Medicinal uses of *Cannabis* sp.

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Abstract
The therapeutic properties of *Cannabis* have been described since antiquity and are of great relevance for the Egyptian, Chinese, Indian, Arab and Latin people. *Cannabis*-based medicines show several therapeutic purposes, mainly to treat disorders as constipation, some types of pain, epilepsy, anxiety and among others. In addition, the genus *Cannabis* exhibits great clinical relevance due to its Central Nervous System activities attributed to some phytochemicals compounds, as cannabidiol and Δ9-tetrahydrocannabinol. The interest in the pharmacological properties of *Cannabis* is growing and several new studies are being carried out to prove its pharmacotherapeutic use which are important to design of novel drugs with different routes of administration and for multiple pathologies resistant to the conventional treatments. In this context, there is a pressure on countries to review the laws that still limit the research development related to medicinal *Cannabis* purposes. Herein, our aim is to perform an overview about the plant, endocannabinoid system, *Cannabis*-based medicines and clinical uses, regulatory aspects of *Cannabis sp* and its chemical compounds of therapeutic interest.
Keywords: *Cannabis* sp.; Medicinal *cannabis*; Medical *cannabis*; Cannabinoids; *Cannabis sativa*; Marihuana.

Resumo
As propriedades terapêuticas da *Cannabis* são descritas desde a antiguidade e são de grande relevância para os povos egípcios, chineses, indianos, árabes e latinos. Os medicamentos à base de *Cannabis* apresentam vários fins terapêuticos, principalmente para tratar distúrbios como a constipação, alguns tipos de dor, epilepsia, ansiedade, entre outros. Além disso, o gênero *Cannabis* apresenta grande relevância clínica devido seu efeito sobre o Sistema Nervoso Central atribuído a alguns compostos fitoquímicos, como o canabidiol e o Δ9-tetrahidrocanabinol. O interesse pelas propriedades farmacológicas da *Cannabis* é crescente e vários novos estudos estão sendo realizados para comprovar seu uso farmacoterapêutico, estudos que são importantes para o planejamento de novos fármacos com diferentes vias de administração e para múltiplas patologias resistentes aos tratamentos convencionais. Nesse contexto, há uma pressão sobre os países para que revisem as legislações que ainda limitam o desenvolvimento de pesquisas relacionadas aos fins medicinais da *Cannabis*. Aqui, nosso objetivo é realizar uma visão geral sobre a planta, sistema endocanabinoide,

medicamentos à base de *Cannabis* e usos clínicos, aspectos regulatórios da *Cannabis sp* e seus compostos químicos de interesse terapêutico.
Palavras-chave: *Cannabis* sp.; *Cannabis* medicinal; Canabinóides; *Cannabis sativa*; Maconha.

Resumen
Las propiedades terapéuticas del *Cannabis* se han descrito desde la antigüedad y son de gran relevancia para los pueblos egipcio, chino, indio, árabe y latino. Los medicamentos a base de *Cannabis* tienen varias finalidades terapéuticas, principalmente para tratar trastornos como el estreñimiento, algunos tipos de dolor, la epilepsia, la ansiedad, entre otros. Además, el género *Cannabis* tiene una gran relevancia clínica debido a su efecto sobre el Sistema Nervioso Central atribuido a algunos compuestos fitoquímicos, como el cannabidiol y el Δ9-tetrahidrocannabinol. Crece el interés por las propiedades farmacológicas del *Cannabis* y se están realizando varios nuevos estudios para comprobar su uso farmacoterapéutico, estudios que son importantes para la planificación de nuevos fármacos con diferentes vías de administración y para múltiples patologías resistentes a los tratamientos convencionales. En este contexto, se ejerce presión sobre los países para que revisen la legislación que aún limita el desarrollo de la investigación relacionada con los fines medicinales del *Cannabis*. Aquí, nuestro objetivo es proporcionar una descripción general de la planta, el sistema endocannabinoide, los medicamentos a base de *Cannabis* y los usos clínicos, los aspectos regulatorios de *Cannabis sp* y sus compuestos químicos de interés terapéutico.
Palabras clave: *Cannabis* sp.; *Cannabis* medicinal; Cannabinoides; *Cannabis sativa*; Marijuana.

1. Introduction

The Therapeutic effects of *Cannabis* sp have been reported since ancient times for several medicinal purposes, such as constipation, some types of pain, epilepsy, anxiety, among others (Fankhauser, 2002; Pamplona, 2014; Pain, 2015; Pisanti, Bifulco, 2017). In 1830, the German Theodor Friedrich Ludwig Nees von Esenbeck was the first to describe the therapeutic uses of *Cannabis indica*. In 1839, William Brooke O'Shaughnessy related his clinical experiences with *Cannabis* in India, highlighting its therapeutic potential to modern medicine (Grotenhermen, Müller-Vahl, 2016). Initially, he performed experimental studies in animals to verify safety, then O'Shaughnessy tested the *Cannabis* in patients with tetanus, epilepsy, cholera or rheumatism. The findings showed *Cannabis* analgesic, and myorelaxant activities. Regarding tetanus and epilepsy, *Cannabis* was not able to cure, though it is known as an adjuvant, increasing the treatment efficiency (Cunha et al., 1980; Leghissa et al., 2017; Pisanti, Bifulco, 2017). The Italian Raffaele Valier (1887) observed that inhalation of *C. sativa* or *C. indica* presented similar effects and were effective for the treatment of neuralgia, insomnia, migraine, pulmonary emphysema and asthma (Pisanti, Bifulco, 2019).

Several researches have shown the potential medicinal activity of *Cannabis* and its chemical compounds. There is still a huge prejudice in society in relation to medical *Cannabis* due to its recreational use. However, this scenario is changing, and the social resistance is decreasing for the medicinal use of *Cannabis*. In this context, plant derivatives were identified, such as Δ9-tetrahydrocannabinol (Δ9-THC or THC) and cannabidiol (CBD), as well as, the endocannabinoid system, cannabinoid receptors type 1 and type 2 (CB1 and CB2, respectively) (Mechoulam, Parker, 2013; Macarrone et al., 2015; Pain, 2015; Grotenhermen, Müller-Vahl, 2016; Pisanti, Bifulco, 2017). Herein, our aim is to provide an overview about the plant, endocannabinoid system, available *Cannabis*-based medicines and clinical uses, regulatory aspects of *Cannabis sp* and its chemical compounds of therapeutic interest.

2. Methodology

This research is an integrative literature review of a qualitative nature regarding medicinal uses of *Cannabis*. The study was based on the analysis of scientific papers that cover: the plant characteristics, its therapeutic properties, endocannabinoid system and regulatory aspects of *Cannabis* sp. The databases employed were: Scielo, Google Academic, Pubmed and Researcher (application, version 2.10.3). Some parameters were established for researching, such as: theme identification; definition of inclusion and exclusion criteria, as articles indexed in journals classified by QualisCAPES in A and B; identification, pre-selection and categorization of papers; analysis and interpretation of results and presentation of the review/synthesis of

knowledge.

In order to research, the following key words were employed: "cannabinoids", "medicinal *Cannabis*", "THC pharmacodynamic", "medicines cannabinoids", "medicinal use *Cannabis sativa*", "endocannabinoids", "endocannabinoid system", "pharmacokinetics cannabinoids". A total of 104 articles were selected, being that 15 papers related to *Cannabis* composition, 13 about endocannabinoids and 49 regarding the therapeutic use of *C. sativa* and other information. Considering the exclusion criteria, 77 articles were chosen to build the study, besides current legislation on the medicinal use of *Cannabis*. In the Figure 1 shows the flowchart employed to the study development. Additionally, the information related to the medicines and extracts on the commercially available, mainly reports from pharmaceutical industries responsible for production, in addition to legal documents from regulatory agencies of some countries were employed.

Figure 1. Flowchart of the article selection process and inclusion criteria of studies.
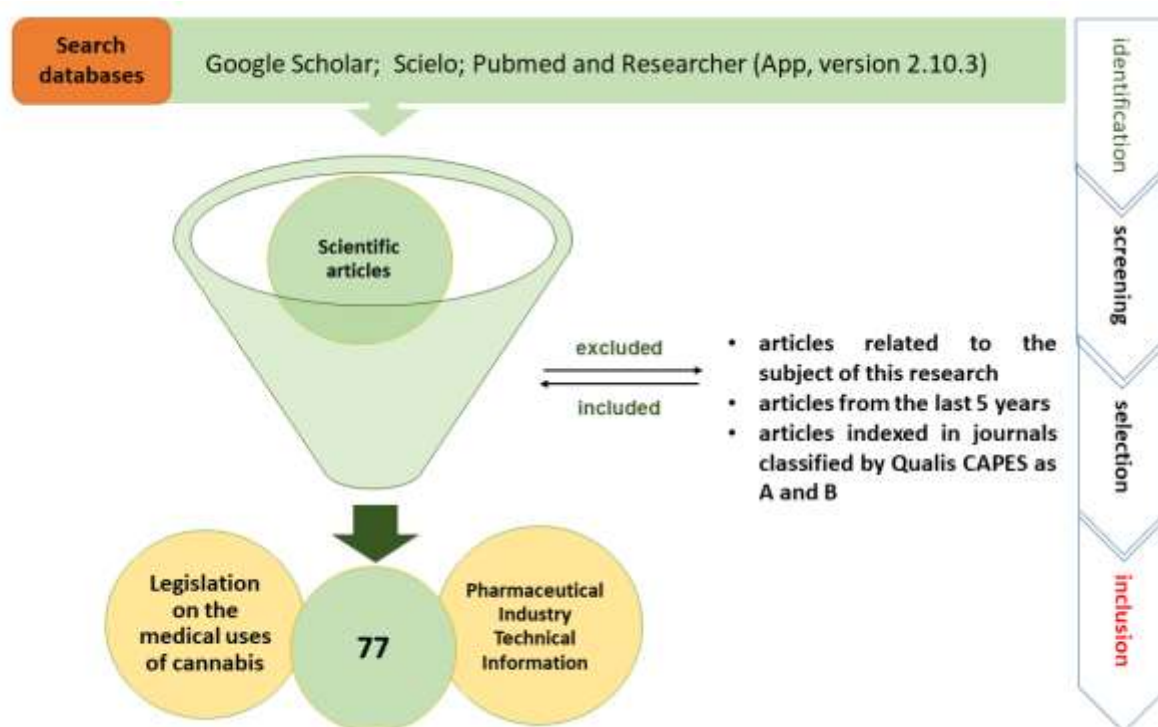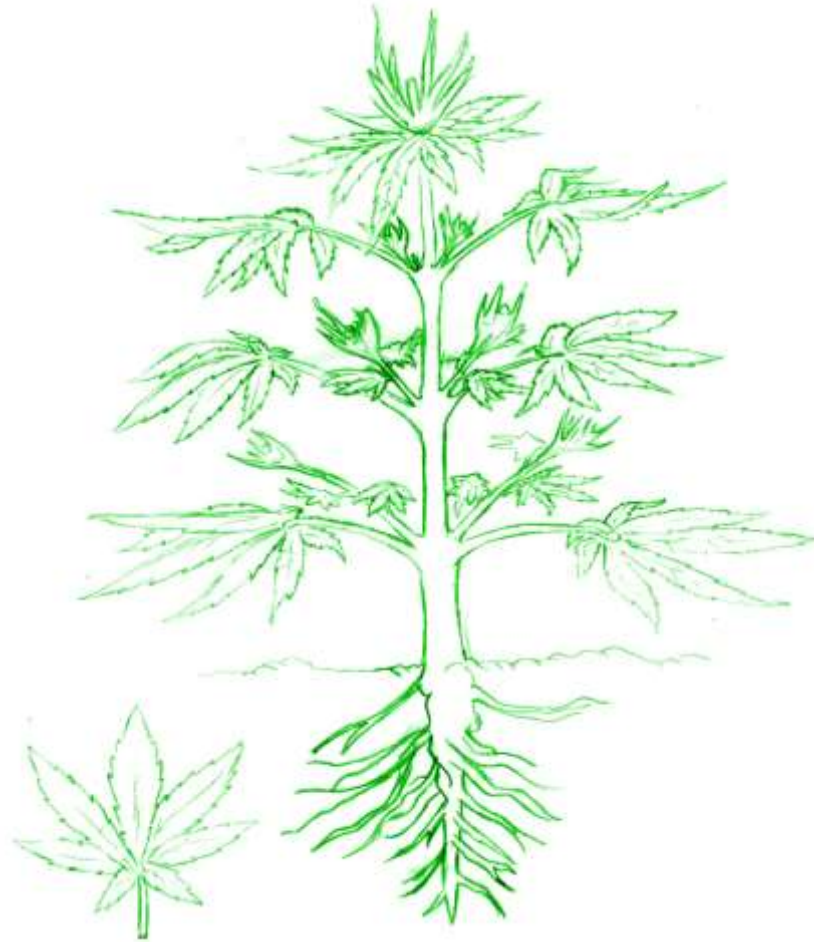

Source: Authors.

3. Plant Characteristics

First *Cannabis sativa* records were in Central Asia around 4000 years b.C., more precisely in China (Russo et al., 2008; Fathordoobady et al., 2019). *Cannabis* is a genus of angiosperm from *Cannabaceae* family (Zlas et al., 1993; Tagne et al., 2019) (Figure 2), being botanically classified as an annual herbaceous plant and its leaves are thin, pointed and serrated. There are three *Cannabis* strains: *sativa*, *indica* and, *ruderalis* (Figure 3). The Figures 2 and 3 demonstrate the *Cannabis* species employed therapeutically. *Cannabis* can be female plant, being more robust, or male one, whose main role is to pollinate the female flowers and, it is rarely hermaphrodite (Lewis et al., 2017).

Figure 2. *Cannabis sativa.*

Source: Authors.

**Figure 3**. Botanical difference between species of the Cannabaceae family.

Source: Authors.

Cannabis contains a wide range of compounds, including fatty acids (protect cell membranes), cannabinoids (active in CB1 or CB2 receptors), flavonoids (plant pigments and control of cell growth), phenols (as THC), terpenes (confer smell), and other secondary metabolites are still under investigation (Lewis et al., 2017). Furthermore, in *Cannabis* are found substances beneficial to health with nutritional value, such as: vegetable oils between 19-38%, protein around 20-30%, fiber ranging from 27-36%, minerals between 4-6%, besides tocopherol, carotenes and other phenolic compounds (Fathordoobady et al., 2019). There are around 550 chemical constituents identified in the *Cannabis sativa*, being 113 phytocannabinoids and 120 terpenes (Aizpurua-Olaizola et al., 2016), though only 90 components were purified and characterized (Fathordoobady et al., 2019).

Cannabinoids are isolated from leaves, flowers, stems, roots and seeds, but the main source of phytocannabinoids are trichomes of unfertilized female flowers, which secrete a resin loaded of phytocannabinoids, as the THC (López et al., 2014; Pollastro et al., 2017; André, Hausman, Guerreiro, 2016).

According to André and colleagues (2016), there are limitations regarding the research of phytochemical constituents and clinical aspects of *Cannabis*, due to illegal cultivation or manufacturing in many countries, such as Brazil, and also different cultivation conditions. The most important and abundant pharmacological compounds are the cannabinoids: cannabinol (CBN), CBD and THC, the Figure 4 presents the chemical structures of therapeutic agents. CBN is a THC metabolite, with potential immunosuppressive and anti-inflammatory activities. THC exhibits a great homeostatic influence at the Central Nervous System (CNS) (Glass et al., 1997; Russo, 2016). CBD is considered a non-psychoactive agent and CB1 and CB2 receptors antagonist, even in small concentrations (Russo, 2011; André, Hausman, Guerreiro, 2016).

Figure 4. Chemical structure of CBN (1), THC (2) and CBD (3).
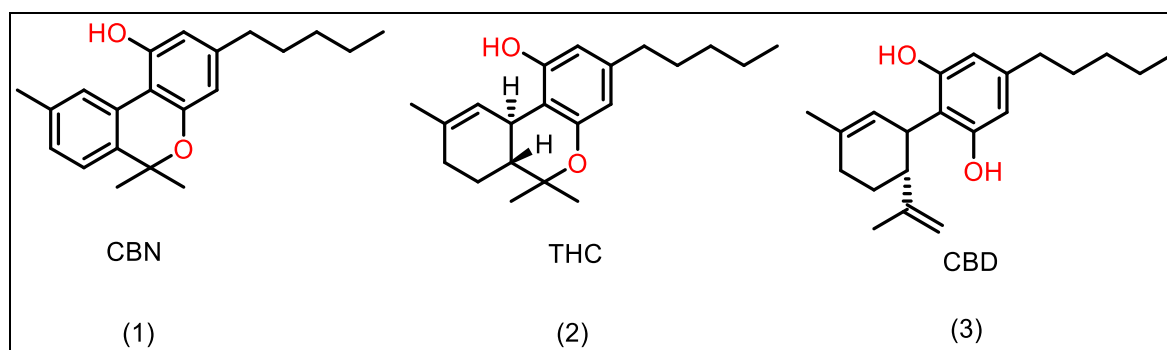
Source: Authors.

Researches have been revealed the cannabinoids potentialities on the treatment of neuropathic, pelvic, pancreatic pains, fibromyalgia, overactive bladder, dermatological diseases, migraine, irritable bowel syndrome, among others (Russo, 2016). The finding of new *Cannabis* constituents has been exponential and constant due to the growing interest in the therapeutic potential shown by strains (Russo, 2004; WHO, 2015).

4. Endocannabinoid System

The endocannabinoid system (ECS) is composed of cannabinoid receptors, endocannabinoids (EC), enzymes and proteins related to their synthesis, transport and degradation. In the 1960s, the discovery of Δ9-THC was the first step in developing the ECS hypothesis, then there was the elucidation of CB1 receptor in the brain, where Δ9-THC binds, as well as, CB2 receptor in immune cells (Munro, Thomas, Abu-Shaar, 1993; Stella, 2009; Di Marzo, Stella, Zimmer, 2015; Lutz et al., 2015; Nicolussi, Gertsch, 2015; Parsons, Hurd, 2015; Iannotti, Di Marzo, Petrosino, 2016; Morena et al., 2016).

Cannabinoid receptors are metabotropic G protein-coupled receptors (Devane et al., 1988; Di Marzo, Stella, Zimmer, 2015; Atwood, Mackie, 2010; Wei et al., 2017). CB1 receptor is encoded by the CNR1 gene, consisting of 472 amino acids in humans and there are two isoforms containing a shorter N-terminus (Devane et al., 1988; Shire et al., 1995; Ryberg et al., 2005; Pertwee, 2010; Di Marzo, Stella, Zimmer, 2015; Grotenhermen, Müller-Vahl, 2016; Iannotti, Di Marzo, Petrosino, 2016; Zou, Kumar, 2018). CB1 receptors are mainly located at axon terminals and their activation causes high suppression of neurotransmitters by regulating neuronal activity and chemical mediator releasing. CB1 mechanism consists of inhibiting adenylyl cyclase, resulting in decreasing cyclic adenosine monophosphate (cAMP) or activation of mitogen-activated protein kinases (MAPK) and it is also associated with inhibition of N-type calcium channels (Howlett, 1998; Turu, Hunyady, 2010;

Iannotti, Di Marzo, Petrosino, 2016; Morena et al., 2016; Zou, Kumar, 2018). CB2 receptors are more concentrated in immune system cells, though CB2 has also been found in neuronal, glial and brain endothelial cells. CB2 receptors may regulate the neuronal excitability through modulation of the calcium-activated chloride channels, but information regarding their role in neuronal regulation are still scarce (Den et al. 2012; Parsons, Hurd, 2015; Iannotti, Di Marzo, Petrosino, 2016; Zou, Kumar, 2018).

The endogenous ligands for these receptors are N-arachidonoyl ethanolamine, named anandamide (AEA), and 2-arachidonoyl glycerol (2-AG), both compounds are the main known endocannabinoids (Figure 5) (Di Marzo, Stella, Zimmer, 2015; Nicolussi, Gertsch, 2015; Iannotti, Di Marzo, Petrosino, 2016; Zou, Kumar, 2018). AEA has higher affinity for CB1 than CB2 receptor, being a weak agonist. In addition, AEA activates the vanilloid receptor 1 (TrpV1), which possibly participates in endocannabinoid signaling, through inhibition of L-type calcium channels, as well as in the downregulating of 2-AG biosynthesis (Gonsiorek, 2000; Morena et al., 2016; Zou, Kumar, 2018). 2-AG is a moderate to weak cannabinoid receptor agonist and is related to the sustained neuronal depolarization and, mediation of multiple forms of synaptic plasticity (Di Marzo, Petrocellis, 2012; Morena et al., 2016; Zou, Kumar, 2018). In the Figure 5 are displayed other endocannabinoids as: virodhamine, which is a moiety of arachidonoyl coupled to an ethanolamine by an ester bond, acts as a full and selective CB1 agonist; *N*-arachidonyl-dopamine (NADA) is a CB1 agonist and potent activator of TrpV1; and palmitoylethanolamide (PEA) is involved with anti-inflammatory, analgesic and neuroprotective processes (Petrosino, Di Marzo, 2010; Nicolussi, Gertsch, 2015; Iannotti, Di Marzo, Petrosino, 2016). ECs acts in the reduction of synaptic transmission by several mechanisms with important action on CB1, but there are still few evidences of CB2 activity on CNS modulation (Lutz et al., 2015; Zou, Kumar, 2018).

Figure 5. Endocannabinoid structures: (4) anandamide; (5) 2-AG; (6) virodhamine; (7) NADA; (8) PEA.
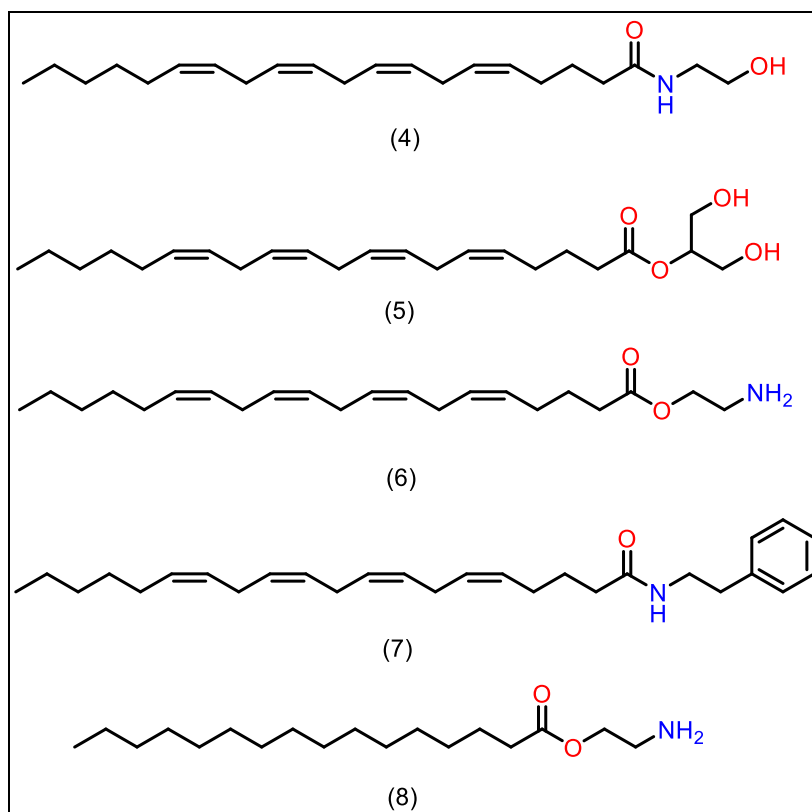
Source: Authors.

5. *Cannabis*-based Medicines

Raphael Mechoulam developed a hypothesis to explain the therapeutic action of *Cannabis* sp., named "entourage effect", which is characterized by synergistic activity of phytocannabinoids with other plant secondary metabolites. This theory was based on the observation that the presence of phytocannabinoids, glycerol fatty acid esters, alongside 2-AG, reduced the hydrolysis rate of 2-AG, increasing its activity. Currently, the entourage effect has been contested by searches that have proven the same therapeutic action of isolated compounds and phytocomplexes (Hazekamp et al., 2013; Bonn-Miller, Loflin, Chandra, 2018).

Cannabis-based medicines are marketed in many countries, either as herbaceous products, *Cannabis* extract or isolated cannabinoid drugs. In Netherlands, herbaceous products and dried unfertilized female flowers, named "flos" are sold e may be administered orally or by inhalation. Other preparations are liquid extracts from *Cannabis*, which can be administered by sublingual route or even in food and capsules containing standardized THC and CBD concentrations. Standardized *Cannabis* extracts are prepared by drying processes, thus the final product remains of high levels of bioactive agents from vegetable drug (Hazekamp et al., 2013; Parmar, Forrest, Freeman, 2016; Grof, 2018).

In the Figure 6 is demonstrated the decarboxylation reaction after heating from tetrahydrocannabinolic acid-A (THCA-A) and cannabidiolic acid (CBDA), compounds with the highest concentration in the plant, and after this process results in bioactive compounds THC (2) and CBD (3), respectively. By inhalation, the maximum plasma concentration is reached within 3 to 10 minutes, after 15 minutes the concentration decreases to about 60% and, in 20 minutes is already around 20%. Thereby, the bioavailability is variable and depends on factors as number of inhalations and breath-holding duration (Grant, 2012; Borodovsky et al., 2016; Lanz et al., 2016; Lucas, Galettis, Schneider, 2018; Maccallum, Caroline, Russo, 2018; Martin et al., 2018).

There are *Cannabis* vaporizers able to aerosolize and disperse cannabinoids, in which the dried drug or extract are electronically heated at a lower temperature than burn. This process provides the decarboxylation of compound in a mixture of water vapor. Taking this into account, the vaporizers received attention for therapeutic use, as they present lower respiratory hazards than other *Cannabis* combustion products. The vaporizers have pharmacodynamics and pharmacokinetics like compounds derived from thermal decomposition of burning. Furthermore, there is a difference between the vaporizer types, being that the electric ones with controlled temperature perform the decarboxylation better than gas-powered vaporizers (Biehl, Burnham, 2015; Newmeyer et al., 2017; Russell et al., 2018).

Figure 6. Decarboxylation reaction after heating of THCA-A (9) and CBDA (10), resulting in bioactive compounds THC (2) and CBD (3), respectively.
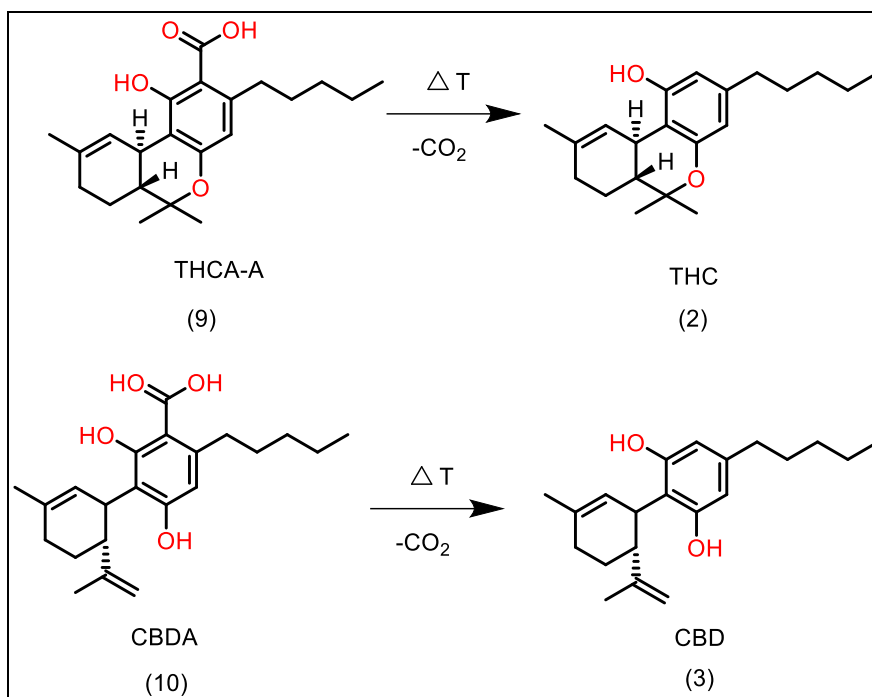
Source: Authors.

Cannabinoids Pharmacokinetics and Side Effects

Cannabinoids are highly lipophilic, they often need a carrier to facilitate their absorption into oral and topical routes. Oral absorption of THC and CBD range from 10 to 20%, being slow, erratic, unpredictable by THC, which is sensitive to gastric acid. Additionally, the type of feeding and the first pass effect on the intestine and liver can interfere in bioavailability. Maximum concentration happens within 1 to 6 hours upon ingestion and has prolonged action. Formulations designed to buccal mucosa present faster and higher absorption than oral route, useful for rapid symptom relief (Huestis, 2007; Maccallum, Caroline, Russo, 2018). The transdermal route does not suffer the first pass effect and ensures more limited local action. However, there is a great difficulty for transdermal release, which requires the improvement and development of new technologies for drug delivery (Grant, 2012; Lanz et al., 2016; Carcieri et al., 2018; Lucas, Galettis, Schneider, 2018; Maccallum, Caroline, Russo, 2018).

The distribution of cannabinoids is fast on highly vascularized tissues, as lung and brain, whereas in least vascularized regions, they are distributed by balance. In chronic use, these compounds can accumulate in adipose tissue, cannabinoids are released and redistributed, providing prolonged action. THC predominantly undergoes hepatic metabolism by cytochrome P450, especially by CYP2C9, CYP2C19 and CYP3A4 isoenzymes, though organs as small intestine and brain also metabolize it. The main metabolites of THC are 11-hydroxy-THC and 11-carboxy-THC, which suffer glucuronidation and are excreted via feces and urine. The half-life of THC ranges from the initial half-life (approximately 6 minutes) and the longer half-life (22 hours) (Hunt, Jones, 1980; Lucas, Galettis, Schneider, 2018).

CBD is metabolized in the liver by isoenzymes CYP2C19, CYP3A4, CYP1A1, CYP1A2, CYP2C9 and CYP2D6, it undergoes hydroxylation resulting in 7-hydroxy cannabidiol, followed by other metabolism steps and, finally its metabolite is eliminated in the feces and a lesser extent by urine. The mean half-life of CBD ranges from 18 to 30 hours when administered intravenously, from 27 to 35 hours by inhalation route, and 2 to 5 days by oral use (Lemberg, Crabtree, Rowe, 1972; Eichler et al., 2012; Schwope et al., 2011; Lucas, Galettis, Schneider, 2018).

Acute and chronic side effects related to *Cannabis* sp. are gastrointestinal disorders, fatigue, hypotension, nausea, paranoia, psychiatric symptoms, dizziness, impaired neurocognitive and psychomotor performances, attention and memory deficits, increase of psychiatric disorders, risk for addiction, airway trauma and lung diseases. Regarding the synthetic cannabinoids, acute adverse events are tachycardia, acute myocardial infarction, acute kidney injury, seizure, sedation, confusion and impaired motor skills, while the prolonged use is associated with withdrawal symptoms, including restlessness, anxiety and mood swings (Cranford et al., 2016; Parmar, Forrest, Freeman, 2016; Akram, Mokrysz, Curran, 2019). Considering the several adverse effects, the treatment with *Cannabis* sp. is contraindicated in patients with psychiatric, cardiovascular, renal or liver diseases. In addition, cannabinoids cross the placenta even at lower doses and are carried to breast milk, thus they are not recommended for pregnant and lactating women, as they can cause newborn weight-loss and neurobehavioral disorders (TGA, 2013; Parmar, Forrest, Freeman, 2016; Lucas, Galettis, Schneider, 2018).

Available Cannabinoid-based medicines

The Table 1 highlights and summarizes the commercially available cannabinoid drugs, which are employed to different therapeutic applications.

Table 1. Approved drugs containing synthetic cannabinoids and/or natural extracts of *Cannabis sativa* or *indica*.

Product	Active principles	Therapeutic indications
Acomplia®	Rimonabant	Appetite suppressant for obesity/overweight treatment (Smerp, 2019)
Marinol®	Dronabinol	Treatment of nausea and vomiting in cancer or AIDS patients (Becker, Nardin, 2011)
Cesamet®	Nabilone	Treatment of nausea and vomiting in cancer or AIDS patients (Becker, Nardin, 2011)
Bedrocan®	THC e CBD	Treatment of insomnia, neuropathic pain, stress, spasms, multiple sclerosis and depression (Bedrocan, 2019)
Sativex®	THC e CBD	Treatment of spasticity related to multiple sclerosis (Gw Pharmaceuticals, 2019a)
Epidiolex®	CBD (98%)	Treatment of seizures associated with Lennox-Gastaut and/or Dravet syndrome (Gw Pharmaceuticals, 2019b)
Mevatyl®	THC e CBD	Treatment of spasticity related to multiple sclerosis (Gw Pharmaceuticals, 2019c)

Source: Authors.

In 1983, Cesamet® and Marinol® were approved by FDA, in order to treat nausea and vomiting in cancer and AIDS patients, when conventional therapies present no more effects (Barnes, 2006; Becker, Nardin, 2011). Cesamet®, whose active

principle is nabilone (Figure 7), a synthetic THC analogue, was initially marketed by Eli Lilly, which discontinued production in 1989 on commercial reasons. In 2004, Valeant Pharmaceuticals acquired the nabilone rights, but the approval for commercialization happened in 2006. Currently, Cesamet® is sold in the United States and Europe (Fonseca et al., 2013). Nabilone has several adverse effects, the most observed are drowsiness, dizziness, dry mouth, euphoria, ataxia, headache and concentration problems. Although the nabilone structure is different from THC, it presents the same pharmacological activity, interacting similarly to the THC, as partial agonist on CB1 receptors and a small part on CB2. It is important to highlight that nabilone is more psychoactive than THC, thus it causes more side effects than the latter (FDA, 2019a; Pamplona, 2014).

Marinol® contains the active principle dronabinol, the synthetic THC, and is marketed by AbbVie Pharmaceuticals in Canada and the United Kingdom. Dronabinol is a sympathomimetic drug and its most common adverse events are anorexia, asthenia, heart palpitations, ataxia, confusion, euphoria and drowsiness. Therefore, its use is limited due to several side effects (Clermont-Gnamien et al., 2002; Cichewicz, McCarthy, 2003; FDA, 2006; Lessa et al., 2016).

In 2003, Bedrocan, a Dutch pharmaceutical company, received authorization from Netherlands Ministry of Health to produce and distribute standardized extracts of *C. sativa* and *C. indica* for medicinal uses. Currently, Bedrocan owns several extracts with specific concentrations of THC and CBD. Products from Bedrocan on the market are: Bedrocan® containing THC at 22% and CBD at 1% (2003), Bedrobinol® containing THC at 13.5% and CBD at 1% (2005), Bediol® with THC at 6.3% and CBD at 8% (2007), Bedica® with THC at 14% and CBD at 1% (2011), and Bedrolite® containing THC at 1% and CBD at 9% (2014). These products are indicated for insomnia, neuropathic pain, stress, spasms, multiple sclerosis, and depression. Therefore, it is essential to evaluate the risk-benefit, according to the clinical needs of patients (Bedrocan, 2019; Pamplona, 2014).

Rimobabant (Figure 7 - Acomplia® from Sanofi-Aventis) was a selective CB1 receptor antagonist, it inhibits 2-arachidonoylglycerol activity, causing the decrease hunger, since this endocannabinoid modulates the appetite. Therefore, rimonabant was employed to treat obese and overweight patients with health risks. In 2007, the drug was approved in Brazil as film-coated tablets containing 20 mg rimonabant, being a controlled drug (Valvassori et al., 2011; Ribeiro, 2014; Crippa et al., 2010; Smerp, 2019). However, in 2008, the product was suspended worldwide, due to the high risk of developing mental illness, such as anxiety, depression and suicidal thoughts (Fonseca et al., 2013). The Figure 7 shows rimonabant and nabilone structures, both drugs were designed from natural cannabinoids, being that rimonabant is an antagonist and nabilone is a partial agonist of endocannabinoid system.

Figure 7. Cannabinoid-based drugs (11) rimonabant and (12) nabilone.
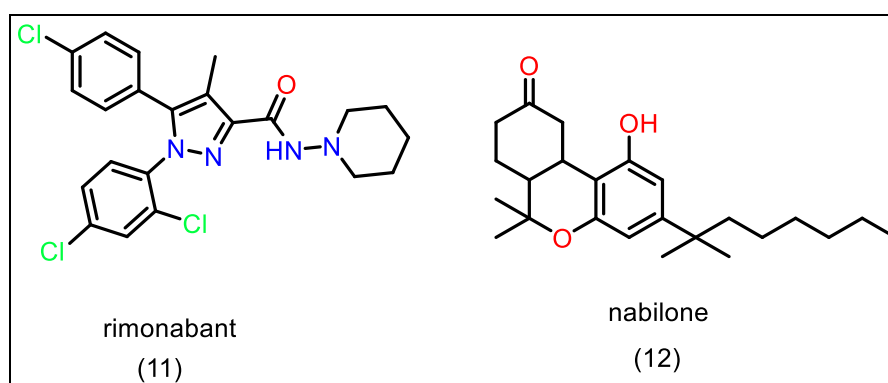
Source: Authors.

The first legal *Cannabis*-based drug approved in some countries was Sativex®, produced by GW Pharmaceuticals, it

consists of an oral spray composed of two cannabinoids: THC and CBD in 1:1 ratio. THC acts as a CB1 and CB2 receptors partial agonist, performing an important role in retrograde signaling in the regulation of synaptic. CBD and THC inhibit the endocannabinoid system, researches have been shown that cannabinoid receptor antagonists modulate muscle stiffness. Therefore, this medicine is indicated to treat moderate to severe spasticity related to multiple sclerosis in patients unresponsive to conventional therapy (Ribeiro, 2014; Drugbank.Sativex, 2019; Lessa et al. 2016). Regarding the side effects are described dizziness, anorexia, depression, disorientation, constipation, among others (ANVISA, 2017). Sativex® began to be marketed in Canada in 2005. Currently, it was approved and sold in the United Kingdom, Germany, Denmark, Sweden, Switzerland, Canada, Australia, New Zealand, Israel, the United States and, Brazil. In addition, FDA approved it as pain relief medicines (Russo, Guy, 2006; GW Pharmaceuticals, 2019a; Fonseca et al., 2013; Lessa et al., 2016). In Brazil, Sativex® is marketed using the Mevatyl® brand, as an antispasmodic drug distributed by Ipsen Pharmaceuticals, being approved in January 2017 and sold as a controlled substance (Smerp, 2019).

In 2018, FDA approved Epidiolex® (GW Pharmaceuticals), a CBD extract at 98%, which consists of an oral solution indicated for treating seizures associated with Lennox-Gastaut or Dravet syndromes. Epidiolex® acts as an endocannabinoid, inhibiting to CB1 and CB2 receptors. In relation to the adverse events, Epidiolex may cause hepatocellular injury, drowsiness, sedation, suicidal thoughts, and hypersensitivity reactions (Matos et al., 2017; Gw Pharmaceuticals, 2019b; Drugbank.Epidiolex, 2019; FDA, 2019b).

6. Legislation on *Cannabis*-based Products

Herein, we focused on Brazilian regulation, though other countries have been mentioned. In Brazil, based on the increase in judicial petitions requesting the importation of medicinal *Cannabis* products, the Brazilian Health Regulatory Agency (ANVISA) published the first regulation on the subject through Resolution RDC n° 17/2015, which defines the criteria and procedures for importing of products containing cannabidiol and other cannabinoids for the health treatment. In order to import, it is required the prescription of a legally qualified professional for patient own use, thus by restricting to patients with the need attested to the product (Brazil, 2015). An ANVISA update in 2016 of the Ordinance n° 344 of 1998 included CBD and THC on the list of substances of special control, through the Resolution RDC n° 66 (March 2016), regulating the use of medicinal *Cannabis*-derived products, since the *Cannabis* sativa is still on the list of plants prohibited in Brazil, due to its recreational use (Brazil, 2016). In addition, *Cannabis sativa* was included as a medicinal plant in Common Brazilian Denomination by Resolution RDC n° 156 (May 2017) (Brazil, 2017). Recently, the Resolution RDC n° 327 of December 9, 2019 established the required quality parameters for the regulation of these products from the granting of health authorization for the manufacture and import to the criteria for use in the marketing, prescription, dispensing, monitoring and inspection of *Cannabis*-based drugs for medicinal purposes (Brazil, 2019).

In other Latin America countries such as Peru, Argentina and Mexico, there was needed the pressure from citizens and patients for the approval of policies that allow the sale and use of medicinal *Cannabis*. In 2017, Peru approved a law that allows, upon registration, the medicinal *Cannabis* access for patients, importers, research and public entities. Also, the Peruvian government developed a system where the registered person or entity can obtain a license for researching, importing, commercializing and producing (Peru, 2019). Argentina on the other hand, issued a rule that allows patients to import *Cannabis* while the government is responsible for the local production (Vito, 2017). In Mexico, a reform on the General Health Law and Federal Criminal Code in 2017 authorized the *Cannabis* uses for medical and scientific purposes, ensuring that patients have access to pharmacological products containing THC or not (Mexico, 2017).

In the United States, the *Cannabis* use is not approved by the FDA, only one *Cannabis*-derived product is allowed, as previously mentioned, Epidiolex is a CBD purified employed for the treatment of seizures associated with Lennox-Gastaut

syndrome or Dravet syndrome in patients with 2 years of age and older. Moreover, three others *Cannabis*-based compounds were approved: Marinol and Syndros (dronabinol) for therapeutic use in patients with nausea associated with cancer chemotherapy and for patients with anorexia related to weight loss due to AIDS. Another *Cannabis* derivative compound approved by the FDA is Cesamet (nabilone), which is indicated for nausea associated with cancer chemotherapy. These are the only *Cannabis*-derived products authorized by the American agency upon prescription from a licensed healthcare professional (FDA, 2020).

7. Final Considerations

Several studies have been demonstrated the remarkable therapeutic potential of the genus *Cannabis*. Thereby, the plant and its derivatives present medicinal uses in diseases such as pulmonary emphysema, asthma, intestinal constipation, some types of pain, besides Central Nervous System disorders, as epilepsy, anxiety, insomnia, neuralgia, migraine, among others. The discovery of cannabinoid receptors and endocannabinoids have further assisted in the search for new therapeutic applications for *Cannabis.*

Regarding the commercially available medicines, we can observe that the adverse effects of isolated cannabinoids are more pronounced and severe than natural *Cannabis* extracts, because isolated cannabinoids are more concentrated in comparison to the secondary metabolites found in plant. In this context, further studies are needed from natural cannabinoids for designing of safer and more effective drugs.

There are several barriers to carry out experiments and researches involving *Cannabis*, both in its phytochemical evaluation and in terms of its therapeutic use. Among these difficulties, there is prejudice and some countries still consider it only as an abuse drug due to its psychoactive components and thus prohibiting its cultivation. Despite these difficulties, there are already cannabinoid-like drugs playing in the treatment of many patients who showed non-responsive to several conventional therapies without positive results. All findings show that *Cannabis*-based drugs are a promising source for the search for new drugs for therapeutic indications still untreated.

Currently, we can see major changes in regulation in some countries with the revision of laws, which hinder the development and use of *Cannabis*-derived medicines due to the pressure generated by several judicial petitions to use and import of these drugs, as an alternative to conventional treatments. In Brazil, a resulting movement was the publication of Resolution RDC n° 327/2019 by ANVISA responsible for regulate the *Cannabis* derivative products for medicinal purposes. These actions coupled with the wide therapeutic interest aroused by these compounds have been enabling new researches involving to the plant and its compounds, which have encouraged the expansion of our *Cannabis* knowledge and the development of new drugs.

The plant decriminalization or even legalization in several countries worldwide has provided naturally the expansion and financial market movement around *Cannabis*, mainly boosting the pharmaceutical field. The prospects are great for medicinal applications, and in the near future we believe it will be able to better understand the endocannabinoid system and its physiological role in the regulation of different biochemical pathways, which is quite complex and poorly explored. Thereby, this is a promising field for designing of new drugs with novel targets in the central and peripheral nervous systems involved, for instance, with neurodegenerative disorders, as Alzheimer's, Parkinson's diseases and multiple sclerosis. However, it is essential to reduce bureaucracy in researching *Cannabis*, specially in countries as Brazil, where the plant and derivatives still face several obstacles for its cultivation or even the import for scientifically proven biomedical applications, making it difficult to establish safe, adequate dosage and reproducibility parameters. Finally, we believe that the studies showing the benefits of medicinal uses of *Cannabis* will induce the bureaucracy reduction regarding this topic, which will stimulate national development and production of *Cannabis*-based products, decreasing the costs for treatment with these therapeutic agents.

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