Life Sciences 224 (2019) 120–127

Contents lists available at ScienceDirect

Life Sciences

journal homepage: www.elsevier.com/locate/lifescie

Review article

Cannabidiol: Recent advances and new insights for neuropsychiatric disorders treatment

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ARTICLE INFO

Keywords:
Cannabidiol
Cannabis sativa
Epilepsy
Psychiatric disorders

ABSTRACT

The pharmacological research on the *Cannabis sativa*-derived compounds has never terminated. Among the phytocannabinoids without psychotropic effects, the prevalent one in *Cannabis* is cannabidiol (CBD). Although CBD was initially considered a type 2 cannabinoid receptor (CB2R) antagonist, it did not show a good cannabinoidergic activity. Furthermore, heterogeneous results were obtained in experimental animal models of anxiety disorders, psychotic stages and neurodegenerative diseases. Recently, CBD has been authorized by the FDA to treat some rare forms of epilepsy and many trials have begun for the treatment of autism spectrum disorders.

This review aims to clarify the pharmacological activity of CBD and its multiple therapeutic applications. Furthermore, critical and conflicting results of the research on CBD are discussed with a focus on promising future prospects.

1. Introduction

Humankind has associated the use of *Cannabis sativa* (*C. sativa*) to its therapeutic virtues owing to the more than 100 phytocannabinoids present [1]. However, modern medicine has yet to define the potential therapeutic applications of cannabis phytoextracts. Indeed, licensed clinical use of *C. sativa* phytochemicals remains limited to a small number of diseases such as colitis, pain in multiple sclerosis, appetite stimulation in AIDS and cancer chemotherapy [1]. These pathological conditions benefit from the action of trans-Δ9-tetrahydrocannabinol (D9-THC), which is also responsible for psychoactive side effects [1]. Indeed, the psychoactive responses of D9-THC include anxiety, paranoia, perceptual alterations, and cognitive deficits; they are caused by the perturbation of GABA/glutamatergic neurotransmission and dopamine release [2]. Currently, this is the reason why, today, neurobiological research on *C. sativa* is complex and difficult, and consequently, its cultivation and use are illegal/banned in most of the countries [3]. Recently, preclinical and clinical trials on cannabidiol (CBD), a phytocannabinoid devoid of psychoactive effects, have highlighted encouraging results. Indeed, CBD is the second most abundant phytocannabinoid after D9-THC and it represents a potential pharmacotherapy for treating symptoms of various neuropsychiatric disorders such as addiction, anxiety and psychosis, disorders of motility, and epilepsy [4–11]. However, despite the therapeutic utility of CBD, its specific pharmacological mechanism remains not entirely clear. Indeed, CBD in addition to interacting with the endocannabinoid system (ECS), it can also act on serotonin, adenosine, dopamine and opioid receptors [12,13] behaving as a multi-target drug.

Here, the synthesis and metabolism of CBD in *C. sativa* will be initially evaluated. Furthermore, the latest evidence on the interaction between CBD and the ECS will be analyzed. Finally, a critical and comprehensive evaluation of the CBD pharmacological mechanism in several disorders will be presented.

2. Botanical origins and pharmacological activities of cannabidiol

C. sativa produces more than 100 phytocannabinoids chemically well identified and characterized. Phytocannabinoids are biosynthesized during specific extreme environmental conditions of humidity, temperature, radiation, soil nutrients, and parasites and they are accumulated in the trichomes of *C. sativa* as cannabinoid acids [1]. The plant uses phytocannabinoids as a defense against herbivores and

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https://doi.org/10.1016/j.lfs.2019.03.053
Received 13 February 2019; Received in revised form 21 March 2019; Accepted 21 March 2019
Available online 22 March 2019

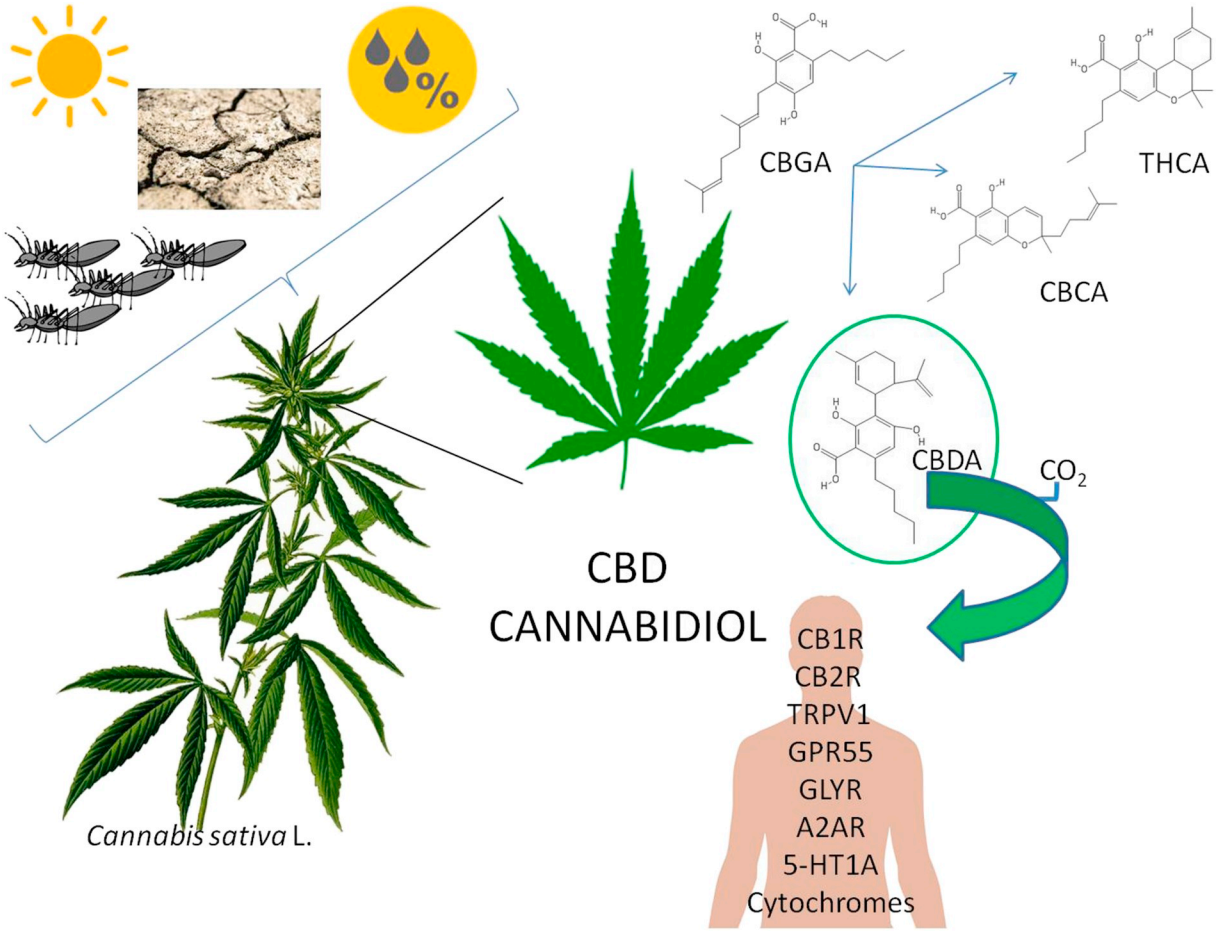

Fig. 1. Extreme environmental conditions, such as parasites, light intensity, dryness of the soil and low humidity, favor the production of phytocannabinoids such as cannabidiol (CBD). Cannabigerolic acid (CBGA) is the precursor of tetrahydrocannabinolic acid (THCA), cannabichromenic acid (CBCA), and cannabidiolic acid (CBDA). The decarboxylation of CBDA leads to the formation of CBD, which acts on different receptor systems. CBD is not naturally present in the inflorescences and conversion by decarboxylation occurs at 120 °C. CB1R, cannabinoid receptor 1; CB2R, cannabinoid receptor 2, TRPV1, vanilloid receptor 1; GPR55, G protein-coupled receptor 55; GLYR, glycine receptor; A2AR, adenosine receptor type 2A, 5-HT1A, serotonine receptor type 1A, hepatic cytochromes.

parasites, indeed it does not have receptors for them [14]. Olivetolic acid and divarinic acid are the two phytocannabinoid precursors that generate cannabigerolic acid (CBGA). CBGA is the central precursor for phytocannabinoids biosynthesis in *C. sativa*, from which tetrahydrocannabinolic acid (THCA), cannabichromenic acid (CBCA) and cannabidiolic acid (CBDA) originate [1]. CBDA forms cannabidiol (CBD), the most abundant non-psychotropic phytocannabinoid of *C. sativa* [15]. CBD was originally purified in 1940 and its structure characterized in 1960 [4] (Fig. 1). Since then, the phytoextracts have been characterized and the therapeutic potential of *C. sativa* has begun to be understood.

In order to understand the mechanism of action of CBD it is necessary to discuss how the endocannabinoid system (ECS) is organized. The ECS is composed by endocannabinoids, their receptors and the enzymes for their biosynthesis and degradation. N-arachidonoylethanolamine (AEA), also called anandamide, and 2-arachidonoyl glycerol (2-AG) are the most studied endocannabinoids, a family of fatty acid derivatives. AEA and 2-AG are synthesized on demand from membrane phospholipids and then rapidly released [16]. Several enzymes participate in the production of these endocannabinoids. N-acylphosphatidylethanolamine-selective phospholipase D (NAPE-PLD) is responsible for the hydrolysis of N-acylphosphatidylethanolamide (NAPE) and the synthesis of AEA (Fig. 2). Whereas, phospholipase C (PLC) and diacylglycerol lipase α (DAGLα) or β (DAGLβ) hydrolyse 2 arachidonic acid in 2-AG [17]. Furthermore, there are other important enzymes that regulate the degradation of AEA and 2-AG, such as fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) respectively that produce arachidonic acid and ethanolamine or glycerol [17]. Endocannabinoids interact with two G protein-coupled receptors composed by seven transmembrane domains and the intracellular C-terminal extremity and extracellular N-terminal extremity: the type 1 cannabinoid receptor (CB1R) and the type 2 cannabinoid receptor (CB2R). The CB1R is localized in the brain and in peripheral tissues such as the intestine, liver, adipose tissue and immune cells [18]. Instead CB2R is distributed on spleen, tonsil, and immune cells and recently they have been found in glial and neuronal cells [19]. In addition, AEA and 2-AG are involved in different (*i.e.*, independent to the CBR1 and CBR2) pathways interacting with non-cannabinoid receptors including the transient receptor potential vanilloid 1 (TRPV1) channel, transient receptor potential ankyrin 1 (TRPA1), the peroxisome proliferator-activated receptor-gamma (PPARγ), nuclear receptor and the orphan G protein-coupled receptor (GPR55) [18].

CBD has a very low affinity (in the micromolar range) for CB1R and CB2R [20], and nevertheless CBD is able to bind to these receptors. In addition, it antagonizes CB1R and CB2R synthetic agonist action such as that of CP55940, in the nanomolar range; this concentration is lower that the concentration necessary for CBD to interact with the cannabinoid receptors, due to the action at different prejunctional sites [21,22]. Moreover, recently CBD has been considered an allosteric negative modulator of CB1R and CB2R, and it highlighted a pharmacological promiscuity towards many receptors. Indeed, CBD interacts with numerous non-cannabinoid receptors associated with G proteins

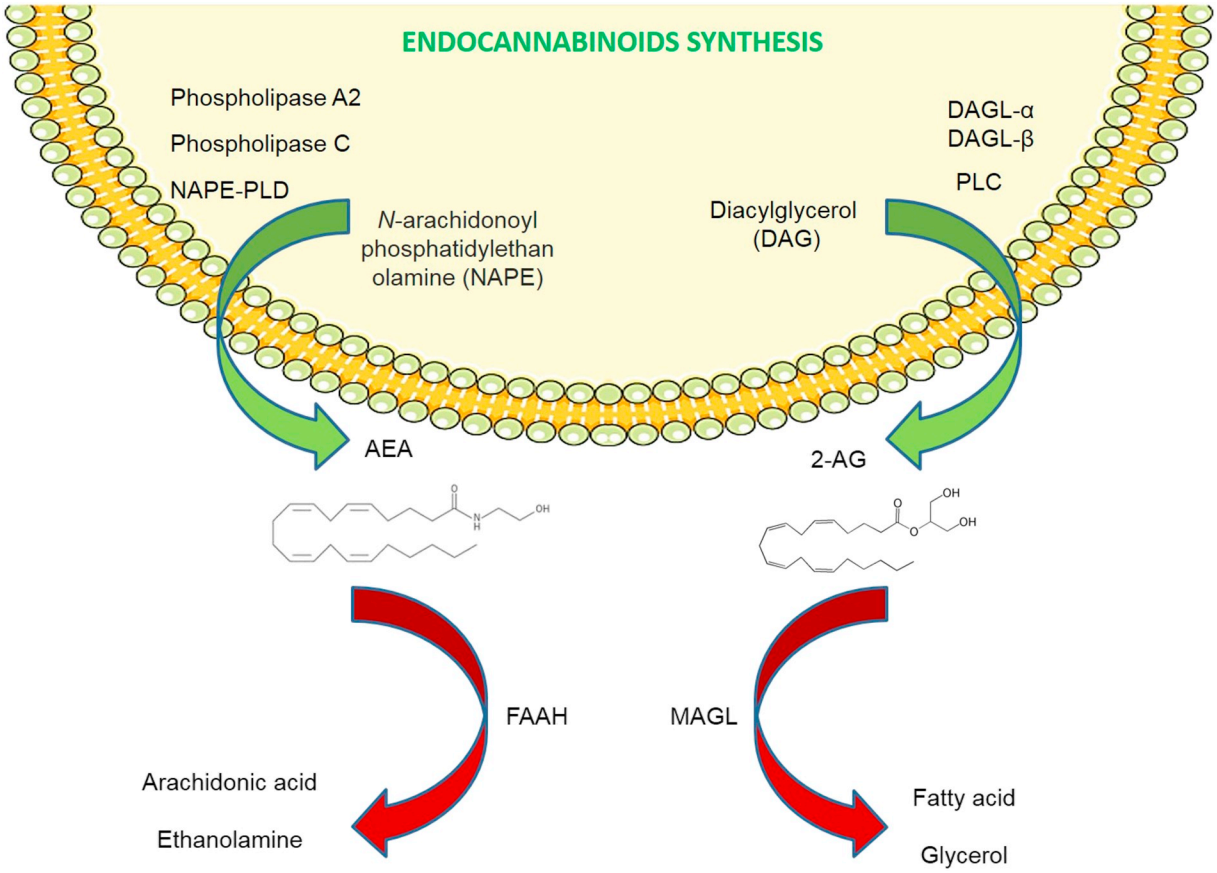

Fig. 2. N-arachidonoylethanolamine (AEA) and 2-arachidonoyl glycerol (2-AG) are synthesized on demand from membrane phospholipids and released. N-acylphosphatidylethanolamine-selective phospholipase D (NAPE-PLD), phospholipase A2 and phospholipase C enzymes synthesize AEA from N-acylphosphatidylethanolamide (NAPE). Phospholipase C (PLC) and diacylglycerol lipase α (DAGLα) or β (DAGLβ) synthesize 2-AG by hydrolyzing 2-arachidonic acid containing diacylglycerol (DAG). Fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) are degradation enzymes of AEA and 2-AG respectively.

(GPCR) but it does not have a high affinity as observed for serotonin receptor 5-HT1a [23]. In addition, high concentrations of CBD are able to modulate allosterically glycine receptors activated by specific ligand by influencing the role of glycine in post-synaptic transmission [24]. Furthermore, the protective effect of CBD is partially stopped in the inflammatory early stages by administering adenosine A2a receptor antagonists [25]. Also, in models of acute central nervous system (CNS) injury, CBD decreases neuroinflammation through adenosine A2a receptor stimulation [25]. CBD has also immunity functions, by reducing the leukocytes transmigration and down-regulating the expression of the vascular cell adhesion molecule-1 (VCAM-1). Furthermore, a reduced activation of microglia and reduced expression of chemokine ligand 2 (CCL2), chemokine ligand 5 (CCL5) and Interleukin 1 beta IL-1β has been observed after CBD treatment in murine models [25]. Lastly, CBD shows a high affinity towards transient receptor potential (TRP) channels, in particular towards TRPV1 and TRPV2 receptors [26].

Finally, CBD is able to modulate different enzymes belonging to the cytochrome P450 (CYP450) family, the main enzymatic system involved in the metabolism of phase 1 of xenobiotics [27]. In particular, CBD can inhibit CYP2C19 and may be involved in the therapeutic effects of some brain disorders, such as epilepsy, psychosis and neurodegeneration. CBD completely inhibits CYP29C and CYP2D6 and has a strongly inhibitory action on the CYP1 family, in particular on CYP1A1, CYP1A2 and CYP1B1. Finally, CBD inhibits members of the CYP3 family such as CYP3A5, CYP3A4 and CYP3A7 [27].

3. Therapeutic actions of cannabidiol

While the preclinical and clinical aspects of D9-THC and its derivatives have been studied extensively [28–34], on the CBD only recently a lot of data has been collected. Here the effects of CBD in the treatment of some psychiatric disorders will be discussed (Table 1).

3.1. Epilepsy

Epilepsy belongs to neurodevelopmental disorders with a predisposition to generate epileptic seizures, and neurobiological, cognitive, psychological and social alterations [35]. Recent clinical studies have shown that CBD reduces seizure frequency in patients with refractory epilepsies [36–38] although some limitations have been highlighted [36,39,40]. Among these refractory epilepsies, the most studied are the Dravet syndrome (DS) and Lennox-Gastaut syndrome (LS).

DS is a severe childhood disorder characterized by treatment-refractory epilepsy, autism, severe cognitive deficits and frequent premature death [41]. DS is caused by heterozygous loss of function mutations in the cerebral voltage-gated sodium channel (SCN1A) [42], which selectively reduces sodium current and excitatory drive in many types of GABAergic interneurons [43]. Scn1a$^{+/-}$ mice are a murine model of DS. They manifest symptoms of human DS such as spontaneous and thermally induced seizures, and autism-like social deficits [44]. It has been demonstrated that high doses of CBD (100 mg/kg) effectively reduce the frequency, duration and severity of seizures and autism-like social deficits in DS mice, but low doses of CBD (10–20 mg/kg) enhance social behaviors [45]. These results have revealed the difficulty to design a treatment for DS that is able to control both

Table 1
Diseases and CBD doses in several preclinical and clinical trials.

Diseases	Doses and duration of CBD treatment	Rodents/human	Effects	References
Epilepsy	10–20 mg/kg, daily for 14 weeks	Human	Reduced the frequency of drop seizures in Lennox-Gastaut and Dravet syndromes	[36,38,49]
Psychotic disorders	600 mg/kg, daily for 3 weeks	Human	Normalization of brain dysfunctions in individuals at clinical high risk of psychosis	[87]
Parkinson's disease	75–300 mg/kg, daily for two weeks	Human	CBD significantly improves the quality of life in PD patients	[88]
Anxiety disorders	1–15 mg/kg, acute	Rat	Improvement of contextual fear conditioning deficit	[60,89]
Post-traumatic stress disorder	10 mg/kg, acute	Rat	Therapeutic benefits for disorders related to inappropriate responses to traumatic memories	[90]
Autism spectrum disorders	10–20 mg/kg, acute	Mouse	Improvement of social behaviors	[45]
Depression	10 mg/kg, acute and sub-chronic	Mouse	Antidepressant-like effects in mice submitted to forced swimming test	[7]
Alzheimer's disease	20 mg/kg, sub-chronic	Mouse	CBD reverses cognitive deficits in object recognition memory and social recognition memory	[91]

seizures and improve social behaviors [45]. Allegedly, these effects are dependent on different molecular mechanisms originated from various doses of CBD. Indeed, CBD at high doses acts as an antagonist on lipid-activated G protein-coupled receptor 55 (GPR55), modulating the hippocampal synaptic plasticity [46]. Moreover, CBD (100 mg/kg) restores inhibitory interneuron excitability in the dentate gyrus of the hippocampus and reduces excitatory output from neurons of dentate gyrus by enhancing GABA-A receptor-mediated inhibition [47].

Regarding Lennox–Gastaut syndrome (LS), it is a severe developmental epileptic encephalopathy that has multiple causes and an incidence of approximately two cases per 100,000 population [48]. LS is characterized by several seizure types, severe cognitive impairment and abnormal electroencephalographic pattern of slow spike and complex waves [48]. Seizures usually begin to occur before the age of 8 years and persist into adulthood in more than 90% of patients. Drop seizures due to an increase or loss of motor tone are characteristic of this disorder and often result in serious injury. A promising new drug for LS is CBD, which has proved effective in reducing the frequency of seizures in animal models of epilepsy. It was seen that both children and adults with LS, treated with a purified pharmaceutical form of CBD at doses of 10 mg/kg or 20 mg/kg daily showed a considerable reduction in the frequency of drop seizures than placebo [49]. Moreover, CBD (20 mg/kg) appeared to be a safe drug because the most common adverse events were somnolence, decreased appetite and diarrhea [49]. However, in some patients treated with CBD (20 mg/kg) and valproate, an increase in hepatic aminotransferase concentrations was seen. This effect could depend on a pharmacodynamic interaction between CBD and valproate [49]. In 2018, CBD Epidiolex received FDA approval for the treatment of epileptic seizures associated with LS and DS in 2-year-old patients.

3.2. Autism spectrum disorders

Autism spectrum disorders (ASD) are characterized by social behavioral deficits and neuropsychiatric symptoms. Even today the etiopathogenesis of ASD is not known, but recently the idea that alterations in neurodevelopment during pregnancy could be the cause of ASD is prevailing [50]. Indeed, neuroanatomical and cytoarchitectonic abnormalities were observed in many brain regions, such as the cortex, cerebellum, hippocampus, amygdala [51]. Moreover, several studies have suggested that social deficits come from inadequacy in reward system functioning [52]. Considering the role of the ECS in controlling emotional responses, behavioral reactivity to context and social interaction, it was hypothesized that it is involved in the autistic phenotype [53]. In addition, a recent study displayed lower plasma levels of AEA in ASD patients as compared to healthy controls, suggesting its involvement in the pathophysiology of ASD [54]. Other studies have shown an interaction between ECS and oxytocin mediated social reward. It seems that oxytocin induces AEA mobilization in the mouse nucleus accumbens contributing to social impairment in ASD [55]. It should be noted that some studies suggest that intra-nasal administration of drugs that acts on the oxytocin pathway may have therapeutic effects in ASD [52]. Thus, a possible mechanism of action of CBD is based on the activation of TRPV2 which may play a role in the regulation of oxytocin and vasopressin secretion [56]. In addition, preliminary data showed that CB2R is highly expressed in peripheral blood mononuclear cells of young children with ASD compared with controls [57].

3.3. Psychotic disorders

Psychosis literally means degeneration of the soul and it is used to describe the illness generated from alterations in the thought. These disorders involve several neurotransmitter systems and brain regions making treatment difficult and accompanied by heavy side effects for patients. Recently, the ECS seems to have an important role in these

disorders, contrary to what was previously believed. Indeed, psychotic-like symptoms seem to be produced by D9-THC and its derivatives [58].

Initial studies have shown that CBD, other than not showing psychotic symptoms, prevents some of the effects produced by D9-THC [59], supporting the idea that the CBD may have antipsychotic activity or exhibits a profile similar to atypical antipsychotic drugs. Other studies displayed that CBD reduced stereotypies induced by apomorphine, hyperlocomotion induced by amphetamine and ketamine and the perception of illusory image induced by nabilone [59]. On the contrary, in patients treated with ketamine, that induces psychotic symptoms, CBD did not reduce dissociative effects induced by ketamine, but rather augmented the effects of ketamine [60]. These contradictory data propose to investigate mainly the role of CBD in psychotic disorders. Biological mechanisms of the CBD antipsychotic effects may depend on an increase in neuronal activation (measured by cFos-protein expression) in the prefrontal cortex and also in the nucleus accumbens, effect shared by typical and atypical antipsychotic drugs [61]. In addition, cerebroventricular administration of CBD enhanced extracellular levels of dopamine in the nucleus accumbens; how it is related to the antipsychotic properties of CBD is unclear. Probably the antipsychotic-like doses of CBD are higher than those needed to induce anxiolytic effects [61]. Recently, some authors showed that schizophrenic patients treated with CBD present higher AEA serum levels compared with those that received antipsychotics, and they showed an improvement of psychotic symptoms [62,63]. Probably, CBD inhibiting FAAH activity (10 μM) increases the level of AEA, which actives CB1R. Another mechanism associated with CBD is a negative allosteric modulation of the CB1R, which could explain the protective action of CBD when it was administered with D9-THC [64].

3.4. Anxiety disorders

Anxiety is a physiological aspect of our organism that warns us when we are facing a danger. Anxiety becomes pathological when it conditions life expectancy resulting in a somatic as well as psychological symptomatology. There are many types of therapies and treatments for anxiety disorders, but not all of them are effective or devoid of side effects. Therefore, new drugs are being studied to improve these consequences.

CBD seems to have an anxiolytic effect, but the results are contradictory. For instance, CBD 100 mg/kg in rats has no effect in the Geller Seifer conflict model of anxiety as reported by a comprehensive review of Blessing and colleagues [65]. In addition, CBD 10 mg/kg attenuated conditioned emotional responses [65]. Subsequently, these apparent contradictory results have been explained. CBD promoted anxiolytic-like effects with an inverted U-shaped dose-response curve: higher doses (more than 20 mg/kg) were ineffective [66]. Further studies confirmed the anxiolytic properties of CBD also in other animal models and in humans. Clinical studies have shown that a single dose of CBD (300/600 mg/kg) reduced anxiety in healthy volunteers during neuroimaging studies or in public speaking and in never treated social phobic patients [65]. Probably, these effects could depend on changes in brains regions involved in emotional processing. These clinical findings were complemented by studies in rodents, using direct administration into brain sites related to anxiety or panic-like responses. Microinjection of CBD (15, 30 and 60 nmol) into the dorsal portions of the periaqueductal grey (DPAG) or into bed nucleus of the *stria terminalis* (BNST) promoted anxiolytic-like effects in several behavioral tests [67,68]. This effect supports results showing that the effects of CBD in a contextual fear-conditioning model was associated with decreased neuronal activation in this area [69]. This same treatment attenuated the activation of the pre and infra-limbic cortical regions. However, in these two areas, CBD produced opposite effects, decreasing and facilitating, respectively, conditioned emotional responses. Other possible brain sites of CBD anxiolytic-like effects have not yet been investigated (*e.g.*, the hippocampus).

Molecular mechanisms underlying of anxiolytic effects of CBD could be related to different molecular concentrations of the drug [92]. Moreover, CBD is proposed to activate or modify the function of many receptors in the central nervous system. Therefore, defining the role of CBD in the molecular mechanisms of anxiety is still difficult.

3.5. Post-traumatic stress disorder

Until some time ago, post-traumatic stress disorder (PTSD) was included in the classification of anxiety disorders. According to the DSM-5, PTSD is relocated from the anxiety disorders category to a new diagnostic category named “Trauma and Stressor-related Disorders”. The necessary conditions in order to develop PTSD are: direct or indirect exposure to a strong trauma, frequent involuntary and intrusive memories of the experienced trauma, persistent avoidance and denial of everything related to the trauma, general negative emotional state with constant feelings of fear, horror, anger, guilt or shame towards the world, irritable behavior, hypervigilance, exaggerated startle response, concentration problems, sleep difficulties [70]. Unfortunately there are no effective pharmacological or psychological treatments for PTSD [71]. Approved treatments for PTSD are anxiolytics and antidepressants, but they have considerable side effects and are inefficient probably because they do not specifically target the memory process [71]. For these reasons, today, the research is aiming towards new therapies, such as phytoextracts from *C. sativa*. In a proposed model of panic attacks and PTSD, CBD decreased defensive behaviors evoked by predator exposure [72]. In fact, CBD blocked trauma-related responses when given before the acquisition phase or before the phase of adverse memory recovery [73]. Other studies have shown that CBD interferes in learning and memory of aversive events, processes that have been associated with PTSD pathophysiology [74]. Contrasting with this latest result, Elbasth and colleagues have reported that repeated administration of CBD (14 days) increases state of fear rather than reducing it [75]. The reason for these conflicting results is unknown but may involve a different drug administration regime used (chronic *versus* acute) and distinct conditioning protocols compared with other studies that investigated the effects of CBD in this model. Finally, CBD can control sleep disturbances by increasing duration and depth, and decreasing anxiety as observed in some *in vivo* models [65].

Finally, CBD can facilitate the extinction of aversive memories also in humans PTSD affected, but only when it is administered immediately after, and not before, a traumatic event.

3.6. Depression

Depression is a mood disorder characterized by a permanent and constant psycho-physical illness. *C. sativa* exerts significant effects upon state of mind, such as euphoria and mood elevation [76]. Considering these observations, a supposed role for ECS in mood disorders has been proposed. However, the CBD effects on depressive symptomatology have been scarcely investigated. Probably CBD has antidepressant-like proprieties, because it actives 5HT1a receptor [7]. Indeed, some studies showed that an acute administration of CBD at high doses has antidepressant effects [76]. However, depression requires chronic treatment, so, recently CBD has been tested against the consequences of chronic unpredictable stress, which includes anhedonia and anxiety-like behavior [77]. Chronic treatment with CBD was able to prevent these behavioral changes, an effect that depends on hippocampal neurogenesis [78]. These observations proved that CBD should be considered as a potential drug for the treatment of mood disorders.

3.7. Alzheimer's disease

Alzheimer's disease (AD) is a progressive, chronic, and neurodegenerative disease caused by a loss of cholinergic neurons leading to a memory deficit (both short and long term) followed by other

psychiatric disorders. It is characterized by two well-known pathological hallmarks: senile plaques, due to the extracellular accumulation of the amyloid beta (Aβ) protein, and neurofibrillary tangles (NFTs), caused by the aggregation of hyperphosphorylated tau [79]. CBD *in vitro* inhibited the hyperphosphorylation of tau and reduced Aβ production by promoting APP ubiquitination [80]. In addition, *in vivo* CBD treatment has been shown to reverse the cognitive deficits in a double transgenic AD mouse model (APP/PS1) [81]. The anti-inflammatory and neuroprotective effects of CBD could be connected to its ability to reduce the level of iNOS, GFAP, calcium binding protein B, and nuclear factor kappa-light-chain-enhancer of activated B cells (NF-κB). These actions may be mediated, at least partially, through the PPAR-γ receptor [82]. Other studies have demonstrated, instead, that it is the combination of CBD and D9-THC that prevents the learning deficit [81].

3.8. Parkinson's disease

Parkinson's disease (PD) is a neurodegenerative disorder, with affects 1% of the population, usually, over 60 years old [83]. Characteristic symptoms of this disease are motor deficits (hypokinesia, tremors, muscle rigidity) accompanied in the final phase by psychiatric illness (sleep disturbances, cognitive deficits, anxiety, depression, psychotic symptoms) [83]. The first studies with CBD on PD have demonstrated that it reduces psychotic symptoms and reduces the frequency of events related to REM sleep behavior disorder. Unfortunately, CBD did not act on motor symptoms, but could prevent and/or reverse catalepsy behavior in rodents, probably because it acts on the 5-HT1A receptor [84]. In *in vivo* studies CBD has shown neuroprotective effect: it increases mRNA level of antioxidant enzyme Cu, Zn-superoxide dismutase in *substantia nigra* and prevents depletion of dopamine and reduction in tyrosine hydroxylase activity in caudate-putamen [85]. Furthermore, CBD could induce neuroprotection through the normalization of homeostasis of glutamate, the reduction of microglia activation and through neuritogenesis [86]. This final biological mechanism is based on synaptogenesis and axonal growth that are typically induced by NGF. CBD can induce neuritogenesis by activating tropomyosin receptor kinase A (trkA) also without NGF [86]. CBD significantly increases the synaptophysin expression, Growth Associated Protein 43 (GAP-43) and synapsin-1 expression, thereby inducing neurite formation and elongation in addition to synaptic vesicle formation [86].

4. Conclusion

C. sativa is rich in terpeno-phenolic molecules that are produced as a plant defense against environmental stress; they have been used by humans for therapeutic and voluptuary purposes. CBD is the main phytocannabinoid that does not induce psychotropic action and it has shown protective and therapeutic effects in multiple preclinical and clinical models. Some receptor binding studies have investigated the pathways involved in its pharmacological action but with conflicting results. Indeed, it seems that CBD acts in a non-specific way on multiple receptor systems generating a concert of responses to both central and peripheral therapeutic actions. The emergence of CBD as a therapeutic strategy for some forms of epilepsy has been an important pharmaceutical achievement in neurodevelopmental pathologies. Hereupon today, some clinical trials are investigating the action of CBD in ASD. However, the pathways involved in the biological responses of CBD remain poorly understood. In addition, the ability of CBD to interact with hepatic cytochromes has still to be well defined. Finally, the roles and mechanisms of CBD in many neuropsychiatric disorders have not yet been well explored. Therefore, more in-depth studies on biological responses to CBD administration will be needed to better understand the genesis and progression of neuropsychiatric diseases.

Conflict of interest

Nothing to declare.

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