3 Neuropharmacological Effects of the Main Phytocannabinoids: A Narrative Review

Rafael G. dos Santos, Jaime E. C. Hallak, and José Alexandre S. Crippa

Abstract

Cannabis can synthetize more than 400 compounds, including terpenes, flavonoids, and more than 100 phytocannabinoids. The main phytocannabinoids are Δ-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). Cannabis-based products are used as medicines in several countries. In this text, we present an overview of the main neurochemical mechanisms of action of the phytocannabinoids, especially THC and CBD. We also reviewed the indications and adverse effects of the main cannabis-based medicinal products. THC acts as a partial agonist at cannabinoid 1/2 receptors ($CB_{1/2}$). It is responsible for the characteristic effects of cannabis, such as euphoria, relaxation, and changes in perceptions. THC can also produce dysphoria, anxiety, and psychotic symptoms. THC is used therapeutically in nausea and vomiting due to chemotherapy, as an appetite stimulant, and in chronic pain. CBD acts as a noncompetitive negative allosteric modulator of the CB_1 receptor, as an inverse agonist of the CB_2 receptor, and as an inhibitor of the reuptake of the endocannabinoid anandamide. Moreover, CBD also activates $5\text{-}HT_{1A}$ serotonergic receptors and vanilloid receptors. Its use in treatment-resistant epilepsy syndromes is approved in some countries. CBD does not produce the typical effects associated with THC and has anxiolytic and antipsychotic effects. Some of the most common adverse effects of CBD are diarrhea, somnolence, nausea, and transaminase elevations (with concomitant use of antiepileptics). The mechanisms of action involved in both the therapeutic and adverse effects of the phytocannabinoids are not fully understood, involving not only the endocannabinoid system. This "promiscuous" pharmacology could be responsible for their wide therapeutic spectrum.

Keywords

Cannabinoids · Phytocannabinoids · Endocannabinoids · Mechanisms of action · Neuropharmacology

3.1 Introduction

Cannabis is a botanical genus composed of three species (*C. sativa*, *C. indica*, and *C. ruderalis*) that are broadly differentiated by their genetic and chemical ability to produce more or less of the two main phytocannabinoids: Δ-9-tetrahydrocannabinol (Δ-9-THC or simply THC) and

R. G. dos Santos · J. E. C. Hallak · J. A. S. Crippa (✉)
Department of Neurosciences and Behavior, Ribeirão Preto Medical School, University of São Paulo, Ribeirão Preto, Brazil

National Institute of Science and Technology–Translational Medicine, Ribeirão Preto, São Paulo, Brazil
e-mail: jcrippa@fmrp.usp.br

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cannabidiol (CBD). Thus, species rich in THC are used for recreational and medicinal properties, while species with low THC content and high CBD content are used to produce seed and fiber and are also used for medicinal purposes (Hillig 2005; Andre et al. 2016). Cannabis can synthetize more than 400 compounds, including terpenes, flavonoids, and more than 100 phytocannabinoids including THC, CBD, Δ-8-tetrahydrocannabinol (Δ-8-THC), Δ-9-tetrahydrocannabivarin (Δ-9-THCV), Δ-9-tetrahydrocannabinolic acid (Δ-9-THCA), cannabinol (CBN), cannabidivarin (CBDV), cannabigerol (CBG), cannabichromene (CBC), cannabidiolic acid (CBDA), etc.(Andre et al. 2016; Izzo et al. 2009; Ranieri et al. 2016). Thus, the pharmacology, psychoactivity, therapeutic or toxic effects of cannabis varieties and "strains" will depend on the synergetic effects of all these compounds (Andre et al. 2016; MacCallum and Russo 2018). Accumulating evidence shows that *skunk*-like (high-potency) cannabis, rich in THC, is associated with a higher frequency of adverse reactions compared to low-potency (low THC/high CBD content) cannabis (Di Forti et al. 2015; Volkow et al. 2016).

Cannabis-derived products are available in different forms (Table 3.1). Herbal or raw cannabis (from nonstandardized to standardized varieties with known content THC and CBD, e.g., Bedrocan®, Bedrobinol®, Bediol®, Bedica®, Bedrolite®) and cannabis extracts/oils (from homemade to standardized medications, e.g., Sativex®, Epidiolex®, Purodiol®, TIL-TC150) are currently authorized for medicinal purposes including chronic pain, sleep disorders, anxiety and mood disorders, Parkinson disease, epilepsy, etc. in 30 States of the United States (US) and in some countries such as Canada, the Netherlands, Italy, Germany, Israel, and Brazil (Abuhasira et al. 2018; Bramness et al. 2018). In some countries such as the US and Brazil, several of the available extracts (except for Sativex® and Epidiolex®) are not standardized and show wide variation in cannabinoid content (Vandrey et al. 2015; Crippa et al. 2016). Moreover, some medicinal indications for these products were not assessed and approved after randomized controlled trials (RCTs) (for example, Parkinson disease in some US States and in Brazil). Furthermore, in other contexts, such as in some European countries, cannabis-based products are used only in rare or specific diseases (such as palliative care) (Abuhasira et al. 2018; Bramness et al. 2018). Nevertheless, although the recreational use of cannabis is associated with several adverse effects such as cognitive impairment and psychiatric disorders (Di Forti et al. 2015; Volkow et al. 2016), observational, open-label, and RCTs suggest that medicinal cannabis and cannabis-based products (standardized and nonstandardized) could be effective for some indications such as chronic pain, epilepsy, cancer-associated pain, and nausea, and are generally well tolerated (Gruber et al. 2016; Yassin and Robinson 2017; Abuhasira et al. 2018; Bellnier et al. 2018; de Hoop et al. 2018; Gruber et al. 2018; Hausman-Kedem et al. 2018; McCoy et al. 2018; Mondello et al. 2018; Sarid et al. 2018). However, most of these studies only reported short treatment periods and short follow-up periods, thus possible long-term effects of these cannabis-based products are largely unknown and should be further investigated. In fact, that is also true for pure cannabinoids such as THC- and CBD-based products.

Until June 2018, neither the US Food and Drug Administration (FDA) nor the European Medicines Agency (EMA) had approved a drug product containing or derived directly from herbal cannabis. This scenario has recently changed when the FDA approved on June 25, 2018 the use of Epidiolex® (a purified oral cannabis extract rich in CBD; GW Pharmaceuticals Plc.) for treating seizures associated with Lennox-Gastaut syndrome or Dravet syndrome in patients with 2 years of age and older (Kaufman 2018; Rubin 2018). This is the first FDA-approved drug that contains a purified component derived directly from cannabis. Another cannabis-based medicinal product from GW Pharmaceuticals is Nabiximols (Sativex®), an oromucosal spray containing THC and CBD in a 1:1 THC:CBD ratio approved in 29 countries for the treatment of multiple sclerosis associated spasticity and neuropathic pain (Abuhasira et al. 2018; Bramness et al. 2018).

Table 3.1 Summary of the main cannabis-derived products[1]

Product	Active compounds	Administration routes
Herbal cannabis (*Cannabis sp.*, Bedrocan®, Bedrobinol®, Bediol®, Bedica®, Bedrolite®) and nonstandardized cannabis extracts/oils	Mainly THC and CBD, but also dozens of phytocannabinoids, terpenes, etc.	Smoked, vaporized, oral
Dronabinol (Marinol®, Syndros®)	Synthetic THC	Oral
Nabilone (Cesamet®, Canemes®)	Synthetic THC analog	Oral
Nabiximols (Sativex®)	Cannabis extract with THC and CBD in a 1:1 THC:CBD ratio, with minor quantities of other phytocannabinoids, terpenes, etc.	Oromucosal spray
TIL-TC150	Cannabis extractcontaining only purified CBD and THC in50:1 CBD:THC ratio	Oral
CBD (Epidiolex®)	CBD extract, with minor quantities of phytocannabinoids, terpenes, etc.	Oral
CBD	Purified or synthetic CBD	Oral

[1]Adapted from the following references: Koppel et al. 2014; Whiting et al. 2015; Abuhasira et al. 2018; Bramness et al. 2018; MacCallum and Russo 2018; McCoy et al. 2018
CBD cannabidiol, *THC* tetrahydrocannabinol

Epidiolex® is not currently approved by the EMA, and Sativex® is not currently approved by the FDA, but things might change in 2019 for both substances in both agencies. More recently, TIL-TC150 (Tilray Inc.), a cannabis extract with purified CBD and THC in a 50:1 CBD:THC that complies with GMP standards is being investigated in Canada for the treatment seizures in children with Dravet syndrome (McCoy et al. 2018).

Moreover, the synthetic versions of the main phytocannabinoids (THC and CBD) are currently approved medications (THC) or are under clinical investigation (CBD) in some countries. For instance, synthetic THC or Dronabinol (Marinol®, AbbVie Inc.; Syndros®, Insys Therapeutics Inc.), used in capsules or as an oralsolution, is approved since the 1980s for the treatment of anorexia associated with weight loss in patients with AIDS (Acquired Immunodeficiency Syndrome) and for nausea and vomiting associated with cancer chemotherapy by the FDA and by some European countries (Whiting et al. 2015; Abuhasira et al. 2018; Bramness et al. 2018). A synthetic analog of THC, Nabilone (Cesamet®, Meda Pharmaceuticals Inc.; Canemes®, AOPOrphan Pharmaceuticals AG), is also approved since the 1980s for the treatment of nausea and vomiting associated with cancer chemotherapy by the FDA and by some European countries (Whiting et al. 2015; Abuhasira et al. 2018; Bramness et al. 2018). A synthetic pharmaceutical-grade version of CBD (STI Pharmaceuticals) is currently being investigated as an anticancer drug (Kenyon et al. 2018), and other synthetic derivatives CBD and other phytocannabinoids are being investigated in basic studies (Ranieri et al. 2016; Morales et al. 2017).

In this text we will present an overview of the main neurochemical mechanisms of action of the above mentioned phytocannabinoids, especially THC and CBD. We focused on human studies including both healthy volunteers and clinical samples. Human data for the other phytocannabinoids are very limited or do not exit at all, so when human studies were not available we tried to fulfil this gap with preclinical data.

3.2 Neuromolecular mechanisms of action of the main phytocannabinoids

3.2.1 THC

THC is the main psychotropic ingredient of cannabis, being responsible for its euphoriant effects, but also for some of its therapeutic effects (analgesia, increased appetite, hypnotic, etc.). THC

acts as a partial agonist at the cannabinoid receptors 1 and 2 (or simply CB_1 and CB_2), and this is thought to be the main mechanism of action of this phytocannabinoid (Izzo et al. 2009; Weinstein et al. 2016; Colizzi and Bhattacharyya 2017; Sagar and Gruber 2018; Schonhofen et al. 2018). The cannabinoid receptors, their ligands (the endocannabinoids anandamide (AEA) and 2-arachidonoylglycerol (2-AG)), and the enzymes responsible for the synthesis and degradation of the endocannabinoids (fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL)) form the endocannabinoid system (ECS) (Ranieri et al. 2016; Schonhofen et al. 2018). The CB_1 receptoris distributed throughout the brain, with particularly high densities in the amygdala, hippocampus, striatum, frontal/prefrontal cortex, and motor areas. These areas are implicated in emotion processing and cognitive effects, including anxiety/relaxation (amygdala), learning/memory (hippocampus), reward processing (striatum), euphoria/ "high" (frontal/prefrontal cortex), and altered balance (motor areas). The ECS, mediated mainly by the CB_1 receptor, is also involved in regulating striatal dopamine release and glutamatergic and GABAergic neurons (Weinstein et al. 2016; Sagar and Gruber 2018; Schonhofen et al. 2018). CB_2 receptors are expressed in both the brain and peripheral organs and are involved in homeostasis, pain, and inflammation. The ECS is also implicated in the growth, differentiation, positioning, and connectivity among neurons and in neuroplasticity, including neurogenesis (Ranieri et al. 2016; Weinstein et al. 2016; Sagar and Gruber 2018; Schonhofen et al. 2018).

THC can also activate other receptors in nano/micromolar concentrations, such as the peroxisome proliferator-activated receptor γ (PPARγ) and the transient receptor potential Ankyrin 1 (TRPA1), which could be involved in the neuroprotective/inflammatoryand analgesic effects of THC (Izzo et al. 2009).

3.2.2 CBD

CBD is the second most abundant phytocannabinoid and the major noneuphoriant phytocannabinoid. CBD has several therapeutic potentials, including anxiolytic, antipsychotic, antiepileptic, and neuroprotective effects, but the mechanisms of these multiple pharmacological effects are complex and poorly understood. For instance, CBD neither directly binds to nor activates $CB_{1/2}$ receptors, as THC does. Some of the multiple mechanisms of action of CBD described in preclinical studies are summarized in Table 3.2.

3.2.3 Δ-9-THCV

This compound is derived from the phytocannabinoid cannabigerovarin (CBGV), and usually exists in very low quantities in cannabis varieties. Δ-9-THCV acts as a CB_1 receptor antagonist at lower doses and as an agonist of the same receptor at higher doses, and acts as a CB_2 receptor partial agonist (Izzo et al. 2009; dos Santos et al. 2015; Hill et al. 2010; Englund et al. 2016; Ranieri et al. 2016). Preclinical studies suggest that Δ-9-THCVdecreases food intake in animals and has antiepileptic properties (Izzo et al. 2009; dos Santos et al. 2015; Hill et al. 2010; Ranieri et al. 2016). In a study with 10 cannabis users, volunteers received 10 mg of Δ-9-THCV(oral) or placebo for 5 days, followed by 1 mg of intravenous THC on the fifth day.Δ-9-THCV was well tolerated and did not induce subjective effects, but it inhibited the heart rate increases produced by THC and potentiated the memory impairment induced by this phytocannabinoid (Englund et al. 2016). A recent neuroimaging study replicated the absence of subjective effects of Δ-9-THCV and showed that this compound reduced functional connectivity between the amygdala and parts of the default mode network (precuneus and the posterior cingulate cortex) and increased connectivity between the amygdala and parts of the executive control network (dorsal anterior cingulate cortex and premotor area) (Rzepa et al. 2016). These effects seem to be the neural basis

Table 3.2 Main mechanisms of action of cannabidiol (CBD)[a]

Target	Action
$\alpha 1/1\beta/3$ glycine receptors	Agonist/Positive allosteric modulator
Adenosine reuptake	**Inhibitor**
$A_{1/2A}$adenosine receptors	**Modulator**
Anandamide reuptake	**Inhibitor**
Ca^{2+} (intracellular)	**Regulator**
Ca^{2+} channels (voltage-gated T-type)	**Inhibitor**
CB_1cannabinoid receptor	**Noncompetitive antagonist/Noncompetitive negative allosteric modulator**
CB_2cannabinoid receptor	**Inverse agonist**
COX activity	**Inhibitor**
DA_2 dopamine receptor	**Partial agonist**
δ-opioid receptor	Positive allosteric modulator
FAAH	**Inhibitor**
Glutamate release	**Inhibitor**
GPR55 receptor	**Antagonist**
Hydroperoxide-induced oxidative damage	Inhibitor
mTOR pathway	**Activator**
μ-opioid receptor	Ligand/Positive allosteric modulator
NO production	Inhibitor
PGE2 production	**Inhibitor**
PPAR-γ receptor	**Agonist**
Putative abnormal-CBD receptor	Antagonist
σ1 receptor	Antagonist
Na^+ channels	**Inhibitor**
TRPA1channel	Agonist
TRPM8 channel	Antagonist
TRPV1–4channels	**Agonist**
TNFα	**Modulator**
Tryptophan degradation	Inhibitor
VDAC1	Modulator
5-HT_{1A}	**Agonist**
5-HT_{2A}	Partial agonist
$5HT_{3A}$	Antagonist
5- and 15-lipoxygenase	Inhibitor

[a]Adapted from the following references: Izzo et al. 2009; dos Santos et al. 2015; Gobira et al. 2015; Ranieri et al. 2016; Seeman 2016; Campos et al. 2017; Morales et al. 2017; Perucca 2017; Crippa et al. 2018; Rodríguez-Muñoz et al. 2018; Schonhofen et al. 2018

The above list of targets/actions is not exhaustive. Targets/actions marked in bold seem to be the most relevant to the anxiolytic, antipsychotic, antiepileptic, and neuroprotector effects of CBD

CBD cannabidiol, *COX* cyclooxygenase, *FAAH* fatty acid amide hydrolase, *GPR55* G protein-coupled receptor 55, *mTOR* mammalian target of rapamycin intracellular pathway, *NO* nitric oxide, *PGE2* prostaglandin type E2, *PPAR-γ* nuclear peroxisome proliferator-activated receptor *γ*, *TNFα* tumor necrosis factor *α*, *TRPA1* transient receptor potential of ankyrin type 1, *TRPM8* transient receptor potential of the melastatin type 8, *TRPV1–4* transient receptor potential of vanilloid types 1–4, *VDAC1* voltage-dependent anion-selective channel protein type 1, *5-HT_{1A}* serotonin receptor subtype 1A

underlaying the possible use of this phytocannabinoid in the treatment of obesity. Studies with bigger samples and both healthy and clinical populations are needed to better understand the pharmacology of this compound and its possible therapeutic benefits.

3.2.4 Δ-9-THCA

This phytocannabinoid acts as a transient receptor potential of ankyrin type 1 (TRPA1) agonist and as a transient receptor potential of the melastatin type8 (TRPM8) antagonist, and preclinical studies showed that this compound has antiproliferative, antispasmodic, and analgesic properties (Izzo et al. 2009; dos Santos et al. 2015).

3.2.5 Δ-8-THC

Δ-8-THC results from the isomerization of THC and is found in very small amounts in cannabis. The pharmacology of Δ-8-THC and THC is similar, as both phytocannabinoids induce psychoactive and antiemetic effects in humans by agonism at the CB_1 receptor, butΔ-8-THC is less active (Izzo et al. 2009). Moreover, Δ-8-THC showed antiepileptic effects in animals (Colasanti et al. 1982; dos Santos et al. 2015).

3.2.6 CBDV

CBDV is a CBD analog derived from CBGV. Recent preclinical studies showed that this phytocannabinoid has antiepileptic effects that seem to be independent of $CB_{1/2}$ receptors (Hill et al. 2012, 2013). Furthermore, CBDV inhibits anandamide uptake and the synthetic enzyme of 2-AG and activates transient receptor potential of vanilloidtypes 1–2 (TRPV1/2) and TRPA1 channels (Hill et al. 2012, 2013; Iannotti et al. 2014; dos Santos et al. 2015; Ranieri et al. 2016; Morales et al. 2017).CBDV(800 mg once daily over 5 days) was well tolerated in phase I and II trials, and it is being investigated to treat seizure disorders, Rett syndrome, and autism spectrum disorder (Bialer et al. 2018).

3.2.7 CBN

CBNis a minor constituent of cannabis that is formed by the oxidation of THC. It was the first phytocannabinoid to be obtained in pure form, in 1896. Like CBD and CBDV, CBN inhibits cellular uptake of anandamide. Moreover, it also seems to act as a $CB_{1/2}$ partial agonist, although less potent than that of THC (10% of its psychoactivity) (Izzo et al. 2009). Few studies have investigated the pharmacology of CBN, but there is evidence that it has antiepileptic properties (Consroe and Wolkin 1977; dos Santos et al. 2015).

3.2.8 CBG

CBG is the precursor of THC and CBD, and several mechanisms of action have been proposed for this phytocannabinoid, including inhibition of anandamide and GABA uptake, partial agonism at $CB_{1/2}$receptors, TRPA1 and TRPV1/2 channels, and α2-adrenoceptors, antagonism at $5\text{-}HT_{1A}$ receptors and TRPM8 channels, modulation of phospholipase A_2,COX-1/−2 inhibition, and blockaded of voltage-gated sodium channels (Izzo et al. 2009; dos Santos et al. 2015; Ranieri et al. 2016; Morales et al. 2017). Preclinical studies suggest that at least some of these actions are involved in the analgesic, anti-inflammatory, antibacterial, and anticancer properties of CBG (Izzo et al. 2009; Ranieri et al. 2016; Morales et al. 2017).

3.2.9 CBC

Together with THC and CBD, CBC is one of the most abundant phytocannabinoids, and although it shares a similar pharmacology with THC (inducing hypothermia, sedation, and hypoactivity in animals), it is not euphoriant, and it is 2.5 times more toxic than THC. CBC acts as a TRPA1 agonist and as an inhibitor of anandamide reuptake and MAGL, and there is preclinical evidence that it has anti-inflammatory, analgesic, antidepressant, antibacterial, and anticancer effects (Izzo et al. 2009; Ranieri et al. 2016).

3.2.10 CBDA

CBDA is the acidic form of CBD, which is 95% of the CBD form present in cannabis. CBDA acts as a selective COX-2 inhibitor, a TRPA1 and TRPV1 agonist, a TRPM8 antagonist, and a modulator of the GPR55 receptor, and has showed anti-inflammatory, anticancer, and analgesic actions in preclinical studies (Izzo et al. 2009; Morales et al. 2017).

3.3 Neurochemical and behavioral effects of THC and CBD: Human studies

3.3.1 THC

The action of THC as a partial agonist at $CB_{1/2}$ receptors, but especially at the CB_1 receptor, is its main mechanism of action, being responsible for the characteristic effects of cannabis: euphoria/dysphoria, relaxation/anxiety, and changes in perceptions and thought content/psychotic symptoms. As mentioned above, the CB_1 receptor is high in brain areas related to emotion and cognition, including the amygdala, hippocampus, striatum, and prefrontal cortex. These areas are the neural subtracts of the subjective, emotional, and cognitive effects of THC, including anxiety/relaxation (amygdala), learning/memory (hippocampus), reward processing/motivation (striatum), and euphoria/ "high" (frontal cortex) (Weinstein et al. 2016; Colizzi and Bhattacharyya 2017; Sagar and Gruber 2018).

Studies of acute administration of cannabis or THC to healthy volunteers often report increase in scales measuring "linking", "intoxicated", and "high", but also show impaired cognition and increase in scales measuring anxiety and psychotic symptoms (Bhattacharyya et al. 2009; Fusar-Poli et al. 2009; Morrison et al. 2009; Bhattacharyya et al. 2010; Bhattacharyya et al. 2012; Martin-Santos et al. 2012; Niesink and van Laar 2013; Weinstein et al. 2016; Colizzi and Bhattacharyya 2017; Grimm et al. 2018; Sagar and Gruber 2018), and functional magnetic resonance imaging (fMRI) studies assessing the neural basis of the effects of THC in healthy volunteers suggest that the effects of this compound on fronto-striatal and limbic/paralimbic function are involved in its effects on verbal learning, psychotic symptoms, and emotion processing (Bhattacharyya et al. 2009; Fusar-Poli et al. 2009; Bhattacharyya et al. 2010; Bhattacharyya et al. 2012; Weinstein et al. 2016; Colizzi and Bhattacharyya 2017; Sagar and Gruber 2018). Neuroimaging studies have also shown that acute THC administration stimulates striatal dopamine neurotransmission in healthy human volunteers (Weinstein et al. 2016). However, previous genetic and brain structural and functional characteristics of cannabis users participating in these studies often influence the subjective and cognitive differences among these individuals and controls, suggesting that the observed deficits (when these are observed) are influenced by other factors and not necessarily by cannabis use. Moreover, age and history of cannabis use also influence these results (Weinstein et al. 2016; Sagar and Gruber 2018).

Regarding more prolonged or chronic use, a recent meta-analysis of neuroimaging studies of recreational cannabis users showed that the most consistent functional alterations were decreased activation in the anterior cingulate cortex (ACC) and dorsolateral prefrontal cortex (DL-PFC) and increased activation in the striatum (Weinstein et al. 2016; Sagar and Gruber 2018; Yanes et al. 2018). The ACC and DL-PFC are associated with behavioral control, pain processing, learning and memory, and the striatum with reward and pain processing, social judgments, and attention and inhibition control. Regarding dopaminergic neurotransmission, although acute THC administration stimulates striatal dopamine release in humans, several studies failed to find differences in striatal $D_{2/3}$ dopamine receptor occupancy between regular cannabis users and controls, but regular cannabis use was associated with reduced dopamine transporter (DAT) availability and dopamine synthesis capacity in the striatum (Weinstein et al. 2016).

These functional alterations could be related to the negative effects of cannabis use on reward

processing, memory, and executive function, although a recent meta-analysis of cannabis use and cognitive function in adolescents and young adults concluded that previous studies overestimated the magnitude and persistence of the cognitive deficits associated with cannabis use, since these effects are small and of questionable clinical relevance for most individuals (Scott et al. 2018). Moreover, the observed effects are probably reflecting residual effects from acute use or withdrawal symptoms, since they are reduced in studies reporting abstinence periods longer than72 h (Weinstein et al. 2016; Sagar and Gruber 2018; Scott et al. 2018). Indeed, in several studies cannabis users perform similar to nonusing controls in cognitive tests, even when neurofunctional differences are found (and they are not always found) (Weinstein et al. 2016; Sagar and Gruber 2018). Furthermore, previous genetic and brain structural/functional characteristics of cannabis users influence the results of these studies, suggesting that the functional alterations observed are influenced by other factors and are not necessarily caused by cannabis use (Weinstein et al. 2016; Sagar and Gruber 2018).

Structural studies share these same limitations and also report conflicting results, with some studies failing to find differences and others reporting alterations in brain areas rich in CB_1receptors and involved in executive function and memory, including larger cerebellar and striatal volumes, reduced gray matter volume in the hippocampus, and lower white matter integrity (Weinstein et al. 2016; Sagar and Gruber 2018). However, as with functional findings, results from studies assessing brain structure in cannabis users are contradictory and not always correlated to cognitive or psychiatric deficits and are modulated by previous genetic and structural characteristics (Weinstein et al. 2016; Sagar and Gruber 2018; Scott et al. 2018).

In the case of patients using medicinal cannabinoids, it is important to acknowledge that most studies on the effects of cannabis use on cognitive function and on brain structure and function have examined the impact of heavy, chronic, recreational cannabis use (Sagar and Gruber 2018; Scott et al. 2018). Therefore, conclusions from these studies may neither be generalizable to light/moderate use nor to medicinal use. Indeed, recent observational studies suggest that patients using medicinal cannabis to improve anxiety, depression, chronicpain, and sleep, show improvements not only in their mood, quality-of-life, and sleep, but also on executive function and brain activation after starting cannabis treatment (Gruber et al. 2016; Gruber et al. 2018). Specifically, after 3 months of medical cannabis use, patients showed increased activation on the cingulate and frontal cortices during a cognitive task, effects that were not observed while doing the task at baseline (Gruber et al. 2018). These cognitive improvements could be related to the fact that these patients were typically older than recreational users which reduced the use of conventional medication during the study period. The observed improvements in their mood, quality-of-life, and sleep could also have improved their cognitive performance. Furthermore, in contrast to recreational user, patients usually use products with low THC levels and rich in other therapeutic cannabinoids which can counteract some of the undesired effects of THC, such as CBD (Gruber et al. 2016; Gruber et al. 2018).

However, a neuroimaging study with multiple sclerosis patients using smoked cannabis to reduce spasticity and pain observed reduced brain volume in subcortical, medial temporal, and prefrontal regions, which was associated with cognitive impairments in memory and processing speed (Romero et al. 2015). Therefore, further studies are needed to better understand the possible beneficial or deleterious effects of medicinal cannabis and cannabis-based products in different clinical populations. Moreover, as most of these studies only report short treatment periods/follow-ups, the possible long-term effects of these products are largely unknown and should be further investigated.

3.3.2 CBD

As described above (Table 3.2), the mechanisms of action of CBD are not fully understood, and CBD is known as a "promiscuous" compound, since it interacts with several neural systems. For instance, the actions of CBD include not only modulation of the ECS which is independent of $CB_{1/2}$ receptors, but this phytocannabinoid also activates $5\text{-}HT_{1A}$ serotonergic receptors and inhibits the uptake of serotonin, inhibits the uptake of adenosine, noradrenaline, dopamine and GABA, activates TRPV1/2 and TRPA1channels, antagonizes α1-adrenergic and μ-opioid receptors, and stimulates the activity of the inhibitory glycine-receptor, just to mention some of its possible mechanisms (Izzo et al. 2009; dos Santos et al. 2015; Gobira et al. 2015; Campos et al. 2017; Perucca 2017; Crippa et al. 2018; Rodríguez-Muñoz et al. 2018; Schonhofen et al. 2018). It seems that the pharmacological promiscuity of CBD is the reason for the several therapeutic potentials of this compound (Crippa et al. 2018).

These mechanisms of action of CBD make the pharmacology and toxicology of this compound differ from that of THC. Indeed, human studies show that CBD has a good safety and tolerability profile from a physiological and subjective perspective, both after acute and chronic administration, in a wide range of doses (from a single 6 g dose up to 3.5 g/day for 3 months) (Bergamaschi et al. 2011, 2011; Kerstin and Grotenhermen 2017; Crippa et al. 2018; Schoedel et al. 2018; Schonhofen et al. 2018; Taylor et al. 2018). Moreover, CBD does not produce the prototypical euphoriant and cognitive effects of THC and is devoid of abuse liability (Schoedel et al. 2018). Indeed, since the late 1970s, different research groups have shown that CBD counteracts/reduces some of the negative effects of THC, such as increases in anxiety and psychotic symptoms and cognitive deficits (Karniol et al. 1974; Zuardi et al. 1982; Bhattacharyya et al. 2009; Fusar-Poli et al. 2009; Morrison et al. 2009; Bhattacharyya et al. 2010, 2012; Niesink and van Laar 2013; Weinstein et al. 2016; Colizzi and Bhattacharyya 2017; Crippa et al. 2018). Furthermore, naturalistic studies of cannabis users comparing those who use cannabis varieties with low-CBD/high-THC content versus high-CBD/low-THC content showed that users of varieties with high-CBD/low-THC content had attenuated memory impairment and psychotic symptoms compared with users of low-CBD/high-THC content (Morgan et al. 2010, 2011; Colizzi and Bhattacharyya 2017).

Results from neuroimaging studies in humans comparing the subjective, cognitive, and neural effects of CBD with THC show that these phytocannabinoids have opposite effects on the brain (Weinstein et al. 2016; Colizzi and Bhattacharyya 2017; Crippa et al. 2018). For instance, while acute THC administration increases anxiety and psychotic symptoms, intoxication, and sedation, CBD does not induce any of these psychological effects and is indeed associated with reduced subjective anxiety (Martin-Santos et al. 2012; Colizzi and Bhattacharyya 2017; Crippa et al. 2018). Moreover, while the effects of THC on anxiety seem to be regulated by modulation of frontal and parietal brain structures, the anxiolytic effects of CBD were associated with reduced activation and functional connectivity of limbic and paralimbic regions (such as the amygdala and the ACC) during processing of intensely fearful faces (Fusar-Poli et al. 2009). Further, CBD also showed an opposite pattern of subjective effects (psychotic symptoms) and brain activity compared to THC in prefrontal, striatal, and hippocampal function during auditory, visual, and attentional salience processing (Bhattacharyya et al. 2009, 2010, 2012). In a recent study in healthy volunteers, CBD administration significantly increased fronto-striatal connectivity, while no significant difference was observed with THC (Grimm et al. 2018).

More recently, an open-label study of prolonged administration of CBD to regular cannabis users showed that CBD was well tolerated (no impairments on cognition or psychological function) and reduced the euphoria of participants while they smoked cannabis. Moreover, compared to baseline, cannabis users reported less

depressive and psychotic symptoms and improved attention and memory, and an apparent recovery of hippocampal volume (Beale et al. 2018; Solowij et al. 2018).

Considering the good safety and tolerability profile of CBD in both healthy volunteers and clinical populations and the already recognized therapeutic indications for this compound (Crippa et al. 2018), the potential neuroprotective effects of CBD should be further assessed in randomized trials with clinical populations with marked cognitive impairments, such as patients with psychosis and Parkinson's Disease. In fact, these studies are already being performed (see below). However, it must be acknowledged that most experimental and clinical studies of CBD administration conducted so far only report short treatment periods and follow-ups. Therefore, long-term effects should be further investigated.

3.4 Approved indications of cannabis-based products, THC and CBD

The information gathered in the next sections was extracted and adapted from following citations: a systematic review from the American Academy of Neurology on the efficacy and safety of cannabis and cannabinoids in the treatment of neurologic disorders, published in 2014 (Koppel et al. 2014), a systematic review and meta-analysis of the efficacy and safety of cannabis and cannabinoids for the treatment of several diseases, published in 2015 (Whiting et al. 2015), epidemiological studies on the characteristics, safety, and efficacy of cannabis-based products (Yassin and Robinson 2017; Abuhasira et al. 2018; Bellnier et al. 2018; Hausman-Kedem et al. 2018; McCoy et al. 2018; Sarid et al. 2018), an open-label study involving the administration of synthetic CBD to cancer patients (Kenyon et al. 2018), articles with regulatory information on cannabinoid medications and products (Abuhasira et al. 2018; Bramness et al. 2018), and a recent narrative/expert review on the same topic (MacCallum and Russo 2018). The main therapeutic indications of cannabis-based products, THC and CBD are summarized in Table 3.3.

3.4.1 Cannabis-based products

In the case of herbal (raw) cannabis and cannabis extracts/oils, there is a great variety of products, indications, and legislations. Medicinal cannabis is permitted in 30 US States and in Canada, the Netherlands, Italy, Germany, Israel, and Brazil (Abuhasira et al. 2018; Bramness et al. 2018). Products include herbal cannabis to be smoked, vaporized, or ingested (as sold in several dispensaries across 30 US States), homemade extracts and oils (as sold in the US and Brazil), and standardized medications (Sativex®, Epidiolex®, TIL-TC150; discussed below). The main indications for medicinal cannabis include chronic pain, sleep disorders, anxiety and mood disorders, posttraumatic stress disorder, Parkinson disease, and epilepsy, with some of these indications lacking assessment in RCTs. Thus, the level of evidence for recommending medicinal use in some indications varies from moderate (e.g., epilepsy, Parkinson's disease) to inconclusive (e.g., anxiety and mood disorders). Moreover, available cannabis-based products are often not standardized and show wide variation in cannabinoid content, which could induce intoxications (in the case of a high THC content) or lack of therapeutic efficacy (in the absence of CBD or THC) (Vandrey et al. 2015; Crippa et al. 2016). Other risk of nonstandardized products is intoxication with more toxic products, such as potent synthetic cannabinoids (Horth et al. 2018).

3.4.2 THC

3.4.2.1 Nausea and vomiting due to chemotherapy

There is conclusive/substantial evidence that THC (Dronabinol®, Cesamet®, Marinol®, Syndros®) and Nabiximols (Sativex®) are an effective treatment for chemotherapy-induced nausea and vomiting. The antiemetic effects of

Table 3.3 Summary of approved indications of cannabis-based products, THC and CBD[a]

Product	Indication	Where it is approved[b]
Herbal cannabis (*Cannabis sp.*, Bedrocan®, Bedrobinol®, Bediol®, Bedica®, Bedrolite®) and nonstandardized cannabis extracts/oils	Anxiety disorders, AD, ADHD, ALS, appetite and decreasing weight loss associated with HIV/AIDS, cancer (glioma), cancer-associated pain, CD, chemotherapy-associated nausea, chronic pain, clusterheadache, compassion treatment, CUD, dementia, epilepsy, ET, fibromyalgia, glaucoma, IBS, mood disorders, MS, MSA, nonspecific pain, PD, PTSD, PVD, rheumatoid arthritis, sleep disorders, tension headache, tic disorder, TS, ulcerative colitis, etc.[c]	Australia, Brazil, Canada, Germany, Israel, Italy, Lithuania, Netherlands, New Zealand, Portugal, Spain, UK, Uruguay, 30 US States
Dronabinol (Marinol®, Syndros®)/THC	Appetite and decreasing weight loss associated with HIV/AIDS, nausea and vomiting due to chemotherapy, neuropathicpain, TS	Austria, Belgium, Brazil, Canada, Croatia, Denmark, France, Netherlands, Norway, Romania, Spain, Switzerland, UK, US
Nabilone (Cesamet®, Canemes®)/THC analog	Nausea and vomiting due to chemotherapy	Austria, Croatia, Denmark, France, Germany, Mexico, UK
Nabiximols (Sativex®)/THC:CBD (1:1)	MS-associated spasticity and chronic pain	Brazil, Israel, 22 European countries
TIL-TC150	Treatment of intractable seizures in epileptic syndromes (Dravet syndrome)	Canada
CBD (Epidiolex®, Purodiol®)	Treatment of intractable seizures in epileptic syndromes (Dravet and Lennox-Gastaut syndromes), cancer	Brazil, UK, US

[a]Adapted from the following references: Koppel et al. 2014; Whiting et al. 2015; Yassin and Robinson 2017; Abuhasira et al. 2018; Abuhasira et al. 2018; Bellnier et al. 2018; Bramness et al. 2018; Hausman-Kedem et al. 2018; Kenyon et al. 2018; MacCallum and Russo 2018; McCoy et al. 2018; Sarid et al. 2018

[b]Includes licensed medicinal products, nonapproved products prescribed under specific conditions, off-label use, and compassionate prescribing. Several examples of countries are reported, but this list is not exhaustive

[c]Nonexaustive list of indications

AD Alzheimer' disease, *ADHD* attention deficit and hyperactivity disorder, *ALS* amyotrophic lateral sclerosis, *CBD* cannabidiol, *CD* Crohn's disease, *CUD* cannabis use disorder, *ET* essential tremor, *IBS* irritable bowel syndrome, *MS* multiple sclerosis, *MSA* multiple system atrophy, *PD* Parkinson's disease, *PTSD* post-traumatic stress disorder, *PVD* peripheral vascular disease, *THC* tetrahydrocannabinol, *TS* Tourette's syndrome, *UK* United Kingdom, *US* United States

THC are produced by its agonistic action on CB_1 receptors.

3.4.2.2 Appetite and decreasing weight loss associated with HIV/AIDS

There is conclusive/substantial evidence that THC (Dronabinol®, Cesamet®, Marinol®, Syndros®) is an effective treatment for increasing appetite and improves decreasing weight loss associated with HIV/AIDS. The effects of THC on appetite and weight gain are produced by its agonistic action on CB_1 receptors.

3.4.2.3 Multiple sclerosis symptoms (spasticity and chronic pain)

There is conclusive/substantial evidence that Nabiximols (THC:CBD in a 1:1 ratio, Sativex®) is an effective treatment for multiple sclerosis spasticity symptoms and chronic pain. The therapeutic effects of Nabiximols include the analgesic, anti-inflammatory, and sleep-promoting effects of THC and CBD. In the case of THC, these effects are produced by its agonistic action of THC on $CB_{1/2}$ receptors. The mechanisms of action of CBD are not fully understood but seem to be independent of cannabinoid receptors.

3.4.2.4 Chronic pain (neuropathic and cancer pain)

There is moderate evidence that THC (Dronabinol®, Cesamet®, Marinol®, Syndros®) is an effective treatment for chronic neuropathic and cancer pain. The analgesic and anti-inflammatory effects of THC are mediated by its agonistic action on $CB_{1/2}$ receptors.

3.4.3 CBD

3.4.3.1 Antiepileptic

There is conclusive/substantial evidence that purified CBD (Epidiolex®, Purodiol®) is an effective treatment for intractable seizures in epileptic syndromes such as Dravet and Lennox-Gastaut. There is preliminary evidence from an open-label study that a cannabis-extract with purified CBD and THC in a 50:1 CBD:THC ratio (TIL-TC150) is an effective treatment for intractable seizures in children with Dravet syndrome. The antiepileptic mechanisms of action of CBD are not fully understood but seem to be independent of cannabinoid receptors and involve ion channels and G-protein-coupled receptors (see Table 3.2 above).

3.4.3.2 Therapeutic potentials of CBD with moderate/modest evidence from RCTs

In the last decade, accumulating evidence from clinical studies shows that CBD has anxiolytic effects in social anxiety (Bergamaschi et al. 2011, 2011), antipsychotic effects in schizophrenia (Leweke et al. 2012; McGuire et al. 2018) and Parkinson's disease (Zuardi et al. 2009), improvements on well-being and quality of life in Parkinson's disease (Chagas et al. 2014), antiaddictive effects for tobacco and opioid dependence (Morgan et al. 2013; Hurd et al. 2015), and antitumor effects (Kenyon et al. 2018). It is possible that the therapeutic uses of CBD for some of these indications could be regulated in the near future, especially as an antipsychotic drug and for the treatment of some symptoms of Parkinson's disease (Crippa et al. 2018). However, further controlled trials with bigger samples and longer treatment periods are needed to replicate (or refute) most of these results.

3.5 Adverse effects of THC and CBD

The information gathered in the next sections was extracted and adapted from the following citations: Chagas et al. 2014; Koppel et al. 2014; Whiting et al. 2015; Gaston et al. 2017; Perucca 2017; Yassin and Robinson 2017; Abuhasira et al. 2018; Bellnier et al. 2018; Crippa et al. 2018; Hausman-Kedem et al. 2018; Kaufman 2018; Kenyon et al. 2018; Lattanzi et al. 2018; MacCallum and Russo 2018; McCoy et al. 2018; McGuire et al. 2018; Sarid et al. 2018; Schoedel et al. 2018; Schonhofen et al. 2018; Taylor et al. 2018. The main adverse effects of cannabis-based products, THC and CBD are summarized in Table 3.4.

3.5.1 Cannabis-based products and THC

In the last decades, several observational (Gruber et al. 2016; Yassin and Robinson 2017; Abuhasira et al. 2018; Bellnier et al. 2018; de Hoop et al. 2018; Gruber et al. 2018; Hausman-Kedem et al. 2018; McCoy et al. 2018; Mondello et al. 2018; Sarid et al. 2018; Schonhofen et al. 2018) and clinical (open-label and RCTs) studies (Koppel et al. 2014; Whiting et al. 2015) investigated the effects of medicinal cannabis, cannabis-based products, and THC in a diverse group of clinical populations. These products are generally considered safe and well tolerated, at least when they are administered in short treatment periods (weeks, months). Common adverse effects include dizziness, dry mouth, euphoria, nausea, somnolence, drowsiness/fatigue, confusion and disorientation, cough (smoking only), and headache. Less common and rare adverse effects include orthostatic hypotension, ataxia/dyscoordination, anxiety, depression, diarrhea, tachycardia, psychosis/paranoia, hallucinations,

Table 3.4 Summary of the main adverse effects of cannabis-based products, THC and CBD[a]

Product	Adverse effect
Products in which the main adverse reactions are associated with THC	
Herbal cannabis (*Cannabis sp.*, Bedrocan®, Bedrobinol®, Bediol®, Bedica®, Bedrolite®) and nonstandardized cannabis extracts/oils Dronabinol (Marinol®, Syndros®)/THC Nabilone (Cesamet®, Canemes®)/THC analog Nabiximols (Sativex®)/1:1 THC:CBD	*Most common/Common*: Dizziness, euphoria, nausea, somnolence, drowsiness/fatigue, confusion and disorientation, headache, dry mouth, cough/sore throat (smoking/vaporization only) *Less common/Rare*: Orthostatic hypotension, ataxia/dyscoordination, increased appetite, anxiety, depression, diarrhea, tachycardia, psychosis/paranoia, hallucinations, cannabinoid hyperemesis syndrome, seizures
Products in which the main adverse reactions are associated with CBD	
CBD (Epidiolex®, Purodiol®) TIL-TC150/50:1 CBD:THC	*Most common/Common*: Diarrhea, somnolence, nausea, insomnia, fatigue, sedation, decreased appetite, headache, transaminase elevations (with concomitant use of antiepileptics) *Less common/Rare*: Vomiting, fever, lethargy, sleep disorder, seizures, infections, ataxia, rash

[a]This list is not exhaustive. Adapted from the following references: Chagas et al. 2014; Koppel et al. 2014; Whiting et al. 2015; Gaston et al. 2017; Perucca 2017; Yassin and Robinson 2017; Abuhasira et al. 2018; Bellnier et al. 2018; Crippa et al. 2018; Hausman-Kedem et al. 2018; Kaufman 2018; Kenyon et al. 2018; Lattanzi et al. 2018; MacCallum and Russo 2018; McCoy et al. 2018; McGuire et al. 2018; Sarid et al. 2018; Schoedel et al. 2018; Schonhofen et al. 2018; Taylor et al. 2018

CBD cannabidiol, *THC* tetrahydrocannabinol

cannabinoid hyperemesis syndrome, and seizures. Most adverse effects are temporary and are less common with continuous use and titration of these products, since tolerance seems to occur to adverse effects but not necessarily to therapeutic effects (Whiting et al. 2015; Abuhasira et al. 2018; de Hoop et al. 2018; MacCallum and Russo 2018). However, as most of these studies only report short follow-up periods, long-term effects are unknown. Future studies in this area should include longer treatment periods and follow-ups.

3.5.2 CBD

CBD has a good safety and tolerability profile from a physiological and subjective perspective, both after acute and chronic administration in humans, in a wide range of doses (from a single 6 g dose up to 3.5 g/day for 3 months). The most common adverse effects include somnolence, sedation, nausea, diarrhea, headache, changes on appetite, and transaminase elevations. Moreover, CBD does not induce significant effects on cognition, and does not induce tolerance (Bergamaschi et al. 2011, 2011; Colizzi and Bhattacharyya 2017; Gaston et al. 2017; Kerstin and Grotenhermen 2017; Schoedel et al. 2018; Taylor et al. 2018). RCTs of CBD and patients with schizophrenia (McGuire et al. 2018) and Parkinson's disease (Chagas et al. 2014) did not observed differences between placebo and CBD regarding adverse reactions. Indeed, compared with the antipsychotic amisulpride, CBD administration was associated with less extrapyramidal symptoms, weight gain, and prolactin increase (Leweke et al. 2012). A meta-analysis with data from four RCTs of CBD (Epidiolex®) in 550 patients with Lennox-Gastaut or Dravet syndrome showed that CBD was safely administered and produced significant reductions in seizure frequency compared to placebo. CBD administration was associated with a higher rate of adverse effects compared to placebo, but the most common of these effects had a modest clinical relevance and included somnolence, decreased appetite, diarrhea, fatigue, and increased serum aminotransferases (Lattanzi et al. 2018). Less

common reactions include vomiting, fever, lethargy, sleep disorder, seizures, infections, and rash (Perucca 2017; Kaufman 2018; Schonhofen et al. 2018).

Thus, CBD seems to show a different profile of adverse reactions depending on the sample, with most studies in healthy volunteers and clinical samples showing no or few adverse effects, except for epileptic syndromes (Kerstin and Grotenhermen 2017; Crippa et al. 2018; Schonhofen et al. 2018). These differences could be related to CBD dose, duration of treatment, differences among samples regarding components of the ECS (e.g., $CB_{1/2}$ receptor expression in different brain areas), and interactions with medications being used concomitantly with CBD. Future clinical studies with bigger samples and in different clinical populations will contribute to a better understanding of the complex pharmacology of CBD.

3.6 Conclusions

Since the early 1980s, THC-based products have been recognized and regulated as a medicines. In the same decade, researchers in different laboratories around the world, including in Brazil, began to show that CBD could antagonize some of the negative effects of THC, such as anxiety, psychotic symptoms, and cognitive deficits. These studies formed the basis for the regulation of Nabiximols as a medicine around the world in the following years. In the mid 1990s and early 2000s, medicinal cannabis programs became active in several countries, and neuroimaging studies started to elucidate the neural basis for the therapeutic and deleterious effects of cannabis and THC and shed light on the difference between these substances and CBD. In the last decade, several legislations included cannabis-based products as regulated medicines, and the research on the possible therapeutic uses of CBD increased significantly.

However, many areas of cannabinoids research still need to be better explored. For instance, the increasing use of nonstandardized herbal cannabis and cannabis oils in the US and other countries for the treatment of several diseases without the appropriate RCTs should be carefully evaluated. Although observational studies with both recreational users and patients suggest that cannabis is not a highly toxic drug when compared with alcohol, heroin, or cocaine, it can have significant psychiatric adverse reactions in a minority of users (e.g., psychosis and cognitive deficits) that should be considered. Observational studies are very important but need to be complemented with RCTs so that the possible therapeutic uses of these products can be done with more information on dosage and adverse effects. The placebo effect can be very powerful in such observational studies, especially in people with difficult-to-treat conditions (e.g., epilepsy, chronic pain) and in a context in which the discussion of cannabis legalization for recreational and medical uses can be very polemic, enforced by commercial interests and the media. This generalization of untested medicinal properties and commercialization of untested and nonstandardized products could have a negative impact in public health, such as poisonings, intoxications, and lack of appropriate treatment.

Thus, more RCTs are needed to explore the effectiveness and safety of herbal cannabis and cannabis oils on specific disorders, and these products need to be standardized for cannabinoid content. It is especially important that these studies include long-term follow-ups.

Moreover, more RCTs should be performed with pure CBD to investigate the possible therapeutic use of this compound in anxiety and mood disorders, substance use disorders, psychotic disorders, Parkinson's disease, epilepsy, and autism. These studies need to be performed not only to establish safety (especially to the developing brain) and dosage, but also to answer the still-to-be-answered question of which products (pure compounds or whole-plant products) are more effective and safer, and for which indications.

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Conflict of Interest JECH and JAC are coinventors of the patent "Fluorinated CBD compounds, compositions, and uses thereof. Pub. No.: WO/2014/108899. International Application No.: PCT/IL2014/050023" Def. US no. Reg. 62,193,296; 29/07/2015; INPI on 19/08/2015 (BR1120150164927). The University of São Paulo has licensed the patent to Phytecs Pharm (USP Resolution No. 15.1.130002.1.1). The University of São Paulo has an agreement with Prati-Donaduzzi (Toledo, Brazil) to "develop a pharmaceutical product containing synthetic cannabidiol and prove its safety and therapeutic efficacy in the treatment of epilepsy, schizophrenia, Parkinson's disease, and anxiety disorders." JECH and JAC have received travel support from and are medical advisors of BSPG-Pharm. RGS declares no conflicts of interest.

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