effects is also an important factor to be considered, since 73.6% of the AEs reported in PG therapy were of mild intensity. In the control group, in which patients received Alprazolam, 52.5% were of moderate intensity. Among them, what stands out the most is daytime sleepiness, as it was the reason for dropping out of the study for some participants.

***Table 2**: Comparison between Galphimia and Benzodiazepine therapy for GAD.*

Reference	Outline	Experimental regime	Control regime	Outcome
Romero-Cerecero et al (2019)[a]	RCT double blind and controlled by Alprazolam..	Daily dose of extract standardized from Galphimia (0.374 mg/dose) per 10 weeks.	Daily dose of Alprazolam mg/dose) for 10 weeks.	Decreased Hamilton scale score.
Herrera-Arellano et al (2012)[b]	RCT double blind and controlled by Lorazepam. .	0.350 to 0.700 mg of extract standardized from Galphimia divided in 2 doses daily during 15 weeks[c].	Lorazepam 0.5 mg with the same presentation and dosage of group experimental.	Reduction ≥ 50% at Hamilton scale score.
Andreatini et al (2002)[d]	RCT double blind and controlled by Placebo.	Capsules containing 50 mg of valepotriates were administered 3 times/day during 4 weeks.	Capsules containing 2,5 mg of Diazempam or Lactose (placebo) were administered 3 times/day during 4 weeks.	Decreased Hamilton scale score.
GAD, Generalized anxiety disorder; RTC, Randomized clinical trail				

Regarding the onset of anxiolytic effect, therapy with medicinal herb products Gallophilia glauca showed better results than other non-benzodiazepine anxiolytics such as tricyclic antidepressants and buspirones. In addition, around the 6th week of treatment, Gallophilia showed similar effects to other anxiolytics of the selective serotonin reuptake inhibitor class, such as Paroxetine and Escitalopram, and selective serotonin and noradrenaline reuptake inhibitors, such as Duloxetine. These effects were assessed using the Hamilton scale. One trial also compared benzodiazepines with other terpenoids from the Valepotriate group (Table 2). This was a pilot study that evaluated the anxiolytic effect of this terpenoid through a double-blind placebo-controlled RCT in which participants received formulations with Valepotriates, Diazepam or Placebo. The results found reveal that there is no significant difference between the three groups in the reduction of the Hamilton scale score. In addition, no moderate to severe adverse effects were reported [18]. 167 participants were included in this study. The experimental group consisted in 84 patients' 191 participants were included in this RTC and 94 in the experimental group. C 12 weeks of full treatment, plus 2 weeks on a tapered dose and 1 week without the drug. D 36 patients were included in the study, with 12 allocated to each group.

CBD for the treatment of SAD

A randomized, double-blind, placebo-controlled trial of CBD at 600 mg suggests that pre-treatment with this cannabinoid reduced

anxiety, speech deficits, and increased attention spans in subjects exposed to a simulation test for speak in public. This study was carried out with 24 participants; 12 in the placebo group. In addition, all subjects were treatment-naive and had not used marijuana more than 5 times in their lives [19].

Discussion

Although the mechanism behind the action of the cannabinoid system in the treatment of anxiety disorders is not entirely clear, some actions of compounds based on Cannabis sativa, terpenes and synthetic terpenoids make them important agents to be studied, due to its anxiolytic effects shown in animal models and in vitro. However, most of the included studies were carried out with small samples and for a short period of time (< 1 month), which makes it impossible to build a good level of evidence for the use of this therapy. In this scenario, doctors and other healthcare professionals may feel unsafe to prescribe medications based on synthetic cannabinoids or terpenoids for the treatment of anxiety disorders. Furthermore, studies reveal that the use of cannabinoids can be paradoxical in the treatment of these disorders, because the effectiveness of the therapy depends on the dosage. Therefore, at certain plasma concentrations, compounds based on THC or CBD can cause disorders and negative social consequences [20]. In this sense, CBD-based compounds have been studied for the treatment of SAD and the results are positives. One of the studies reveals that CBD reduces anxiety and speech impairment and increased attention levels in individuals who underwent public speaking tests. However, this study has methodological limitations, such as the relatively small number of participants. Furthermore, plasma CBD levels were not measured, which made it impossible to compare this parameter with its clinical effects. But, despite such limitations, the study provides unprecedented information about this therapy and prompts the development of new related research. Clinical data also suggest that synthetic THC-based formulations have therapeutic potential for PTSD and associated traumatic conditions. In animal models, it is noted that these compounds act in such a way to reduce the state of fear after a threat situation. In this sense, experimental studies suggest that the mechanism behind this therapy is against the neurological modulation of THC in the subdivisions of the insula (superficial, basolateral, amygdalostriatal and centromedial). Based on the analysis of the results of 3 clinical studies, it can also be seen that the treatment with terpenoids has shown significant therapeutic potential, considering the anxiolytic effect close to or greater than the large portion of anxiolytics approved for the treatment of anxiety disorders. In addition, it is perceived that GP is an important therapeutic agent with regard to the safety and tolerance of this drug. It is noted that, compared to other anxiolytics, GP has fewer adverse effects. The low rates of daytime sleepiness reported by the use of GP and its high percentage of tolerance make it an important alternative to benzodiazepines for the treatment of psychological disorders, since, by acting on GABAergic receptors, they cause depression of the CNS, in such a way that daytime sleepiness and the sedative effect make it difficult for patients to adhere to treatment. In addition, BZPs have a significant propensity for dependence and are related to an increased risk of falling in elderly patients. On the other hand, GP has an evidently different mechanism of action in relation to BZP Published studies reveal that this medication does not act in a relevant way on GABAergic receptors, but on specific regions of the brain, such as the Ventral Integumentary Area and the dorsal Hippocampus, which justifies the difference between the adverse effects of both substances compared. A randomized, placebo-controlled clinical trial also evaluated the anxiolytic effect of Valepotriates (valtrate, acevaltrate and didrovaltrate) in GAD. These substances are the main active components derived from Valerian extracts. Some studies with animal models reveal an anxiolytic and sedative effect of these compounds. This RTC, performed by Andreatini , suggests that terpenoids from the Valepotriates group do not have statistical significance in reducing the score on the Hamilton scale, compared to BZP and PBO. However, the study was carried out with a low number of participants, which increases the probability of type II statistical error. In addition, the standard doses of medication ingested by patients are lower than those recommended for therapy for this condition, which may have caused a bias in the therapeutic potential of the drugs in question

Conclusion

This study promoted a review of the neurological and pharmacological aspects involving the treatment with terpenes and terpenoids and/or derivatives of Cannabis sativa. It is noted that synthetic formulations based on THC are potential therapeutic agents for PTSD. In addition, it can be seen that Galphimia is an important therapeutic alternative to benzodiazepines and other anxiolytics for the treatment of anxiety disorders, since it has equal or greater efficacy and a significantly lower incidence of adverse effects. Furthermore, more studies need to be carried out to elucidate questions regarding the mechanism of action of these compounds in the CNS and their interaction with the Endocannabinoid System. Finally, despite the promising results found in this research, the true efficacy of terpenoids and cannabinoids in anxiety cannot yet be affirmed due to major methodological limitations in the present studies, which points to the need for further studies in this field.

Acknowledgments

None.

Conflicts of Interest

There are no conflicts of interest.

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