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Artigo de revisão

Medicinal aspects, pharmaceutical forms and Brazilian legislation regarding cannabinoids

Aspectos medicinais, formas farmacêuticas e legislação brasileira perante os canabinoides

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ABSTRACT

Cannabinoids are substances found in the Cannabis sativa plant, which have relevant legal aspects for their use despite having health benefits. Therefore, this article aimed to conduct a bibliographical survey on the use of cannabinoids in the treatment of severe diseases, presenting its possible pharmaceutical forms, the mechanism of action of isolated drugs and metabolites, and the legalization of *Cannabis sativa* medicines in Brazil. Hence, documents were selected between 2010 and 2020, in Portuguese, English, and Spanish, from the Virtual Health Library, Capes Periodicals, PubMed, and Academic Google databases. 52 documents were used in the results. Cannabidiol and delta-9-tetrahydrocannabinol stood out among the substances by composing medications such as Mevatyl® and Edipiolex®. Mevatyl® for multiple sclerosis, dronabinol/nabilone for nausea and vomiting, and Epidiolex® for severe epilepsies. The most cited pharmaceutical forms are oral and inhaled sprays, whose mechanism of action is acting through the endocannabinoid system. RDC nº 17/15, ordinance nº 344/98, and RDC nº 2.113/14 were the leading legislation cited. We can conclude that the legislation favored the possibility of using cannabinoids. However, there is still bureaucracy, in addition to the high purchase price. Cannabinoids have promising results in the treatment of diseases. However, there are still differences in the benefit against some pathologies, requiring the development of more research to fill the gaps still open regarding the use of medicinal cannabis.

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RESUMO

Os canabinoides são substâncias presentes na planta Cannabis sativa, os quais apesar de apresentarem benefícios medicinais possuem importantes aspectos legais para a utilização. Sendo assim, o objetivo deste artigo foi a realização de um levantamento bibliográfico quanto ao uso dos canabinoides frente o tratamento de doenças severas, apresentando as possíveis formas farmacêuticas utilizadas na dispensação, o mecanismo de ação dos medicamentos e/ou metabólitos isolados, bem como a legalização dos medicamentos de Cannabis sativa no Brasil. Para tal, selecionou-se documentos entre 2010 e 2020, em português, inglês e espanhol das bases Biblioteca Virtual em Saúde, Periódicos Capes, PubMed e Google Acadêmico, dos quais foram utilizados 52 documentos nos resultados. Dentre as substâncias teve destaque o canabidiol e delta-9-tetrahidrocanabinol compondo os medicamentos como Mevatyl® para esclerose múltipla, dronabinol/nabilona para náusea e vômitos e o Epidiolex® em epilepsias

graves. As formas farmacêuticas mais citadas são spray oral e inalatórias, tendo como mecanismo de ação das substâncias a atuação através do sistema endocanabinoide. Dentre as legislações citadas e importantes tem-se a RDC nº 17/15, Portaria nº 344/98 e RDC nº 2.113/14. O trabalho pode concluir que as legislações favoreceram a possibilidade do uso dos canabinoides, entretanto ainda há burocracia, além do alto custo para aquisição. Os canabinoides possuem resultados promissores no tratamento de doenças, entretanto ainda há divergências quanto ao benefício frente a algumas patologias, sendo necessário o desenvolvimento de mais pesquisas de modo a preencher as lacunas ainda em aberto quanto ao uso da Cannabis medicinal.

INTRODUCTION

Cannabis is the criminalized substance most used worldwide. There is a complex matter about its decriminalization due to cannabis association with illegal activities and psychoactive effects, despite cannabidiol's efficacy being already proven for many treatments. The strongest arguments to keep recreational cannabis illegal are its cognitive and psychological adverse effects on people under 20 years old and the possibility of leading to the consumption of more threatening substances1.

The Brazilian Health Regulatory Agency (ANVISA) officially approved medical cannabis commercialization with the Collegiate Board Resolution (CBR) nº 327/19[2]. The primary barrier to that approval was the presence of Δ^9-THC in the drug's composition. It was a concern to have the active psychotropic substance on the prescription, and its effects on under-age patients were still unknown. Nonetheless, the positive results of medical cannabis for different health conditions, especially being the only effective treatment for multiple sclerosis until now, surpassed the previous concern. Medical cannabis is legal for commercialization but is still subject to inspection. Recreational use, possession, and cultivation remain prohibited.

According to CBR nº 327/19, medical cannabis can only be commercialized in oral or nasal administration with Δ^9-THC levels up to 0,2%. If a higher concentration is required, **a formal request to ANVISA is necessary**. Only industrialized recipes are authorized, and patients must sign a free informed consent form[2]. According to Ordinance No. 327/19, 0- 0.2% of Δ^9-THC products are in the "B" revenue notification, and products above 0.2% fall under the "A" revenue notification. *Cannabis*-based medications have their dispensing restricted by the pharmacist[2].

The most popular medical cannabis extract approved by ANVISA is Mevatyl®, as known as Sativex. This medication is sold as a mouth spray, delivering 27 mg/mL Δ^9-THC and 25 mg/mL CBD[3]. Other extracts, such as Epidiolex® (CBD doses only) 4, are being developed.

C. *sativa* L., commonly known as pot or marijuana, is a flowering plant in the *Cannabaceae* family. The most common species are *C. sativa* and *C. indica*[5]. Over the centuries, many civilizations used it for diverse purposes such as religious, recreational, food, medical, and arts and crafts[5].

Δ^9-THC and CBD are active substances found, among others in C. sativa. CBD is a promising non-psychotropic active substance, engaging interest in research for treatments of conditions like epilepsy, schizophrenia, rheumatoid arthritis, Parkinson's disease, Alzheimer's disease, anxiety and depression, multiple sclerosis, and fibromyalgia[6].

Both the physiopathological pathways of those diseases and the drug's mechanisms of action involve the endocannabinoid system. This system is built by CB1 and CB2 receptors; arachnoid acid-delivered endocannabinoids anandamide (ANA), 2-Arachidonoylglycerol (2-AG), and enzymes. CB1 is an inhibitory receptor, lowering neuronal synapses and neurotransmitters released by opening voltage-gated potassium channels and closing sodium channels type P, N, and Q. This receptor is also an appetite and energy metabolism modulator found in central and peripheral

nerves, adipocytes, skeletal muscles, and liver cells. CB2 acts on immunologic responses, acting upon the production and release of cytokines. It explains the anti-inflammatory and anti-hyperallergic effects. Cannabinoid receptors are also found in the hypothalamic and limbic systems[7].

Medical cannabis use advances faster than its surveillance and protocols. That is why assembling the main arguments about C. sativa is essential to understand it by conceiving scientific knowledge from research and analysis. Beyond that, the pharmacist must know this knowledge since he is the foremost professional in drug control and dispensing.

This paper aims to review publications about C. sativa active substances in acute disease treatment, showing their possible pharmaceutical formulation, the mechanism of action of those

MATERIAL AND METHODS

We conducted a systemic online review based on official ANVISA and FDA and undergraduate thesis publications. The database resources were Virtual Health Library (*Biblioteca Virtual em Saúde* - BVS/BIREME), Coordenação de Aperfeiçoamento de Pessoal de Nível Superior (CAPES) publication portal, PubMed, and Google Scholar. The study collection considered both English and Portuguese keywords *Cannabis sativa*, cannabinoids, *canabinoides, legalização*, legalization of cannabinoids medications, cannabinoids treatment, and medicinal cannabis.

The study criteria eligibility considered: language, release date between 2010 and 2020 and full-text availability. We defined dates and publications about dosage, concentration, adverse and collateral effects for exclusion criteria.

We selected 68 studies, with variables such as C. sativa-based medications for severe disease treatments, Brazilian legislation on medical cannabis, therapeutic usage of cannabinoid active substances, and cannabinoid extracts mechanism of actions and pharmaceutical recipes. The studies were analyzed by full reading and data registration on protocol, considering each variable. All data collected were organized on Microsoft® Excel 2010, and we assembled all cited authors on the references.

RESULTS AND DISCUSSION

We selected 52 studies from the previous 68 (table 1). Sixteen studies did not include variables previously presented and then were eliminated. We uncovered it by thoroughly reading them. Thirty-four of these studies are in Portuguese [1, 2, 8-40], twelve in English [6, 39, 41-52], and six in Spanish [32, 35, 53-56].

All 52 studies included the active substances CBD and Δ^9-THC. Both substances are phytocannabinoids, natural extracts from *C. Sativa*, lipophilic, and transverse the blood-brain barrier. It attributed to them the following proprieties: anti-inflammatory [1, 2], antispasmodic [9, 10], antiepileptic/anticonvulsant[11, 41], antiemetic [8, 42, 43], antinociceptive/analgesic[12, 42], anxiolytic[13, 54], antipsychotic[14, 15], antioxidant [16, 44], antidepressant[14, 42], neuroprotective[17, 18, 54], anticancer[18, 19], immunomodulator[20, 21], appetite stimulator[18, 22, 45], and sleep regulator[23, 44]. Those characteristics were the main objectives of their studies. Cannabis active substances are categorized under three types: Phytocannabinoids (natural plant cannabinoids); Endocannabinoids (endogenous human cannabinoids like phytocannabinoids on structure and mechanism of action), and synthetic cannabinoids (lab-designed drugs).

Mechanism of action

Δ^9-THC is cannabis's primary psychoactive constituent with a great affinity to CB1 and CB2 receptors as a partial agonist. It has pro-convulsant proprieties not indicated in epilepsy treatment. CBD, considered a non-psychotic, has an affinity to cannabinoid receptors and serotonin receptors (5HT)[19, 25], vanilloid receptor 1 (TRPV1)[11, 57], adenosine receptor[14, 20], GP55 receptor[13, 26], sodium, potassium, and calcium channels, and others[10, 27].

Drugs' mechanism of action was not com-

Table 1: List of studies found by year of publication.

Year of publication	Results
2010	3
2011	1
2012	2
2013	1
2014	5
2015	4
2016	6
2017	7
2018	3
2019	15
2020*	5
Total: 52	

pletely elucidated. Nevertheless, 40 papers approached the subject meticulously (table S1) and medical cannabis legislation in Brazil (table S2). It involves the endocannabinoid system (ES) built by CB1 and CB2 receptors, endocannabinoids, or endogenous enzymes. CB1 and CB2 are G protein-coupled receptors. CB1 is associated with psychotropic effects and is found predominantly in the central nervous system on both GABAergic and glutamatergic nerves. CB2 is found in the peripheral nervous system and immunologic cells. Only one paper pondered a third kind of receptor, a non-CB1/CB2. CB3 would be linked to vanilloid receptors activation generating stimuli on pain regions[47, 57].

The most common endogenous ligands are AEA and 2-AG. They are arachidonic acid products produced on demand and not stored in vesicles as common neurotransmitters. They are involved in acute and chronic processes, respectively. AEA is synthesized by transacylation-phosphodiesterase, which converts phosphatidylethanolamine (PE) and phosphatidylcholine (PC) to N-arachidonoyl-phosphatidylethanolamine (NAPE). This process is followed by hydrolysis by N-arachidonoyl-phosphatidylethanolamine-phospholipase-D (NAPE-PLD), forming AEA, and degradation is done by the fatty acid amide hydrolase (FAAH) enzyme in postsynaptic neurons. 2-AG is synthesized by phospholipase C-beta (PLC-beta), diacylglycerol-lipase (DGL), converting membrane phosphoinositide into 1,2-diacylglycerol, followed by hydrolysis by DGL forming 2-AG and degraded by monoacylglycerol-lipase (MGL) in presynaptic neurons[10, 14, 26, 42].

The receptors, when activated by stimulators such as cannabinoids or endocannabinoids, especially CB1, inhibit adenylate cyclase (AC). This activation reduces cyclic adenosine monophosphate (cAMP) production, opens potassium channels, and closes calcium channels (voltage-dependent channels), causing neuronal hyperpolarization and reducing the release of neurotransmitters such as dopamine and glutamate, GABA, and serotonin in presynaptic neurons. When CB2 is activated, it inhibits AC and activates the mito-

gen-activated protein kinase (MAPK) cascade [53, 58].

Pharmaceutical dosage forms

Most medical cannabis is made by those two active principles, varying only in their proportion. 30 of 52 studies cited Sativex®, Mevatyl®, and Nabiximols®, being the most famous cannabis drug-based, according to the survey carried out by the authors of this study. Their CBD and Δ^9-THC ratio is 1:1, and only Mevatyl® is commercialized in Brazil. Mevatyl® is indicated for neuropathic pain, multiple sclerosis (spasticity treatment), and epilepsy (convulsion treatment). Mevatyl® is sold as an oral solution (spray), and the active ingredient binds to and is absorbed by the oral mucosa.

After Sativex®, Marinol (dronabinol) was the second most cited medical cannabis, cited by 22 studies. The third most mentioned was Cesanot (19 studies). Both medications are synthetic and analogous to Δ^9-THC and are indicated for nausea and emesis during chemotherapy. Epidiolex was another emphasized medication (8 studies) composed of pure CBD and suggested rare and refractory epilepsy. Acomplia® was cited in 7 studies for obesity treatment and metabolic syndromes but presented many adverse effects, such as hormonal disturbances [24, 53, 55].

As for dosage forms, the oral dosage was the most found, mentioned in 20 studies (not specified for one medication only). The oral spray was the second most found dosage form in 16 studies and the most typical format for Sativex®, Mevatyl®, and Nabiximols®. Nine documents cited inhalation/vaporization as another dosage form. Oral dosage forms have the most uncomplicated manufacturing, while inhalation forms showed promising treatment results. However, long-term collateral effects of this dosage format are problematic, such as respiratory problems (asthma and bronchitis) or even lung cancer [24, 28, 45, 46].

Legislation

Regarding the legislation alluding to the discussion on cannabis-based medicine, 12 documents cited CBR 17 (on importing CBD-based drugs)[22, 24, 29]. Nine citations also evoked ordinance nº 344/98, which notes CBD was leaving the prohibited substances list and becoming a particular (sensitive) controlled substance.

CBR 2113/14 from the Brazilian Federal Council of Medicine (CFM) was the third resolution most cited, and it considers the CBD on treatments for refractory epilepsy in children and teenagers [30-32, 55].

Medicinal aspects

As for the diseases treated or understudy for treatment by medicinal cannabis, multiple sclerosis was cited in thirty-four documents, in which cannabinoids reduce muscle spasticity and stiffness. Twenty-eight documents cited seizure reduction in epilepsy and improving nausea and vomiting caused by chemotherapy for cancer treatment. For neuropathic pain/chronic pain, twenty-eight documents showed cannabinoids' effects on blocking the pain pathway. Nineteen documents cited the effects of Parkinson's: even if the efficacy has not been proven, there was a reduction in inflammation and an antioxidant effect. For Acquired Immunodeficiency Syndrome (AIDS), eighteen documents related cannabinoids with appetite stimulation and weight regulation. Thirteen papers linked cannabinoids and Alzheimer-reducing inflammation as an antioxidant and neuroprotector. For glaucoma, twelve documents show decreasing eye pressure and anxiety due to the anxiolytic effect. The selected studies also mention other diseases but in less significant numbers, such as schizophrenia, fibromyalgia, rheumatoid arthritis, autism spectrum disorder, and others.

Reactions involving cannabinoid receptors, serotonergic receptors, and other receptors are listed in Appendix 1 and the previous paragraphs. Five pathologies were the most related to cannabinoid treatment by the authors: epilepsy, Parkinson's, Alzheimer's, multiple sclerosis, and Autistic

Spectrum Disorder. We described each condition and correlation below.

Epilepsy

It is a neurological disease prevalent in young adults that causes neuronal hyperexcitation. Some unusual synapses lead to seizures, which can occur in one hemisphere called partial seizures, or spread across both brain hemispheres called generalized seizures. Spontaneous and recurrent crises occur of short or long duration, lasting for minutes or seconds. The main symptoms are absence seizures, also known as petit mal seizures. Some sudden discomfort prevails in partial seizures, such as altered perception and uncontrolled body movements. The seizures can be classified as complex partial seizures if there is unconsciousness. In tonic-clonic crises or seizures, unconsciousness occurs and the person will fall, rigid, with trembling and contracted extremities, and excessive salivation will bite the tongue and others. If the crisis remains for a long time, the patient may suffer some brain damage.

Anticonvulsants are the chosen treatment for epilepsy, such as sodium valproate. However, 30% of those affected by epilepsy are drug-resistant and, therefore cannot be treated with medications. Activation of cannabinoid receptors (CB1 and CB2) could reduce neuronal excitability and possibly reduce seizures. This reduction is because CBD has anticonvulsant properties and has excellent results in treating children and cases of refractory epilepsy [24, 27].

Multiple sclerosis

Multiple sclerosis is an autoimmune disease that causes brain and muscle damage with inflammatory, neurological, and chronic characteristics. Its origin is unknown, but there are hypotheses of genetic background associated with environmental factors leading to an autoimmune response target to formation and maintenance of the myelin sheath, leading to demyelination. The autoimmune response causes inflammation, which evolves into a scar, also called sclerosis, due to the death of the oligodendrocyte, resulting in the loss of tissue functions. There is a reduction in nerve impulses as neurons lose their myelin sheath and symptoms appear. The main symptoms are fatigue, intense pain, especially in joints and muscles, tiredness, depression, change in balance and motor coordination, bowel and bladder changes, and loss of physical and cognitive ability. Some outbreaks can also happen.

Multiple sclerosis is classified into four subtypes: 1) relapse remission; 2) progressive primary multiple sclerosis; 3) secondary progressive multiple sclerosis; 4) progressive multiple sclerosis with relapses. Medical treatment involves anti-inflammatory drugs, especially corticosteroids, immunomodulators, and immunosuppressants. Cannabinoids can treat severe pain, both Δ^9-THC and CBD: Δ^9-THC for its anesthetic, analgesic antiemetic effects, and CBD for its anti-inflammatory, analgesic, and anxiolytic properties. Cannabis medications for this treatment work by reducing stiffness, spasticity, and pain. Compared to conventional medications, they have fewer side effects and are more potent[10, 21].

Parkinson's and Alzheimer's

Parkinson's disease is a chronic and progressive neurodegenerative disease of the central nervous system. It occurs due to the decrease of dopamine, a neurotransmitter related to the performance of voluntary movements, causing the patient to develop involuntary movements and lose muscle strength. With this reduction, the dopamine-dependent areas become atrophied. Symptoms are classified as motor and not motor. Motor symptoms are tremors at rest, muscle stiffness; slowness of voluntary movements or absence of them; Parkinsonian gait, which is the slowest gait; body curvature forward; shortening of steps; and decreased facial expression. Examples of not motor symptoms are depression, cognitive changes; changes in voice; and disturbances. The med-

ications used in the treatment are for symptom relief, such as levodopa, but chronic use brings acute adverse effects.

Alzheimer's is also a neurodegenerative disease, frequent in older people, leading to cognitive and memory damage. The main symptoms are memory loss, depression, psychomotor agitation, affective disorders, failure in facial recognition, and others. The cause is related to the erroneous processing of CNS proteins, mainly beta-amyloid and tau protein, with these emerging toxic fragments inside neurons leading to their death in essential brain regions such as memory, language, reasoning, and others. Neuroinflammation starts by activating microglia after phagocyting these proteins and releasing several cytokines. Glutamate and reactive oxygen substances that favor toxicity and oxidative stress are also released. The drugs used in the treatment are donepezil and rivastigmine, but they have many adverse effects. Other classes are used for symptom relief, such as antidepressants, anticonvulsants, and others.

Therefore, using cannabinoids for their anti-inflammatory, neuroprotective, and antioxidant properties seems promising to prevent neurotoxicity, promote anti-apoptotic action, reduce neuron inflammation and oxidation, and improve symptoms. Furthermore, few adverse effects have been reported in human and animal studies. However, more studies are needed to clarify the benefits of cannabinoids in these pathologies[59].

Autism Spectrum Disorder

It is an alteration in neuronal development that affects communication, social behavior, sensations, motor planning, and various brain areas. Several conditions can be involved, such as genetics and environmental factors. Among the symptoms are the absence or not of verbal communication, altered sensitivity in some ways, aggressiveness, convulsion, lack of socialization, and empathy. The treatment of this disease aims to alleviate the symptoms, and for that, several drug classes are used, such as antidepressants, mood stabilizers, benzodiazepines, antipsychotics, and many others. As with the other diseases discussed above, these treatments have several side and adverse effects.

Studies show that the autistic person does not perform homeostasis in the cells where the CB1 and CB2 receptors are found[13]. Thus, the cannabis oil would function as an agonist, stimulating this physiological process, adjusting serotonin and other neurotransmitters levels, and regulating excessive neuronal processes. Cannabis oil could mitigate symptoms for CBD relaxing and antipsychotic properties, similar to traditional medicines with fewer adverse effects [14, 20].

We concluded that the use of cannabinoids, mainly CBD and Δ^9-THC, has shown promise in treating several pathologies and being the primary active substance in cannabis-based medications. However, the research results are still inconsistent. Authors have different opinions as in treating Parkinson's diseases and fibromyalgia, which some show beneficial results. Others do not recommend using Cannabis actives[13, 60]. It is necessary to emphasize that medicinal cannabis is used to treat these diseases and is associated with other standardized medications in therapeutic procedures. In Brazil, the available legislation has enabled the use of medication by patients. However, there is still a strenuous bureaucracy in access and the high cost.

The mechanism of action is not fully understood and is overly complex. However, it is known that cannabinoids interact with components of the endocannabinoid system and inhibit the release of several neurotransmitters, some involved in the development of diseases, such as glutamate and dopamine, in Epilepsy, Alzheimer's, and Parkinson's.

Finally, among the pharmaceutical forms presented, the oral forms are the most cited, as they are easy to administer by the patient and have relatively quick action.

Further research is needed to understand the use of medicinal cannabis. These studies will

enable more knowledge of the diseases this plant treats and possibly facilitate access to these drugs at a more affordable price with support from the population, State, and health teams, without the risk of penalties when seeking quality of life.

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Table S1: Papers that address active ingredients/cannabinoids, Cannabis-based drugs, diseases, mechanism of action, and pharmaceutical presentations.

Author	Year	Title	Active ingredients/ cannabinoids	Medicines (trade name and input)	Pharmaceutical presentations	Conditions	Mechanism of action
Crippa; Zuardi & Hallak	2010	Uso terapêutico dos canabinoides em psiquiatria	CBD; Δ^9-THC; canabigerol; canabicromeno; delta-9-tetrahidrocanabivarina; canabidivarina; ácido tetrahidrocanabinólico; ácido canabidiólico.	Nabilone (Δ^9-THC analogue); dronabinol; rimonabant-CB1 antagonist.	-	Multiple sclerosis: Parkinson, Schizophrenia, associated with Cannabis; anxiety; depression; Fibromyalgia.	Δ^9-THC binds to the CNS via cannabinoid receptors, CB1/CB2. The endocannabinoids, AEA and 2-AG, also compose the SE, which modulates several physiological and pathophysiological processes in psychiatric disorders. CBD interferes with the effects of Δ^9-THC, and when administered concurrently and at a high dose, it attenuates the anxiety and psychotic symptoms induced by Δ^9-THC, attributing to its anxiolytic and/or antipsychotic effects. CBD interacts with 5-HT1A receptors (antidepressant and mood stabilizing effect), which appears to be involved in its anxiolytic action. The antipsychotic effect may involve glutamate and glutamate/aspartate-activated ionotropic receptors and exogenous agonists (NMDA).
Saito; Wotjak & Moreira	2010	Exploração farmacológica do sistema endocanabinoide: novas perspectivas para o tratamento de transtornos de ansiedade e depressão?	Δ^9-THC; CBD; cannabinol and cannabichromene.	Nabilone (Δ^9-THC analogue); rimonabant.	-	Anxiety, metabolic syndrome, depression, antiemetic function.	CB1 and CB2 receptors are G protein-coupled. CB1 is in pre-synaptic terminals responsible for neurobehavioral effects. At the same time, CB2 is present in the immune system but can also be expressed in neurons. The CB1/CB2 agonist endocannabinoids are AEA, 2-AG, dopamine-n-arachidonoyl (NADA), glycerol-2-arachidonoyl ether (noladin), and ethanolamine-O-arachidonoyl (virodamine). can dock to receptors such as TRPV1, possibly activated in the CNS by AEA and in the periphery by capsaicin; GPR55 receptor, and peroxisome proliferator-activated receptor (PPAR). An allosteric site in CB1 was identified as a possible target for pharmacological intervention. Endocannabinoids are synthesized on demand and are not stored in vesicles causing them to act retrogradely. Synthesis occurs in post-synaptic neurons after calcium in-

							flux and activation of phospholipases D for AEA and DGL for 2-AG, converting phospholipids into endocannabinoids. Activation of CB1 receptors results in a decrease in calcium influx into axon terminals, thus decreasing release after activation of CB1 and activation of TRPV1 receptors by AEA, depolarization of post-synaptic membranes increases. The enzymes responsible for degrading AEA and 2-AG are, respectively, fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MGL), both in pre-synaptic (2-AG) and post-synaptic (AEA) forms.
Sewell et al.	2010	Efeitos comportamentais, cognitivos e psicofisiológicos dos canabinoides: relevância para a psicose e a esquizofrenia	CBD; Δ^9-THC	Nabilone and levonantradol (Δ^9-THC analogues)	-	Chemotherapy-induced nausea and spasticity due to Multiple Sclerosis and pain syndromes.	–
Costa et al.	2011	Neurobiologia da Cannabis: do sistema endocanabinoide aos transtornos por uso de Cannabis	Δ^9-THC, CBD, cannabinol, cannabigerol, cannabichromene	-	-	-	CB1/CB2 cannabinoid receptors, enzymes, and endocannabinoid ligands make up SE. The receptors are coupled to the G protein, which CB1 is more present in the CNS in pre-synaptic cells and low density in post-synaptic cells and glia. Besides being responsible for the psychotropic effects, it competes with glutamatergic receptors, and its activation inhibits AC, decreasing the conversion of ATP to cAMP, consequently decreasing the activity of protein kinase A (PKA), which decreases the phosphorylation of K+ channels and increases the output of K+ from pre-synaptic terminals. With the activation of CB1 neuronal hyperpolarization occurs, reducing the release of neurotransmitters. Post-synaptic CB1 receptors regulate synaptic excitability and plasticity by modulating potassium channels and inhibiting AC. CB2 receptors are expressed in the immune system but can also be present in the CNS, microglia, and post-synaptic location. Other receptors interact with

							cannabinoids, such as TRPV1, GPR55, and PPAr receptors. The endocannabinoids are AEA (partial agonist) and 2-AG, in which 2-AG has a greater affinity for CB receptors (full agonists), and AEA has a greater affinity for other receptors and is a full agonist of TRPV1. Synthesis of endocannabinoids occurs through increased intracellular calcium concentration by depolarization or mobilization of in tracellular deposits and direct enzymatic activation by G9/G11 proteins; after synthesis, they are transported to the binding site. The AEA synthesis pathway is the transacylation-phosphodiesterase which converts PE and PC into NAPE, occurring hydrolysis by NAPE-PLD forming AEA. The 2-AG pathway is PLC-beta, DGL, which converts membrane phosphoinositide into 1,2 -DGL, followed by hydrolysis by DGL, forming 2-AG. AEA's activation of post-synaptic TRPV1 may constitute a regulatory feedback mechanism, inhibiting DGL□ and decreasing 2-AG production. Facilitated diffusion transporters mediate AEA and 2-AG, and their inactivation involves pre-synaptic uptake or post-synaptic reuptake and rapid oxidation/hydrolysis of the ester/amide bonds. The enzyme responsible for metabolizing AEA is FAAH (post-synaptic), and 2-AG is hydrolyzed by MGL (pre-synaptic). The existence of non-CB1/CB2 receptors, the CB3, is also discussed.
Duarte	2012	O potencial analgésico dos canabinoides	Δ^9-THC; CBD	Cesamet® (nabilone); Marinol® (dronabinol); Cannador® (CBD/Δ^9-THC); Sativex® (Δ^9-THC and CBD);	Nasal spray; oral spray.	Multiple sclerosis; chronic pain;	Cannabinoid receptors are found on various cells such as neurons, immune cells, endothelial cells, and vascular muscle. In the CNS, signal transmission is mediated by CB1, and its activation also inhibits N/L/P and Q-type calcium channels and potassium channels. CB2 receptors are expressed in organs responsible for the production and regulation of immune cells. Enzymes invol-

							ved in endocannabinoid synthesis are DGL, PLD, NAPE, and in degradation, they are FAAH and MGL. Endocannabinoids are produced when needed from membrane phospholipids; post-synaptic depolarization releases them, they diffuse and activate CB1 at the pre-synaptic termination. Synthesis can also be stimulated by metabotropic and muscarinic glutamate receptors (M1 and M3). They engage in various processes such as thermoregulation, appetite, immune function, perception, cognition, motor function, pain modulation, mood changes, pathological functions. Endocannabinoids have a structure similar to Δ^9-THC (psychoactive); AEA and 2-AG are linked to pain modulation and inhibit pain stimulation. They are released by depolarized post-synaptic neurons, proceeding to pre-synaptic terminals where they activate CB1 receptors by retrograde signaling. The overall effect is to reduce the release of excitatory neurotransmitters such as glutamate. Also involved are TRPV1 and GP55 receptors.
Guevara	2012	Tratamiento de la espasticidad en la esclerosis múltiple: nuevas perspectivas con el uso de cannabinoides	CBD; Δ^9-THC	Sativex® (CBD/THC 1:1); dronabinol; nabilone;	oral spray	Multiple sclerosis; refractory pain.	The endocannabinoids are AEA and 2-AG and are agonists of the CB1/CB2 cannabinoid receptors. CB1 receptors are found in the CNS, nerve endings responsible for movement, postural control, pain perception, and other functions, such as muscle spasticity modulation and psychotropic effects. At the same time, CB2 is less frequent in the brain, found in microglia. Δ^9-THC is a partial agonist of CB1/CB2 receptors, and CBD has a low affinity for CB receptors. CBD antagonizes the psychotropic activity of Δ^9-THC and acts synergistically with it on its anti-inflammatory effects.
Fonseca et al.	2013	Sistema Endocanabinóide – uma perspetiva terapêutica	Δ^9-THC; CBD	ronabinol (Marinol®) and nabilone (Cesamet®); Sativex® (Δ^9-	-	HIV; cancer; neuropathic pain; Multiple sclerosis;	CB1 receptor is found mainly in the CNS and is responsible for mediating psychotropic effects, and CB2 is found in peri-

				THC /CBD); Acomplia® (rimonabant)			pheral organs and tissues. The endocannabinoids are AEA, 2-AG, virodamine, N-arachidonyldopamine, and 2-arachidonylglyceryl ether, are synthesized from membrane precursors and stimulus, not being retained in vesicles like other neurotransmitters. Enzyme NAPE-PLD makes AEA synthesis, and the 2-AG by the enzyme DGL and the degradation of AEA is made by the enzyme FAAH and the 2-AG by MGL. In neurons, CB1 activation inhibits neurotransmitter release, and CB2 activation in immune cells mediates immunosuppressive effects. Cannabinoid signaling engages in several other processes such as memory, pain, inflammation, appetite, reproduction, and the cardiovascular system. CBD blocks AEA uptake and degradation, in addition to having agonistic properties on serotonin receptors.
Fernandéz et al.	2014	xperiencia clínica con los cannabinoides en la terapia de la espasticidad en la esclerosis múltiple	Δ^9-THC; CBD	Sativex® (CBD/Δ^9-THC)	Oral Spray	Multiple sclerosis	-
Lopes	2014	Canabinoides ajudam a desvendar aspectos etiológicos em comum e trazem esperança para o tratamento de autismo e epilepsia	Δ^9-THC; CBD; canabivarina.	Pure CBD	Oral	Autism; Epilepsy	CBD blocks the anxiogenic and psychotomimetic effects of Δ^9-THC, acts on 5-HT1A receptors, has low affinity for CB1/CB2 receptors, and acts on TRPV1, GP55 receptors, adenosine receptors, and glycine receptors, and generates AEA accumulation. Endocannabinoids (AEA and 2-AG) bind to CB1/CB2 receptors and respond to neuronal activation. DGL is responsible for the synthesis of 2-AG and MGL for degradation. Direct antagonism of CBD over CB1 prevents the action of endocannabinoids. CBD prevents the spread of hyperactivation at glutamatergic synapses, where AEA builds up, stimulated by hyperactivation. Δ^9-THC, on the other hand, by acting directly on CB1 receptors in GABAergic cells, may

							contribute to increasing the disinhibition of the system.
Pamplona	2014	Quais são e pra que servem os medicamentos à base de Cannabis?	Δ^9-THC; CBD;	Dronabinol (Marinol®); rimonabant (Acomplia®); nabilone (Cesamet®); Bedrocan®; Bediol®;	Standardized extract; gelatinous oral capsules; oral spray.	Cancer; HIV; neuropathic pain; Multiple sclerosis; Epilepsy.	Endocannabinoids are mainly AEA and 2-AG similar in structure and actions to Δ^9-THC. They act on CB1 receptors expressed in the CNS, reducing neurotransmitter release and neuronal excitation. Endocannabinoids' known functions are body temperature regulation, appetite regulation, pain threshold reduction, and modulation of cognitive processes. CBD balances the effects of Δ^9-THC.
Pedrazzi et al.	2014	Perfil antipsicótico do canabidiol	CBD and Δ^9-THC	Sativex® (50% de CBD e Δ^9-THC)	Oral Spray	Cancer, Neuropathic Pain, Multiple Sclerosis.	CB1 cannabinoid receptors are found in the CNS (pre-synaptic cells) and are responsible for the psychotropic effects of cannabinoids; and CB2, found in the SNP (cells of the immune system and specific areas of the CNS), it is also suggested that they participate in pain modulation. Activation of CB1 inhibits the release of other neurotransmitters, inhibitory or excitatory, such as GABA and glutamate, respectively. Δ^9-THC binds to both CB1/CB2 receptors. CB1/CB2 receptors are coupled to inhibitory G protein, which, when activated, inhibits the AC enzyme, decreasing cAMP levels and inhibiting calcium channels. Endocannabinoids are derived from arachidonic acid, and the main ones are AEA and 2-AG, produced on-demand in post-synaptic terminals. After calcium influx, induced by glutamate or GABA, phospholipases are activated and converted into endocannabinoids, which act on pre-synaptic terminals where they inhibit the release of neurotransmitters. They are retrograde messengers and mediate the transfer of information from post to pre-synaptic terminals. The degradation of endocannabinoids is made by the enzymes FAAH and MGL, which act respectively on AEA and 2-AG. CBD does not act

							on specific cannabinoid receptors and facilitates endocannabinoid signaling by inhibiting AEA reup take; it is also considered a 5-HT1A receptor agonist, activates the TRPV1 receptor, and increases adenosine-mediated signaling.
Pernoncini & Oliveira	2014	USOS TERAPÊUTICOS POTENCIAIS DO CANABIDIOL OBTIDO DA Cannabis sativa	Δ^9-THC (psychoactive); CBD.	Sativex® (Δ^9-THC /CBD); CB1 antagonist ri monabant	-	Cancer; Epilepsy; anxiety; insomnia. AIDS; diabetic retinopathy.	N-arachidonyl dopamine (NADA), and phospholipid derivatives produced on demand. An essential role in modulating neurotransmission is considered as retrograde transmitters and act in various physiological processes. Cannabinoid receptors interact with Δ^9-THC and endocannabinoids. They are CB1 mainly found in the CNS and CB2 in the immune system. Activation of these receptors affects the actions of several neurotransmitters such as acetylcholine, dopamine, GABA, glutamate, serotonin, norepinephrine, and endogenous opioids. CBD does not activate these receptors as it does not have psychoactive properties such as Δ^9-THC. CBD is a CB2 antagonist, with the main targets of CBD being TRPV receptor, transient melastatin potential receptor (TRPM), transient ancrine transmembrane protein (TRPA) receptor potential, 5-HT1A receptor, orphan receptor linked to a G protein (GPR55), and peroxisome proliferator-activated gamma receptors (PPARα). Endocannabinoids are released after post-synaptic activation, and their action ends with uptake in pre-synaptic endings, followed by degradation. The increase in intracellular calcium allows cannabinoids to bind to receptors. When they bind, they lead to reactions in various intercellular components, such as inhibition of AC, opening K+ channels, decreased signal transmission, and closure of calcium channels.
Brucki et al.	2015	Cannabinoids in neurology	Δ^9-THC (psychoactive) and CBD	Epidiolex® (98% CBD); Nabiximols® (Δ^9-THC / CBD 1:1); Cannabis Ex-	Oral; inhalation.	Epilepsy; Multiple sclerosis; neuropathic pain; Parkinson's;	The main endocannabinoids are AEA and 2-AG. They are released due to excitatory activity and synthesized in neurons by

				tract.		HIV; headache.	the increase in intracellular calcium. They inhibit the release of neurotransmitters at GABAergic and glutamatergic terminals, in addition to acting on various plasticity mechanisms.
Larrussa et al.	2015	A influência do sistema endocanabinoide na fisiopatologia da Multiple Sclerosis	Δ^9-THC, CBD, cannabinol and cannabichro- mene.	Sativex® (Δ^9-THC /CBD)	Oral spray	Multiple sclerosis	CB1 receptors are found in the CNS and CB2 in immune cells. The endocannabinoids that make up the SE are mainly AEA and 2-AG, produced on demand and not stored in vesicles like other neurotransmitters; their synthesis occurs in post-synaptic neurons after the activation of the PLD (AEA) and DGL enzymes (2-AG). Activation occurs through the influx of calcium into these neurons. They cross membranes by diffusion and reach receptors on pre-synaptic neurons, resulting in decreased calcium influx into the axon and release of neurotransmitters into the synaptic cleft. Cannabinoids inhibit peripheral blood T lymphocytes through CB2 re ceptors on T lymphocytes, reducing antigen presentation and producing inflammatory and pro-inflammatory cytokines. Endocannabinoids inhibit microglia activation and lymphocyte function to inhibit apoptosis. When inducing AEA, the immune response releases tumor necrosis factor (TNF-alpha), leading to a neuronal rearrangement, releasing glutamate, and causing excitotoxicity. CB1 can interfere with glutamate release by inhibiting pre-synaptic neurons, as it inhibits cAMP and interrupts the influx of calcium into the neuron.
Oliveira & Silva	2015	A inovação na utilização de compostos de Cannabis sativa em medicamentos	Δ^9-THC; CBD	Marinol® (Δ^9-THC); Sativex® (Δ^9-THC /CBD);	-	Multiple Sclerosis, Parkinson's Disease, Cancer, Anorexia, Epilepsy, HIV, Glaucoma.	-

Paulo & Abreu	2015	Cannabis no gerenciamento de patologias-revisão de literatura	Δ^9-THC (psychoactive); CBD; cannabinol; cannabichromene, cannabicyclol.	Dronabinol and nabilone (synthetic analogues of Δ^9-THC); rimonabant (synthetic CB1 antagonist); Sativex (Δ^9-THC and CBD 1:1)	Oral; spray oral.	Epilepsy, Cancer, AIDS, Schizophreni, Glaucoma, Multiple Sclerosis; anxiety; panic syndrome, post-traumatic disorder, obsessive-compulsive disorder; insomnia; Alzheimer's.	Cannabinoid receptors CB1/CB2 and CB3 are G protein-coupled, as are glutamatergic receptors. CB1 is more expressed in the CNS, pre-synaptic, post-synaptic and glia and, in a smaller amount in the periphery, are responsible for the psychotropic effects of cannabinoids and the release of neurotransmitters in pre-synaptic neurons; inhibits AC, resulting in neuronal hyperpolarization and reduced neurotransmitter release; it acts in the regulation of excitation levels and synaptic plasticity through the frequency variation of the K+ channels. CB2 is found in the immune system and some areas of the CNS, mainly microglia and post-synaptic sites. When CB2 is activated, inhibition of AC and activation of the MAPK cascade occurs. The existence of non-CB1/CB2 receptors is considered; some activate vanilloid receptors that generate stimuli in pain nerve endings, known as CB3 receptors.
Corrêa	2016	Utilização dos canabinoides no tratamento de epilepsia em pacientes refratários	Δ^9-THC; CBD: canabinol; canabicromeno.	-	-	Epilepsy	Cannabinoid receptors are CB1 (CNS) and CB2 (cells in the immune system). CB1 is located at excitatory (glutamatergic) and inhibitory (GABAergic) synapses. Their activation results in the inhibition of the neuronal activity of these circuits and the neurotransmitters that activate these pathways. Endogenous CB1 agonists are AEA and 2-AG, with AEA being similar to Δ^9-THC and 2AG, which have an affinity for both receptors, but more so for CB1. The synthesis of endocannabinoids occurs in a retrograde way, from the post-synaptic to the pre-synaptic terminal, arising from the breakdown of phospholipids and having a degradation and capture system, conducted by the FAAH enzymes that act on the AEA and MGL that acts on the 2-AG.
Gontijo et al.	2016	Canabidiol e suas aplicações terapêuticas	Δ^9-THC; CBD	Nabiximols®/Sativex® (2,5mg Δ^9-THC /2,7mg CBD 1:1); pure CBD	Oral spray; oral; inhalation.	Epilepsy; anxiety; neurodegenerative diseases such as Par-	SE is composed of cannabinoid receptors CB1, expressed in the CNS and responsible for the psychoactive effects and CB2

						kinson's; Multiple sclerosis; HIV.	in peripheral organs and tissues; Endocannabinoids like AEA, 2-AG, virodamine; and enzymes. There are also synthetic ligands with an affinity for cannabinoid receptors, such as WIN-55 (agonist) and rimonabant (antagonist). CBD has no affinity for these receptors; its most excellent affinity is for 5-HT1A receptors.
Isaac; Saini & Chaar	2016	The Role of Medicinal Cannabis in Clinical Therapy: Pharmacists' Perspectives	Δ^8-THC, Δ^9-THC, CBD, canabinol.	Sativex®/Nabiximols® 2.7mg Δ^9-THC + 2.5mg CBD; Marinol®/dronabinol 2.5mg, 5mg, 10mg; Cesamet®/nabilone 1mg; Elixinol® (CBD used as a food supplement)	Oromucosal spray, capsule, tablet.	Spasticity, chronic neuropathic pain, chemotherapy-induced nausea and vomiting, cachexia, appetite stimulation and weight loss in HIV patients, Tourette syndrome, sleep improvement.	-
Lessa; Cavalcanti & Figueiredo	2016	Cannabinoid derivatives and the pharmacological management of pain	CBD; Δ^9-THC	dronabinol (Marinol®) nabilone (Cesamet® -Δ^9-THC analogue) Cannador® (Δ^9-THC / CBD 2:1); Sativex® (CBD/Δ^9-THC)	Oral; mouth spray; gelatin capsules; oral capsules.	Migraine, fibromyalgia, other diseases with involved glutamatergic mechanisms, rheumatoid arthritis; Multiple sclerosis.	SE is formed by cannabinoid receptors, coupled to G protein such as CB1, present in the basal ganglia, cerebellum, hippocampus, cortex, spinal cord, and peripheral nerves, in addition to being responsible for the psychotropic effects and CB2 in immune cells, which explains the effects antinociceptives and anti-inflammatory drugs; endocannabinoids, mainly AEA and 2-AG, CB1/CB2 agonists. After their release, they are metabolized by FAAH (post-synaptic) and MGL (pre-synaptic). AEA is hydrolyzed to arachidonic acid and ethanolamine degradation products, and 2-AG to arachidonic acid and glycerol. Δ^9-THC inhibits Prostaglandin E2 and stimulates lipoxygenase without affecting COX 1 and 2. Cannabinoids inhibit glutamate release in the hippocampus by reducing the immediate pain response by NMDA. CBD inhibits FAAH and AEA reuptake, reduces hepatic metabolism of Δ^9-THC, hence its psychotic effects and anxiety symptoms.
Melo & Santos	2016	O uso do Canabidiol no Brasil e o posicio-	CBD; Δ^9-THC	-	-	-	-

		namento do Órgão Regulador					
Tzadok et al.	2016	CBD-enriched medicinal Cannabis for intractable pediatric epilepsy the current Israeli experience	Δ^9-THC; CBD	Pure CBD	Cannabis Oil enriched with CBD	Multiple sclerosis; adverse effects of chemotherapy; phantom pain; diabetic neuropathy; spinal cord injury; post-traumatic stress disorders; Tourette's syndrome; Crohn's disease; severe fibromyalgia.	Δ^9-THC activates SE and CBD is an antagonist of cannabinoid receptors that modulates SE, potentiating AEA-mediated neurotransmission, in addition to being involved in the regulation of neurotransmitters and brain receptors.
Blake et al.	2017	A selective review of medical Cannabis in cancer pain management	Δ^9-THC e CBD	Nabiximols® (Δ^9-THC / CBD); Δ^9-THC puro;	Inhalation, oral as oils or capsules containing oils, oromucosal sprays.	cancer pain	SE is responsible for controlling pain signaling, immune activation and inflammation.
Carvalho; Brito & Gandra	2017	Mães pela cannabis medicinal em um Brasil aterrorizado entre luzes e fantasmas	Δ^9-THC; Canabinol; CBD.	Dronabinol (Marinol®); Mevatyl®/Sativex® (Δ^9-THC /CBD)	Oral; oral spray.	Parkinson, Alzheimer, Multiple Sclerosis, Cancer, Huntington, Epilepsy, Autism.	-
Carvalho et al.	2017	Canabinoides e epilepsia: potencial terapêutico do canabidiol	CBD and Δ^9-THC (psychoactive); cannabigel, cannabichromene, cannabivarin, tetrahydrocannabivarin, cannabichromevarin, cannabigerovar	Bedrocan® (22%Δ^9-THC: <1%CBD); Bedrobinol® (13.5%Δ^9-THC: <1%CBD); Bedica® (14%Δ^9-THC:<1%); Bediol® (6.5%Δ^9-THC:8%CBD); Bedrolite® (0.4%Δ^9-THC:9%CBD); Cannimed® (different proportions between Δ^9-THC and CBD); Sativex® (2.7mgΔ^9-THC / 2.5mgCBD; Marinol® (dronabinol 2.5-10mg in capsules); nabilone (Cesamet® - 1mg/cps); Epidiolex® (0%Δ^9-THC: 98% CBD)	Vaporization, oil, tea, oromucosal spray, oral-capsules and oral solution.	Epilepsy; pain; cardiovascular diseases; glaucoma; cancer; Alzheimer, Multiple Sclerosis; Amyotrophic Lateral Sclerosis; Parkinson's;	Δ^9-THC is a partial agonist of CB1/CB2 cannabinoid receptors. SE has regulatory functions and is mainly composed of cannabinoid receptors (CB1/CB2), endocannabinoids such as AEA, 2-AG, oleamide, virodamine, noladine, and NADA, and synthesis and degradation enzymes. Cannabinoid CB1/CB2 receptors are inhibitory G protein-coupled receptors that inhibit AC activity by reducing cAMP levels. CB1 is found in greater quantity in the CNS, glutamatergic and GABAergic pre-synaptic terminals, and CB2 in the immune system

Hill & Palastro	2017	Medical Cannabis for the treatment of chronic pain and other disorders: misconceptions and facts	Δ^9-THC; CBD	Nabilona, dronabinol	oral extract	HIV; chronic and neuropathic pain; spasticity associated with Multiple Sclerosis; convulsive disorders (Epilepsy); gastrointestinal disorders; glaucoma; Parkinson's; post-traumatic stress.	–
Nunes et al.	2017	Canabidiol (Cannabis sativa): associada no tratamento de doenças neurológicas e sua legalização	Δ^9-THC; CBD; cannabichromene and cannabigerol.	CBD/Δ^9-THC	Inhalation; tea; tablet.	Glaucoma, Multiple Sclerosis; cancer; anxiety, immune disorders, cardiovascular diseases, and neurological disorders; AIDS; Tourette's syndrome.	CB1 cannabinoid receptors are found distributed in many areas of the CNS, and CB2 are not found in the CNS, being located in peripheral areas such as cells of the immune system.
Suryadevara et al.	2017	Pros and Cons of Medical Cannabis use by People with Chronic Brain Disorders	CBD; Δ^9-THC (psychoactive); delta-9-tetrahydrocannabivarin.	Nabiximols® (Sativex® Δ^9-THC /CBD 1:1); Marinol® (dronabinol); nabilona (Cesamet®); rimonabanto.	Extract; oral	Parkinson's, Alzheimer's, Schizophrenia, Bipolar Disorder, Multiple Sclerosis; Amyotrophic lateral sclerosis;	Endocannabinoids (AEA and 2-AG) and cannabinoids activate cannabinoid receptors CB1/CB2, with CB1 being more common in the CNS while CB2 is more commonly found in the periphery but also some areas of the brain.
Trindade et al.	2017	Canabinoides para Tratamento de Epilepsia em Crianças	Δ^9-THC; CBD	Δ^9-THC enriched extracts with CBD	Oral	refractory epilepsy	-
Oliveira; Bernardo & Lima	2018	Cannabis sativa: Política proibicionista e o direito à saúde	CBD, Δ^9-THC, canabigerol; canabinol.	-	-	Cancer, AIDS, Multiple Sclerosis and Tourette syndrome. Amyotrophic Lateral Sclerosis (ALS); diabetes, glaucoma, Alzheimer, Parkinson, schizophrenia,	SE is composed of CB1 cannabinoid receptors found in the CNS, connective tissue, gonads, and glands and CB2 in the Thymus, spleen, lymphoid tissue, palatine tonsils and immune system. Its main function is to maintain the body's homeostasis.
Silva	2018	A maconha nas perspectivas contemporâneas: benefícios e malefícios	Δ^9-THC (psychoactive); CBD cannabinol; Δ^8-THC.	-	-	Alzheimer's; Parkinson's; AIDS; cancer; anxiety; Epilepsy; Multiple sclerosis;	Endocannabinoids have similar effects to Phytocannabinoids, but they are produced in the body and bind to CB1/CB2 cannabinoid receptors.

						neuropathic pain; diabetes; glaucoma; Huntington's disease;	
Agnese	2019	Cannabis medicinal em Argentina: perspectiva desde la salud pública	CBD; Δ^9-THC	Nabilona (Cesamet®); dronabinol (Marinol®)	-	Multiple Sclerosis; Epilepsy; neuropathic pain; HIV; Dravett syndrome, Lennox-Gastaut syndrome, glioblastoma multiforme, pediatric schizophrenia, glioma, infantile spasms, neonatal hypoxic ischemic encephalopathy, fragile X syndrome; chronic pain.	Δ^9-THC is a partial agonist of CB1/CB2 cannabinoid receptors and reduces cAMP, whereas CBD has a low affinity for these receptors and acts as an indirect antagonist.
Alsherbiny & Li	2019	Medicinal Cannabis—Potential Drug Interactions	Δ^9-THC, CBD, Δ^8-THC, canabinol.	Epidiolex®; Sativex®/ Nabiximols® (CBD/Δ-9-THC - 27mg/ml and 25mg/ml; dronabinol 2.5–20 mg capsule and oral or oral solution 2.5–5 mg; (Marinol®); nabilone; bedrocan®;	Oral, oral capsule, oral spray, oral solution, tea, inhalation.	Cancer.	CBD can interact with other receptors such as PPARs, GPR55, and TRPV1 receptors. These receptors are considered endocannabinoids because they assist in endocannabinoid signaling. The most common endocannabinoids are AEA and 2-AG, bind to CB1/CB2 cannabinoid receptors, and have actions similar to Phytocannabinoids. Receptors and ligands make up the SE that acts on several physiological processes. Exogenous cannabinoids or degradation pathways are promising for developing new treatments for neurodegenerative diseases, nausea and vomiting, chronic pain, and various carcinomas.
Basílio & Ferreira	2019	A importância do uso do canabidiol em pacientes com epilepsia	Δ^9-THC; CBD	-	-	Epilepsy; Parkinson's disease; AIDS; Multiple Sclerosis; cancer.	CBD is a competitive antagonist of Δ^9-THC and has low affinity for CB1/CB2 cannabinoid receptors, while Δ^9-THC has high affinity. CB1 receptor is found in the CNS and mediates psychotropic effects while CB2 is found in the immune system. Endocannabinoids (AEA and 2-AG) bind to these receptors. CB1 when activated blocks the release of inhibitory and excitatory neurotransmitters such

							as GABA and Glutamate, respectively, and increases the action of endocannabinoids by inhibiting AEA hydrolysis. CBD is an adenosine receptor agonist, acts on 5-HT1A and CB1 receptors, inhibiting synaptic transmission, blocking K+ and Na+ channels and inhibiting seizures.
Bozkurt	2019	Endocannabinoid System in the Airways	Δ^9-THC as the main compound; CBD; cannabinol.	-	-	-	Endocannabinoids are AEA, 2-AG, virodamine, noladine ether, oleoiol ethanolamine. Endocannabinoids, cannabinoid receptors, and metabolic pathways form SE. AEA is synthesized by NAPE-PLD, alpha/beta hydrolase 4, and PLC enzymes and catabolized by the FAAH enzyme. 2-AG is synthesized by PLC and DGL and catabolized by MGL. COX-2 engages in the oxidation of 2-AG and AEA to generate prostamides such as Prostaglandin H2 ethanolamide, Prostaglandin H2, and Prostaglandin H2 glycerol. CB1/CB2 receptors are transmembrane receptors, G protein-coupled and can bind to other targets such as TRPV1 receptor, GPR55 receptor, GPR18, GPR110, GPR119, and PPAR receptor. Both CB1/CB2 receptors are negatively coupled to AC and stimulate MAPK. They activate Na+ channels and inhibit K+ channels, resulting from inhibition of neurotransmitter release by activation of the Gbeta/gamma subunit. CB1 is commonly found in the nervous system, nerve endings, and tissues, including adipose tissue, liver, gastrointestinal tract, and CB2 is expressed in peripheral tissues, but mainly in immune cells. Δ^9-THC inhibits Th1 lymphocytes and enhances Th2 cytokines. AEA reduces B and T cell proliferation. CB2 contributes to mast cell activation producing nitric oxide and prostaglandin E2.
Müller et al.	2019	Canabinoides como uma nova opção terapêutica nas doenças de Parkinson e de Alzheimer: uma	Δ^9-THC; CBD; tetrahidrocanabivarina.	Mevatyl® equivalent to Sativex® (Δ^9-THC / CBD); Namisol®.	Oral; Tablet	Parkinson's; glaucoma; cancer; Multiple Sclerosis; symptoms caused by AIDS; Alzheimer's.	Activation of SE occurs through cannabinoid receptors that release neurotransmitters, especially glutamate. CB1 receptors are found in the CNS and CB2 in the peripheral nerves in the nervous system,

		revisão de literatura					coupled to a G protein. Binding between receptor and agonist results in the inhibition of AC and voltage-dependent calcium channels, in addition to the activation of K+ and MAPK channels.
Fonseca et al.	2019	Canábis e Canabinoides para fins medicinais	Canabinol; CBD, Δ^9-THC.	Dronabinol (Marinol®); dronabinol (Syndros®); nabilone (Cesamet®); Nabiximols (Sativex® – Δ^9-THC and CBD); Epidiolex® (CBD); Medical cannabis (extract)	Oral; oral spray; inhalation.	Epilepsy, HIV, cancer, glaucoma;	CB1 and CB2 receptors, endocannabinoids, and metabolic enzymes build up the SE.
Guida et al.	2019	Cannabis medicinal como recurso terapéutico: estudio preliminar	Δ^9-THC; CBD	Epidiolex® (CBD); Nabiximols® (Δ^9-THC /CBD); dronabinol (Δ^9-THC synthetic),	-	Parkinson's, Epilepsy, Multiple Sclerosis, neuropathic pain, brain tumors, chronic pain, arthrosis, fibromyalgia, rheumatoid arthritis, cancers such as breast, lung and colon cancer, depression, bipolar disorder and panic, dermatological, gastrointestinal, and pulmonary diseases.	CB1/CB2 receptors interact with endocannabinoids (AEA and 2-AG) and Phytocannabinoids (Δ^9-THC and CBD). CNS and peripheral are where most CB1 receptors and CB2 receptors are found in immune cells, gonadal tissues, and restricted brain areas. SE is formed by cannabinoid, endocannabinoid, and enzyme receptors.
Gurgel et al.	2019	Uso terapêutico do canabidiol: a demanda judicial no estado de Pernambuco, Brasil	CBD; Δ^9-THC	-	-	Alzheimer's, Arthritis, Epilepsy, Anxiety, Parkinson's, Schizophrenia and Marijuana Withdrawal Syndrome, Neuropathic Pain, Kidney Injury, Neurodegenerative Diseases, Multiple Sclerosis and Neoplasm.	-
Leite & Borges	2019	O USO DE MEDICAMENTOS À BASE DE CANABINOIDES NO BRASIL: UM ESTUDO DE CASO	Δ^9-THC; CBD	Mevatyl®	-	Convulsive fits and excruciating pain; Silver-Russel syndrome.	-

Millán-Guerrero & Isais-Millán	2019	Cannabis y los sistemas exocannabinoide y endocannabinoide: Su uso y controversias.	Δ^9-THC, canabinol, CBD, canabigerol e tetrahidrocanabivarina.	-	Inhalation, oral, less frequent in ophthalmic, rectal, sublingual, and dermal forms.	Epilepsy, cancer, pain, sleep disorders, digestive disorders, traumatic brain injury, morbid obesity and diabetes, anxiety, psychosis, Alzheimer, Parkinson, Huntington, Multiple Sclerosis, rheumatoid arthritis, and musculoskeletal pain.	With its receptors, ligands, and enzymes found in the brain and periphery, SE maintains balance in homeostatic processes. Cannabinoid receptors CB1 (CNS and SNP, at the pre-synaptic level at terminals of glutamatergic and GABAergic neurons and astrocytes; regulate the release of neurotransmitters) and CB2 (immune cells, microglia, and activated astrocytes) are G protein-coupled. TRPV1 receptor, receptor from capsaicin, it binds to capsaicin and other ligands such as cannabinoid ligands that activate with physical and mechanical stimuli. GPR55 receptors with an endogenous lysophosphatidylinositol ligand have the opposite effects of CB1 receptors, activating the release of neurotransmitters in pre-synaptic cells. In releasing pre-synaptic neurotransmitters to activate post-synaptic receptors, the ligands diffuse in a retrograde way towards the synaptic cell, bind to CB1 receptors, and initiate the cascade inhibiting the release of neurotransmitters. The endocannabinoids are AEA and 2-AG, with AEA acting in acute processes and 2-AG in chronic With its receptors, ligands, and enzymes found in the brain and periphery, SE maintains balance in homeostatic processes. Cannabinoid receptors CB1 (CNS and SNP, at the pre-synaptic level at terminals of glutamatergic and GABAergic neurons and astrocytes; regulate the release of neurotransmitters) and CB2 (immune cells, microglia, and activated astrocytes) are G protein-coupled. TRPV1 receptor, receptor from capsaicin, it binds to capsaicin and other ligands such as cannabinoid ligands that activate with physical and mechanical stimuli. GPR55 receptors with an endogenous lysophosphatidylinositol ligand have the opposite effects of CB1 receptors, activating the release of neurotransmitters in pre-synaptic cells. In releasing pre-synaptic neuro-

							transmitters to activate post-synaptic receptors, the ligands diffuse in a retrograde way towards the synaptic cell, bind to CB1 receptors, and initiate the cascade inhibiting the release of neurotransmitters. The endocannabinoids are AEA and 2-AG, with AEA acting in acute processes and 2-AG in chronic processes. Enzymes modulate the synthesis and degradation of endogenous ligands, AEA by alpha or beta DGL and FAAH by the enzymes serine hydrolase and 2-AG by MGL. Δ^9-THC is an agonist, while CBD has a low affinity for cannabinoid receptors and inhibits the binding of Δ^9-THC to CB1. Activation of the TRPV1 receptor modulates a different pain stimulus pathway from those occupied by endocannabinoids and has been a potential use in the treatment of epilepsy.
Oliveira	2019	A perspectiva da toxicologia clínica sobre a utilização terapêutica da Cannabis e dos canabinoides	Δ^8-THC (lower concentration psychoactive), Δ^9-THC (psychoactive), Cannabinol (little active) and Cannabidiol (non-psychoactive).	Sativex® (Δ^9-THC /CBD ratio); dronabinol.	Oral, in the form of infusions, sublingual drops, transdermal, vaporizations.	Insomnia, Parkinson's, Multiple Sclerosis, AIDS, Neuropathic Pain, Cancer, Anxiety, Epilepsy, Alzheimer's, Fibromyalgia.	Dopamine is the neurotransmitter responsible for drug addiction. Endocannabinoids act in several physiological processes and bind to CB1 cannabinoid receptors present in neurons and CB2 in immune system cells.
Penha et al.	2019	A regulamentação de medicamentos derivados da Cannabis sativa no Brasil	Δ^9-THC and CBD	Marinol® (dronabinol) – synthetic Δ^9-THC; Cesamet® (nabilone); Sativex®/Mevatyl® (Δ^9-THC /CBD); Bedrocan® 22% of Δ^9-THC and less than 1% CBD; Bedropuur® (24% Δ^9-THC), Bedica® (14% Δ^9-THC), Bediol® (6.5% Δ^9-THC and 8% CBD) and Bedrolite® (0.5% Δ^9-THC and 9% CBD)	-	Epilepsy, Autism, Alzheimer's, Parkinson's disease (there is still no evidence to prove its effectiveness), glaucoma, cancer, chronic pain, HIV.	-
Rabelo; Gomes & Kohn	2019	Uso terapêutico de canabinoides na	Δ^9-THC and CBD	Mevatyl®/ Sativex® (Δ^9-THC /CBD)	Oral Spray	Glaucoma; Multiple Sclerosis; cancer; Epilepsy; Asthma;	CBD antagonizes the effects of Δ^9-THC and is considered a competitive antagonist. The analgesic effect is related to

		Multiple Sclerosis				neuropathic pain; anorexia; rheumatoid arthritis; autoimmune diseases.	o pain transmission mediated by CB1 receptors found in peripheral nerves, spinal cord, and brain, and CB2 in the immune system and SNP. When activated, they reduce pain and inflammation. They are G-protein and AC-coupled and are activated when they interact with ligands, triggering a series of reactions that include AC inhibition, cAMP reduction, K+ channel opening, signal transmission reduction and calcium channel closure (Ca2+), and reduction of neurotransmitters such as GABA, glutamate, dopamine, serotonin, opiates, and others. Cannabinoid receptors, enzymes, and endocannabinoids such as AEA and 2-AG, similar to phytocannabinoids, make up the SE.
Santos; Scherf & Mendes	2019	Eficácia do canabidiol no tratamento de convulsões	CBD; Δ^9-THC	Sativex® (98% de CBD)	Oral	Parkinson's, Epilepsy and Autism.	CBD modulates synaptic transmission by blocking Ca2+ and K+ channels, and this may be done by inhibiting epileptic seizures and seizures, avoiding neuronal overexcitation. Both 5-HT1A and TRPV1 receptors are involved. Δ^9-THC binds to both CB1/CB2 receptors present in the nervous system on inhibitory (GABAergic) and excitatory (glutamatergic) neurons, both in the pre-synaptic membrane. CB1 is expressed in the CNS and CB2 in immune cells.
Tapley & Kellett	2019	Cannabis-based medicines and the perioperative physician	Psychoactives Δ^8-THC, Δ^9-THC and cannabinol; not psychoactive, the CBD.	Dronabinol (Marinol®); Nabiximol®/Sativex®; nabilone (Cesamet®); pure CBD (Epidiolex®) or associated with Δ^9-THC (Syndros®); Spice; Cannador® (Δ^9-THC / CBD)	Inhalation, vapor, oral, spray and transdermal;	Chronic pain, nausea and vomiting caused by chemotherap; Multiple Sclerosis, Epilepsy.	SE consists of the two cannabinoid receptors CB1/CB2 and neurotransmitters, synthesized in the post-synaptic neuron in response to stimuli and acts in various homeostasis processes. CB1 and CB2 are G protein-coupled, reducing the stimulation of cAMP production by inhibiting AC, changing the voltage of Na+ and K+ channels, decreasing neuronal excitability and neurotransmitter release. CB1 is found in the cortex, spinal cord, and periphery, while CB2 participates in immunomodulation, present in spleen cells, Kupffer cells, macrophages, and the, nervous system. Δ^9-THC is a CB1/CB2

							agonist, while CBD is a non-competitive antagonist at high concentrations in CB1 and an inverse agonist in CB2, causes allosteric modulation in both receptors and interacts with other receptors such as serotoninergic, adenosine, adrenergic, nicotinic, acetylcholine, glycine, TRPV1, PPARs, NMDA and GABA. The endocannabinoids that makeup SE are AEA, 2-AG, Virodamine, NADA, Docosatetraenoyl-ethanolamide (DEA), 2-arachidonylglycery, noladine, dihomogamma-linolenoylethanolamide (HEA).
Costa; Brandão & Marinho Segundo	2020	Atualização em epilepsia: revisão de literatura	Δ^9-THC (psychoactive); CBD.	pure CBD	Oral	Epilepsy	Δ^9-THC is an agonist of cannabinoid receptors, mainly CB1 and CBD, reduces the activation effects of this receptor and inhibits synaptic transmission by blocking voltage-dependent calcium and potassium channels. Cannabinoids act by binding to cannabinoid receptors, CB1, which are mainly located in the CNS, both in inhibitory (GABAergic) and excitatory (glutamaergic) neurons.
Goten & Amital	2020	Cannabis and Cannabinoids in the Treatment of Rheumatic Diseases	Δ^9-THC (psychoactive); CBD.	Nabilone (synthetic analogue of Δ^9-THC)	Oral	Fibromyalgia; rheumatoid arthritis; osteoarthritis; systemic sclerosis; depression; anxiety.	Cannabinoid receptors are found in many places in the body such as TGI, immune cells and prefrontal cortex.
Jovel	2020	Cannabinoides em epilepsia: eficácia clinica y aspectos farmacológicos	Δ^9-THC (psychoactive); CBD; canabivarina.	Pure CBD or CBD enriched extracts	-	Multiple Sclerosis, Epilepsy, Neuropathic Pain, Spasms, Tremors, Tourette's Syndrome, Headache, Neurological Disorders, Sleep Disorder.	CBD and Δ^9-THC act on G protein-coupled receptors part of the SE called CB1, present in CNS and peripheral neuronal cells, and CB2, present in immune cells. CB1 decreases neuronal excitability and neurotransmitter release by modulating the opening of K+ channels and blocking Ca2+ channels. Δ^9-THC is a partial agonist of CB1/CB2 receptors, has an anti-inflammatory effect, and is mainly responsible for the psychotropic effects; its use in epilepsy is not recommended as it is proconvulsant. CBD has a low affinity for cannabinoid receptors, but it is hypothesized that it modulates the ENT transporter, GPR55 receptor, and TRPM8

							channel and modulates 5-HT1A receptor activation. Some glycine receptors and the TRPA1 channel help to regulate intracellular calcium concentrations. CBD is believed to enhance the beneficial properties of Δ^9-THC and reduce its psychoactivity.
Mecha et al.	2020	Perspectives on Cannabis-Based Therapy of Multiple Sclerosis: A Mini--Review	CBD; Δ^9-THC	Dronabinol, Epidiolex® (99% CBD); Sativex® (1:1 Δ^9-THC /CBD)	Oral; oral spray.	Multiple Sclerosis, Dravett Syndrome and Lennox-Gastaut Syndrome; Alzheimer's, ischemic injury, Parkinson's.	Cannabinoid CB1/CB2 receptors, endocannabinoids (AEA and 2-AG), enzymes, and other factors constitute the SE. Cannabinoid receptors are G protein-coupled that inhibit cAMP formation, modulate ion channels, synthesize nitric oxide, and regulate extracellular kinases or beta-arrestin. CB1 is most abundant in the brain, spinal column, and SNP, predominantly located in the neuronal synapse, reducing synaptic transmission by retrograde signaling mediated by endocannabinoids. CB2 receptors are expressed in the SNP, gastrointestinal tract, liver, adipocytes, bones, cardiovascular system, and reproductive system, but predominantly in immune cells, including microglia, are associated with anti-inflammatory and immunomodulatory activity. Other receptors such as GPR55, TRPV1, and PPARs can mediate the activity of phytocannabinoids and endocannabinoids. Neuroprotection and CB2 occur through CB1 receptors, remyelination. SE regulates CNS homeostasis and neuroprotection, participates in immune control, and maintains the homeostatic balance of the central immune system.
Morano et al.	2020	Cannabinoids in the Treatment of Epilepsy: Current Status and Future Prospects	CBD; Δ^9-THC; canabigerol; canabivarina	Epidiolex® (CBD in high concentrations)	Oral	Dravett syndrome, Lennox-Gastaut syndrome; infantile spasm, Rett syndrome and fragile X syndrome, in addition to neuropsychiatric diseases such as schizophrenia and autism (fu-	The cannabinoid receptors CB1/CB2 G protein-coupled make up the SE, in which CB1 is responsible for the psychotropic effects of Δ^9-THC and is found in the CNS in both inhibitory and excitatory synapses, and CB2, which is present in the PNS and immune system; endocannabinoids (AEA and 2-AG), retrograde messengers produced on demand by the metabotropic group 1 glutamate receptor

						ture perspectives).	and are activated by glutamate in the pre-synaptic excitatory activation in which there is an activation of PLC beta that catalyzes the synthesis of diacylglycerol (DAG - precursor of the 2-AG). When DAG is highly available, the alpha enzyme DGL converts DAG to 2-AG. In the inhibitory pathway, it acts on GABAergic receptors. SE maintains the body's homeostasis. CBD is an antagonist of CB1 receptors and interacts with GP55 receptors, 5-HT1A receptors, Na+ channels, cation channels, and TRPV1 receptors, whose CBD is an agonist decreasing calcium levels and neuronal excitability.

SUBTITLE: "- "INDICATES THAT THE AUTHOR DID NOT ADDRESS THE ASPECT.

Table S2: Papers that address the medical cannabis legislation in Brazil.

Author	Year	Title	Legislation
Pamplona	2014	Quais são e pra que servem os medicamentos à base de Cannabis?	ANVISA allows import of products based on active ingredients from Cannabis
Oliveira & Silva	2015	A inovação na utilização de compostos de Cannabis sativa em medicamentos	In 2015 ANVISA cleared the import of Cannabis-based medicines, classified CBD as a controlled substance, while Δ^9-THC was banned; Anti-Drug Law – nº 11.343/06 keeps the cultivation, transport, and sale prohibited.
Corrêa	2016	Utilização dos canabinoides no tratamento de epilepsia em pacientes refratários	CBR No. 17/15 which allows the import of CBD and Δ^9-THC-based medicines
Gontijo et al.	2016	Canabidiol e suas aplicações terapêuticas	ANVISA in 2015 approves CBD import
Melo & Santos	2016	O uso do Canabidiol no Brasil e o posicionamento do Órgão Regulador	Ordinance No. 344/98 – list F; CBR nº 2113/14 of the CFM approves the use of CBD in the treatment of children and adolescents with epilepsy; CBR No. 17/2015; CBD becomes a controlled substance, in list C1 of Ordinance No. 344/98.
Carvalho; Brito & Gandra	2017	Mães pela cannabis medicinal em um Brasil aterrorizado entre luzes e fantasmas	Law No. 11.343/06 – anti-drug law; CBR No. 55/13; CBR nº 2.113/14 allowing prescription of CBD for patients with refractory epilepsy; In 2015, ANVISA assigns in list C1 of Ordinance No. 344/98, the CBD; CBR nº 17/2015 allows the import of CBD-based products; CBR #66/16 allows import for personal medical use; CBR No. 38/13; CBR No. 98/00; ANVISA exhibits a mistaken regulation, evidenced by the inclusion of dronabinol in the A3 list in the year 2000, while maintaining the same substance (Δ^9-THC) in the F list of outlaws until early 2016.
Carvalho et al.	2017	Canabinoides e epilepsia: potencial terapêutico do canabidiol	CBR No. 17/2015 - import of CBD-based products
Nunes et al.	2017	Canabidiol (Cannabis sativa): associada no tratamento de doenças neurológicas e sua legalização	The first drug was approved in 2017 by ANVISA for the treatment of Multiple Sclerosis, but it is not allowed for epilepsy as it has the Δ^9-THC (psychoactive) component. Law nº 11.343/06 – Law on Drugs regulates the matter, but it does not define what drugs mean and which substances would be understood as such. The complement that makes it effective in the criminal sphere is ANVISA Ordinance No. 344/98.
Trindade et al.	2017	Canabinoides para Tratamento de Epilepsia em Crianças	Brazil included CBD in the list of psychotropic substances in Ordinance No. 344/98 in 2016, its sale as a type A prescription, and concentrations should be at most 30mg/ml of THC and 30mg/ml of CBD.

Basílio & Ferreira	2019	A importância do uso do canabidiol em pacientes com epilepsia	CBR No. 2.113/14 - allows CBD to treat epilepsy
Müller et al.	2019	Canabinoides como uma nova opção terapêutica nas doenças de Parkinson e de Alzheimer: uma revisão de literatura	ANVISA in 2015 approved the import of CBD - CBR nº 17/15; CBD goes to list C1 of Ordinance No. 344/98;
Gurgel et al.	2019	Uso terapêutico do canabidiol: a demanda judicial no estado de Pernambuco, Brasil	CBR nº 2.113/2014 of the CFM – treatment with CBD for children and adolescents with epilepsy; ANVISA, through CBR nº 3/15, inserted the CBD in list C1 of Ordinance nº344/98, leaving the ban for controlled use; CBR nº 156/17 assigned to C. sativa the list of medicinal plants; Art.3 of CBR nº 17/15 which allows the import of Cannabis-based products; Law No. 6.437/77 - it is prohibited to import medicines without registration or authorization from the health surveillance agency.
Leite & Borges	2019	O USO DE MEDICAMENTOS À BASE DE CANABINOIDES NO BRASIL: UM ESTUDO DE CASO	Ordinance No. 344/98 - substance considered proscribed; CBR nº 2.113/14 (CFM) allows the CBD for the treatment of refractory epilepsy in children and adolescents; In 2016, ANVISA placed CBD on the list of psychotropic substances that can be sold with type A prescription; CBR nº 17/15 - CBD--based products that can be imported.
Penha et al.	2019	A regulamentação de medicamentos derivados da Cannabis sativa no Brasil	ANVISA removes CBD from the list as an illicit substance. Law nº 11.343/06 allows the cultivation of C. sativa for medicinal purposes. CBD is placed on list C1 of Ordinance No. 344/98 as a controlled substance; Anti-drug law which penalizes cultivation, transport, and other actions; CBR nº 17/15 allows the import of CBD for own consumption; The substances on list C1 require a particular prescription that must be issued in two copies, the first being retained at the pharmaceutical establishment or drugstore and the second stamped and returned to the patient. Medicines derived from C. sativa with a concentration of at most 30 mg/ml of Δ^9-THC and 30 mg/ml of CBD were included in the list A3 of psychotropic substances of Ordinance No. 344/98, requiring notification of prescription A, notification is withheld at the drugstore, and the prescription is returned to the patient. Mevatyl® is the only drug that can be marketed in Brazil.
Rabelo; Gomes & Kohn	2019	Uso terapêutico de canabinoides na Multiple Sclerosis	Law No. 11.343/06 – anti-drug law criminalizes the purchase, possession, and storage of illegal substances; Ordinance No. 344/98 – list of psychotropic, narcotic, precursor, and particular control substances; CBR nº 2.113/14 approves the compassionate use of the CBD; In 2015 ANVISA withdraws the CBD from Ordinance No. 344; Δ^9-THC remains prohibited, but for specific cases may be prescribed in compliance with ANVISA rules.
Santos; Scherf & Mendes	2019	Eficácia do canabidiol no tratamento de convulsões e doenças do sistema nervoso central: revisão sistemática	Permission from ANVISA in 2015 for import and medicinal use of products based on Δ^9-THC and CBD
Costa; Brandão & Marinho Segundo	2020	Atualização em epilepsia: revisão de literatura	CBR No. 2.113/14 - CFM (Brazilian Federal Council of Medicine) Law