Marijuana beyond stigma: Demystifying the uses of *Cannabis sativa*

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ABSTRACT

Cannabis sativa, commonly known as marijuana, has long carried a cultural and social stigma. However, it is essential to explore beyond ingrained prejudices and demystify the uses of this plant, especially in its medicinal role. The scientific community has been dedicated to unraveling the therapeutic properties of Cannabis, revealing a vast potential for the treatment of various medical conditions. Far from being just a recreational substance, *Cannabis* has active compounds such as THC (tetrahydrocannabinol) and CBD (cannabidiol), which have been shown to have significant medicinal effects. CBD has been noted for its anti-inflammatory, analgesic, and anxiolytic properties, offering a natural alternative for conditions such as chronic pain, anxiety, and even refractory epilepsy in children. Additionally, cannabis has shown promising applications in treating neurological diseases such as multiple sclerosis, providing symptom relief, and improving patients' quality of life. Demystifying these uses goes beyond mere acceptance; It involves recognizing the therapeutic potential of the plant and exploring ethical and responsible ways to incorporate it into medical treatment options. However, it is crucial to approach these issues with caution, considering the legal and ethical context surrounding the use of *cannabis*. Proper regulation is essential to ensure safe and controlled access to these treatments, preventing abuse, and ensuring that therapeutic benefits are maximized. Ultimately, demystifying the uses of *Cannabis sativa* is opening the door to a more informed and balanced conversation about its role in modern medicine. Ongoing research and education are key to dispelling myths and allowing society to fully harness the potential benefits of this plant, contributing to the evolution of the medical landscape and a more comprehensive and inclusive approach to healthcare.

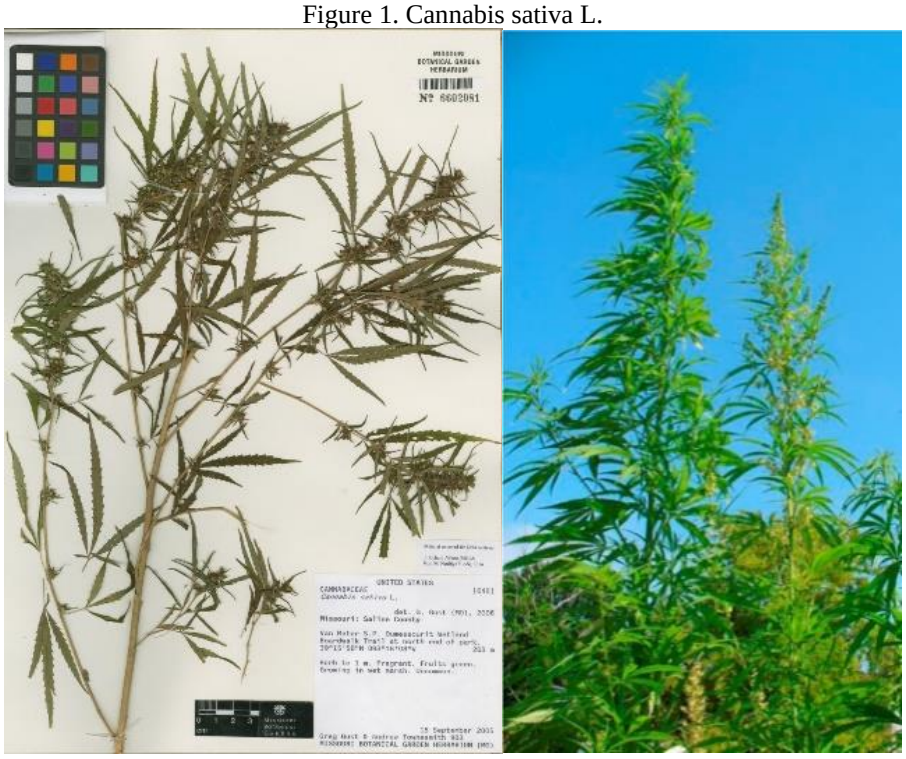
Keywords: *Cannabis sativa*, Therapeutics, Stigma.

1 INTRODUCTION

1.1 HISTORY OF USE AND DIFFUSION OF THE BOTANICAL SPECIES

Cannabis sativa L. (Figure 1) is an important herbaceous species, cultivated mainly in Central Asia (India and China) since ancient times (Russo et al., 2008). *C. sativa* has been used as a source of fiber, food, oil, and medicine, as well as for recreational and religious purposes over the centuries (Piluzza et al., 2013).

Figure 1. Cannabis sativa L.



Source: Google Images

Historically, Central Asia and Southeast Asia have been proposed as potential regions for the natural origin and/or primary domestication of *C. sativa* (Stevens et al., 2016). In addition, *C. sativa* has followed the progress of early human societies in the changes that occurred after the Pleistocene glacial epoch. The earliest archaeological evidence of the use *of C. sativa* has been found at Czech Paleolithic sites, where this species was used in the production of sophisticated woven baskets. (Adovasio et al., 1996). In addition, various Neolithic evidence found in Taiwan suggests that *C. sativa* was used 12,000 years ago for a number of different purposes (Li, 1973) and played a significant role in the manufacture of ropes and textiles. In fact, it has been referred to as the oldest known cultivated fiber plant (Cherney and Small, 2016), and to this day it is used as a constituent of fishing nets (Savo et al., 2013).

C. sativa has also been recognized as a sacred plant by various religions over the centuries. In fact, the sacred texts of Asian cultures refer to it as a plant with sacred virtues and consider it part of religious rituals. In India and Tibet, the traditions of Hinduism and Tantric Buddhism used C. *sativa* flowers and resins to facilitate meditation and communication with spirits (Touwn, 1981).

According to some authors, the word *Cannabis* was present in Semitic languages such as Hebrew and appears several times throughout the Old Testament. In fact, in some passages of Exodus, Isaiah, Jeremiah, and Ezekiel, the use of *C. sativa* as incense and sacred oil is cited (Heilig, 2011).

The medical use of *C. sativa* dates back to about 5000 years ago, when Emperor Chen Nung, king and "father" of Chinese agriculture, devised the first Chinese pharmacopoeia. According to this

ancient text, *C. sativa* was prescribed for fatigue, rheumatism, and malaria. In addition, Chinese physicians used *C. sativa* seeds primarily for their vegetable oils and proteins (Heilig, 2011).

In addition, the use of *C. sativa* as a medicine is widely reported in Assyrian clay tablets and in Egyptian papyri dated to about 3000 years ago. *C. sativa* was also well-known among the ancient Greeks and Romans. The historian Herodotus (circa 400 B.C.) mentioned its use and Diodorus Siculus (circa 60 B.C.) reported that ancient Egyptian women used C. *sativa* to reduce pain and improve their mood. In addition, the Roman historian Pliny the Elder reported the use of *C. sativa* roots to relieve pain (Ryz et al., 2017). In the same period, Pedacius Dioscorides, a Greek physician, classified different plants, including *C. sativa*, and described their useful benefits. A Roman physician, Galen, considered very influential in the Ancient and Middle Ages, also wrote some notes on *C. sativa.* In particular, he described a practice, widespread among Roman aristocrats, of concluding their lunch with a cannabis-based dessert (Butrica, 2002).

The various forms of *C. sativa* were known in medieval Europe. In particular, the Italians began the first large-scale cultivation and commercialization of the plant in the Mediterranean area. On the other hand, *C. sativa* was not known in the Americas until the arrival and settlement of the first European settlers.

The myth of the East that pervaded the nineteenth century also brought with it the development of private clubs of hashish consumers. In 1830, French physician Jacques Joseph Moreau studied the effects of *C. sativa* on mental illness. He thought that the voluptuous use of *C. sativa* could generate sensations common to hallucinations and delusions in psychotic individuals. In nineteenth-century English medicine, *C. sativa* was introduced as an analgesic, anti-inflammatory, antiemetic, and anticonvulsant (Allen, 2013).

Despite the benefits described above, *C. sativa* was heavily banned in the twentieth century due to its remarkable psychoactive effects and was removed from the British Pharmacopoeia in 1932 and included as a banned substance for therapeutic use in the UK Parliament's Drug Misuse Act in 1971. In 1937, production, possession, or trade was banned in the U.S. by the federal law "The Marihuana Tax Act" (Bonnie and Whitebread, 1974).

In fact, modern botanical varieties of *C. sativa* used primarily for the manufacture of fish nets (Savo et al., 2013), ropes, fabrics, and even paper have a low amount of D9-THC. On the contrary, the D9-THC content in the plant used both as a medicine and recreational drug is much higher than in *C. sativa* grown for fiber. This is the reason why, today, the cultivation and use of *C. sativa* with a high D9-THC content is illegal/prohibited in most countries, being allowed only for research and medical purposes (Tang et al., 2016).

2 BOTANICAL FAMILY

The C. *sativa* species belongs to the *Cannabaceae* family, which is widely distributed in the world, occurring in different ecosystems, including tropical to temperate zones of all continents, with the exception of Antarctica. The *Cannabaceae* family is part of the order Rosales and is represented by 10 genera and more than 110 species, with wide morphological diversity. Representatives of the family can be herbs, lianas, shrubs, or trees with simple or digitized leaves, usually alternate. Floral features that circumscribe *Cannabaceae* include unisexual, non-showy flowers with antetepal stamens and free fillets, inconspicuously attached to the tepals. The family includes economically important species such as hemp (*Cannabis sativa* L.) and hops (*Humulus lupulus L.)* (Viana, 2018).

3 USED PART

Cannabis *varieties* that are low in psychoactive cannabinoids are used for fiber production. For medicinal purposes, the resin produced and accumulated in the glandular trichomes that densely cover the surfaces of the female inflorescences (pistils) and, to a lesser extent, the foliage of male and female plants is used (Hanus, 2016).

Figure 2. Use of Cannabis sativa for fiber production.

Source: Google Images

Figure 3. Highlight of the glandular trichomes that densely cover the surfaces of the female inflorescences Cannabis sativa, from which the resin used for medicinal purposes can be extracted.

Source: Google Images

4 COMMON NAMES

C. sativa is known by the name "hemp of India". Other names given to Cannabis products are marijuana, hashish, charas, bhang, ganja and sinsemila. Hashish and charas are the names given to the dry resin extracted from the flowers of female plants, which has the highest percentage of psychoactive compounds (from 10 to 20%). The terms ganja and synsemila are used to define the dry material found at the top of female plants, containing about 5 to 8% psychoactive compounds. Bhang and marijuana are preparations with a lower content (2 to 5%) of psychoactive substances extracted from the rest of the plant. The term marijuana is used in Brazil for the preparations of *Cannabis sativa* (Honorio, 2006)

5 BOTANICAL SPECIES

According to The *Plant List*, in November 2020, 32 synonyms are recognized for the species *Cannabis sativa L.* As described in Table 1:

Table 1. Synonyms of *Cannabis sativa* L.

Cannabis americana Pharm. ex Wehmer
Cannabis chinensis Delile
Cannabis erratica Siev.
Cannabis foetens Gilib.
Cannabis generalis E.H.L.Krause
Cannabis gigantea Crevost
Cannabis indica Lam.
Cannabis indica f. afghanica (Vavilov) Vavilov
Cannabis indica var. kafiristanica Vavilov
Cannabis intersita Soják
Cannabis kafiristan (Vavilov) Greyhound
Cannabis lupulus Scop.
Cannabis macrosperma Stokes
Cannabis ruderalis Janisch.
Cannabis sativa f. afghanica Vavilov
Cannabis sativa f. chinensis (Delile) A.DC.
Cannabis sativa var. gigantea (Delile ex Vilm.) Alef.
Cannabis sativa var'indica (Lam.) Wehmer
Cannabis sativa subsp. indica (Lam.) E.Small & Cronquist
Cannabis sativa var. indica (Lam.) E. Small & Cronquist
Cannabis sativa subsp. intersita (Soják) Soják
Cannabis sativa var. kafiristanica (Vavilov) E.Small & Cronquist
Cannabis sativa var. kif A.DC.
Cannabis sativa var. macrosperma (Stokes) Ash. & Graebn.
Cannabis sativa var. monoica Hol.
Cannabis sativa f. pedemontana A.DC.
Cannabis sativa var. praecox Serebr.
Cannabis sativa var. ruderalis Janisch.
Cannabis sativa var. ruderalis (Janisch.) S.Z.Liou
Cannabis sativa var. Sativa
Cannabis sativa var. spontanea Vavilov
Cannabis sativa var. vulgaris Alef. [Invalid]

Fonte: *The Plant List*, 2020

6 GEOGRAPHICAL DISTRIBUTION

Cannabis sativa L. It is a highly variable species that has been distributed worldwide by humans. The plant is a popular recreational drug source and is banned by law in many parts of the world. There are licensing schemes in some countries to allow the cultivation of low-THC Cannabis for agronomic purposes.

Some authors divide C. sativa *into two subspecies*, sativa and *indica*, based on intoxicating properties, and each with a domesticated and wild variety. In the context of medicinal plant breeding, the indica taxon generally refers to Asian medicinal plants, especially with prominent characteristics in Afghanistan strains of wide leaflets, compact habit and early maturation. These are strains that have

traditionally been used in the production of resin (hashish). The taxon *sativa* is used to refer to a collection of narrow-leaved strains from Colombia, Thailand, South Africa, and Mexico and is usually used to produce marijuana leaves or inflorescence (Gilmore; Peakall; Robertson, 2007).

7 DESCRIPTION

C. sativa is a dioecious plant, with upright stems, which, depending on environmental conditions and genetic variety, can reach up to 5 m (Farag and Kayser, 2017). The leaves, usually composed of five to seven leaflets, are linear-lanceolate, tapering at both ends and the margins sharply serrated. Male flowers have no petals, axillary or terminal panics, and have five anthers. Female flowers germinate with a single ovulated periander attached. A single small, smooth, light-bluish-gray fruit is produced by flower and propagated by birds.

In addition, C. *sativa* is rich in trichomes, epidermal glandular protuberances that cover the leaves, bracts, and stems of the plant (Huchelmann et al., 2017). These glandular trichomes contain phytocannabinoids, responsible for defending and interacting with herbivores and pests, and terpenoids, which generate the typical smell of *C. sativa* (Andre et al., 2016). The shape of the plant varies according to the climate and variety. It grows most commonly as a persistent herb at the edge of fields cultivated on high-nitrogen land (Raman, 1998). After 8-12 days, the *C. sativa seeds* germinate and divide, open and expose the root and two circular embryonic cotyls come out. During its growth, the plant requires a moderate level of environmental and soil moisture and a good light intensity. *C. sativa* grows vertically and produces continuously new leaves, especially in the pre-flowering stage, with the production of new branches and nodules. These phases last about 6-22 weeks and need little light (Raman, 1998).

Figure 4. On the left, botanical illustration representative of *Cannabis sativa*. In the center, image of the male inflorescence. On the right, image of the female inflorescence.

Source: Google Images

8 CHEMICAL CONSTITUENTS

Currently, 538 natural compounds have been identified from *C. sativa.* Of these, more than 100 are identified as phytocannabinoids, due to the shared chemical structure. From a chemical point of view, phytocannabinoids have a lipid structure featuring alkylresorcinol and monoterpene fractions in their molecules (Hanus et al., 2016). In addition, they are mainly present in the resin secreted by the trichomes of female plants, while the male leaves of *C. sativa* have few glandular trichomes that can produce small amounts of psychoactive molecules. Phytocannabinoids are classified as neutral cannabinoids (without carboxyl group) and cannabinoid acids (with carboxyl group) (Hanus et al., 2016). In *C. sativa*, cannabinoids are biosynthesized and accumulated as cannabinoid acids and subsequently decarboxylated into their neutral forms. In particular, the alkylation of olivetolic acid with geranyl pyrophosphate by a prenyltransferase yields cannabigerolic acid (CBGA). Thanks to the action of cannabinoid synthase enzymes, CBGA generates cannabidiolic acid (CBDA), cannabichromenic acid (CBCA) and Δ-9-tetrahydrocannabinolic acid (D9-THCA) (Sirikantaramas and Taura, 2017).

Phytocannabinoids can be divided into 10 subclasses, as reported by several authors (Hanus et al., 2016, Sirikantaramas and Taura, 2017). Some of these are discussed below.

Cannabigerol (CBG): These phytocannabinoids have a heterogeneous chemical structure and do not produce CB1 receptor-mediated psychoactive action (Izzo et al., 2009). On the other hand, it appears that a *C. sativa* extract with a high concentration of CBG, without D9-THC, increases food consumption in rats (Brierley et al., 2017). CBG-like compounds exhibit a weak inhibition of serotonin 5HT1A receptors and bind to the TRPM8 menthol receptor blocking its action on sensory neurons (Borrelli et al., 2014, Cascio et al., 2010). In addition, CBG is a α-2 adrenergic receptor agonist capable of inhibiting the release of catecholamines with effects of sedation, muscle relaxation, and analgesia (Cascio et al., 2010). In addition, CBG decreases acetylcholine-induced contractions in the human bladder, and this action is not affected by CB1 or CB2 receptor antagonists (Pagano et al., 2015). Recently, Smeriglio et al. reported that *C. sativa* extracts, with CBD/CBDA or CBG/CBGA, inhibit aldose reductase activity and may be useful in the prevention and therapy of diabetic complications (Smeriglio et al., 2018).

Cannabichromene (CBC): From a structural point of view, CBC is one of the most stable phytocannabinoids; in fact, it has been detected in centuries-old samples of *C. sativa* (Russo et al., 2008). The amount of CBC is closely associated with D9-THC, suggesting a chemical relationship between the oxidase involved in CBC generation and CBG D9-THC (Izzo et al., 2009). Higher levels of BCC were found in the vegetative stage of *C. sativa* compared to its reproductive stage. In addition, CBC-like compounds do not exhibit any CB1-mediated psychoactivity, although CBC is a potent activator of a potential transient receptor channel, TRPA1, in inflammatory processes (De Petrocellis

et al., 2008). In particular, CBC appears to reduce levels of nitric oxide, IL - 10, and interferon γ in LPS-activated peritoneal macrophages, as reported by Dr. Romano and colleagues (Romano et al., 2013). So, the action of CBC can limit the effects of NO and have a curative effect on inflammatory bowel disease. In particular, CBC can positively influence the viability of the Nestin-positive stem cell population in NSPCs differentiation through the upregulation of adenosine A1 receptor-mediated ERK phosphorylation (Shinjyo and Di Marzo, 2013).

Type of cannabidiol (CBD): Cannabidiolic acid (CBDA) and CBD are the most abundant phytocannabinoids in textile cannabis species (Hanus et al., 2016, Izzo et al., 2009). Despite the structural similarity between CBD and D9-THC, CBD has a low agonism to cannabinoid receptors; in particular, it is considered as a negative allosteric modulator of CB1 and CB2 receptors (Pertwee, 2008, Casajuana Köguel et al., 2018). However, CBD can be electrophilically cycled into D9-THC in an acidic environment. This could also explain the production of D9-THC in tobacco cigarettes (acidic water suspensions) when added with CBD. Current evidence has shown that CBD exerts pharmacological effects through specific molecular targets such as adenosine receptors, glycine receptors, opioid receptors, serotonin receptors, non-endocannabinoid G protein-coupled receptors, nicotinic acetylcholine receptors, proliferator-activated receptors (Ibeas Bih et al., 2015). In addition, CBD exhibits anticonvulsant, antispasmodic, anxiolytic, antinausea, antirheumatoid, and neuroprotective properties (Pertwee, 2008). Recently, CBD has been shown to be an inverse agonist for orphan G protein-coupled receptors such as GPR3, GPR6, and GPR12, suggesting new therapeutic uses of CBD for Alzheimer's disease, Parkinson's disease, cancer, and infertility (Laun et al, 2018).

Tetrahydrocannabinol: Trans-Δ-9-tetrahydrocannabinol (D9-THC) is the main compound in *C. sativa* with major psychoactive effects (Pertwee, 2008). The main precursors of D9-THC, without psychotropic action, are D9-THC acids A and B. Several D9-THC stereoisomers, degradation products or enzymatically generated by products, occur as minority constituents of this class. In fact, D9-THC in *C. sativa* or chemically extracted and purified is unstable, presenting as an amorphous gum that quickly changes to brown (Hanus et al., 2016). The degradation of D9-THC is mainly oxidative, as it was estimated to be about 10% of the pure product, but CBN, the main final metabolite, was significantly lower. Therefore, *C. sativa* has other metabolic pathways for the degradation of D9-THC as hypothesized (Hanus et al., 2016, Andre et al., 2016). Among the most stable metabolites, it is worth mentioning Δ-8-tetrahydrocannabinol, derived from an acid isomerization of D9-THC with displacement of the endocyclic double bond (Hanus et al., 2016). In addition, from dihydrocannabinol, the D9-THC intermediate, trihydrocannabinol, identified in cannabis pollen, could be derived. Other D9-THC isomers have also been identified, such as cis-Δ-9-tetrahydrocannabinol, perhaps a chemical artifact, Δ-6a- and Δ-10a-tetrahydrocannabinol, unknown as natural products but synthesized by oxidative aromatization of D9-THC (Hanus et al., 2016). From a pharmacological point of view, D9-

THC is a partial agonist of both cannabinoid receptors: CB1, a modulator of psychoactive effects, and CB2, a modulator of immunological and anti-inflammatory effects (Pertwee, 2008). The psychoactive effects of D9-THC include anxiety, paranoia, perceptual changes, and cognitive deficits. All of these CB1-mediated effects are caused by disruption of GABA/glutamatergic neurotransmission and dopamine release and, above all, are usually acute, transient, and self-limiting (Pertwee, 2008). In addition, a low acute toxicity of D9-THC in murine models was also observed. Lastly, following D9-THC administration, hypolocomotion, hypothermia, catalepsy, analgesia, and increased food intake have been reported (Pertwee, 2008).

Δ-9-tetrahydrocannabivarin (D9-THCV) is another THC-type compound, mainly identified in *C. sativa* hashish from Pakistan (Tayyab and Shahwar, 2015). This molecule is considered a CB1 receptor antagonist (Dennis et al., 2008), because at low doses (<3 mg/kg) it antagonizes the effects of D9-THC by acting on food intake in mice. On the contrary, at higher doses (10 mg/kg) D9-THCV shows an agonist profile (Pertwee, 2008). In addition, D9-THCV can activate CB2 receptors (Bolognini et al., 2010) and inhibit LPS-stimulated nitric oxide production in macrophages (Romano et al., 2016).

Cannabicyclol (CBL): A racemic mixture of phytocannabinoids that occurs during storage of C. *sativa parts* in the presence of light, but with biological properties that are still unknown (Hanus et al., 2016).

Cannabinol (CBN): The concentration of CBN in *C. sativa* products depends on age and storage conditions. CBN is highly stable with respect to oxidative degradation. In addition, many derivatives of CBN degradation are the same as those obtained by spontaneous oxidative aromatization of D9-THC in *C. sativa.* A low affinity of CBN for CB1 and CB2 receptors has been observed (Hanus et al., 2016).

More than 200 terpenoids, responsible for the fragrance of *C. sativa*, have been identified in the flower, leaves of the plant, and may represent 10% of the trichome content (Booth et al., 2017). Limonene, myrcene, and pinene are the most common and highly volatile. They are insect repellent and act as anti-food for grazing animals. The mixture of different terpenoids and phytocannabinoid acids shows a synergistic mechanochemical defensive strategy against many predators (Farag and Kayser, 2017).

The production of terpenoids changes with specific environmental conditions. In fact, as noted for phytocannabinoids, terpenoids are produced as a defense mechanism: the amount of terpenoids increases with exposure to light (stressful condition for the plant) but decreases with soil fertility (Farag and Kayser, 2017). Terpenoids are lipophilic molecules that interact with the cell membranes of animals, at the brain and peripheral level (Russo, 2011). In particular, a smell test on mice exposed to

terpenoids for 1 h demonstrated profound effects on the behavior of mice, suggesting a potential effect on the brain (Russo, 2011).

D-limonene, common in lemons and other citrus essences, is a terpenoid widely distributed in nature, but little investigated in *C. sativa.* The molecular structure of this terpenoid shows strong free radical scavenging properties (Bai et al., 2016). In addition, serotonin and dopamine-mediated anxiolytic activity of D-limonene in the prefrontal cortex and hippocampal region of mice has been reported (Yun, 2014). In addition, perillyl acid, an immediate hepatic metabolite of limonene, shows anti-stress effects in the rat brain (D'Alessio et al., 2014). Subsequent investigations have highlighted various effects on breast cancer cell apoptosis (Jia et al., 2013). In addition, limonene's efficacy against gastroesophageal reflux has resulted in a patent application (Wilkins, 1999).

Beta-myrcene is a terpenoid widespread in *C. sativa*, with prominent brain activity. In particular, myrcene exhibits an analgesic profile in mouse models (from Cássia da Silveira et al., 2017). It is added to preparations based on *Humulus lupulus* with known sedative effects (Russo, 2011, by Cássia da Silveira et al., 2017). In addition, myrcene acts as a muscle relaxant in mice and has demonstrated anti-inflammatory activity via prostaglandin E-2 (Russo, 2011). These data suggest that myrcene, along with some phytocannabinoids, contributes to the sedative and anti-inflammatory effects of *C. sativa.*

Alpha-pinene is a bicyclic monoterpene, appears in conifers and other numerous plants in nature, with an insect repellent function. Pinene has been shown to have bronchodilator anti-inflammatory and antibacterial effects in several experimental models (Kim et al., 2015). In addition, this monoterpenoid appears to be an acetylcholinesterase inhibitor. This feature could counteract D9-THC-induced short-term memory deficits (Owokotomo et al., 2015).

D-linalool is a monoterpenoid alcohol with anxiolytic and sedative activity (Souto-Maior et al., 2011). Linalool also shows local anesthetic effects comparable to those of procaine and menthol. In fact, it was able to produce hot plate analgesia in mice after administration of an adenosine antagonist (Tsuchiya, 2017). Linalool has high-dose anticonvulsant, antiglutamatergic, and antinociceptive activities in mice (Souto-Maior et al., 2017). In addition, linalool may affect several components of glutamatergic transmission, as previously reported (Elisabetsky et al., 1995).

Beta-caryophyllene is the predominant sesquiterpenoid found in *C. sativa* and other plants such as *Carum nigrum, Syzygium aromaticum, Humulus lupulus, Ocimum gratissimum, Ocimum micranthum, Origanum vulgare, Piper nigrum* (Russo, 2011). The evolutionary ability of caryophyllene is due to its ability to attract predatory insects, such as lacewings, while also inhibiting herbivorous insects (Russo, 2011). It shows anti-inflammatory and antimalarial activities and has been claimed in the past to treat duodenal ulcers in the UK with a cannabis extract. The total selectivity of the agonist at the CB2 receptor is the biggest revelation regarding caryophyllene (Fidyt et al., 2016).

In fact, some authors have demonstrated that this terpenoid produces anti-inflammatory and analgesic activities at a dose of 5 mg/kg in wild-type mice, but not in CB2 knockout mice (Russo, 2011, Fidyt et al., 2016, Klauke et al., 2014). Caryophyllene offers great promise as a therapeutic compound.

Caryophyllene oxide is a sesquiterpenoid oxide with antifungal and insecticide/anti-feeding in plant defense (Yang et al., 1999). In addition, this molecule also demonstrates anti-platelet aggregation properties in vitro. Lastly, caryophyllene oxide is the component responsible for the identification of cannabis by sniffer dogs (Opdyke, 1983).

Phytol is a diterpene, present in *C. sativa extracts* as a product of the degradation of chlorophyll and tocopherol. Phytole-inhibited GABA degradative enzymes increase its expression, contributing to the relaxing effects of *C. sativa* (Bang et al., 2002).

9 PHYSICAL AND CHEMICAL ANALYSIS

Several chromatographic methods for the analysis of naturally occurring cannabinoids are reported in the literature. While simple methods based on HPLC-UV or HPLC-UV-PDA are common in cannabinoid analysis, HPLC-MS, HPLC-MS/MS, UPLC (or UHPLC)-UV-PDA, UPLC (or UHPLC)-MS, and UPLC (or UHPLC)-MS/MS, are also frequently used. UPLC and UHPLC methods have been shown to be superior to conventional HPLC methods. (Nahar, 2019)

The German Pharmacopoeia already contains a monograph for "*Cannabis Flowers*" (Cannabis flos*) and in 2020 the monograph entitled "Standardized Cannabis Extract* (*Cannabis extractum normatum*)" was published in the same *pharmacopoeia*. According to this monograph, Cannabis extract is "the extract produced and adjusted from whole or fragmented, flowering, and dried flowering tips of the female plants of Cannabis *sativa L. (Cannabaceae*)." This extract must have a content of Δ9-Tetrahydrocannabinol (THC) from 1% to 25% (w/w) and no maximum limit of Cannabidiol (CBD), but the range of 90 to 110% of the nominal content indicated on the label is allowed for both substances (ECA ACADEMY, 2019; ECA ACADEMY, 2020).

Quantification of chemical markers is performed by HPLC. Identification is performed by high-performance thin-layer chromatography. The maximum allowable water content is 0.5% (ECA ACADEMY, 2019).

Also according to the German Pharmacopoeia, the standardized extract of *Cannabis* should be prepared by an appropriate extraction process, preferably CO2 extraction. The extract obtained is refined, if necessary, and adjusted to the declared content with an inert excipient, preferably with medium-chain triglycerides. Cannabinoid acids are decarboxylated during the preparation of the extract or during the drying of the herbal medicine. The extract should be stored tightly closed, protected from light and between 2 and 8 °C. The label should indicate the THC and CBD content (ECA ACADEMY, 2019; ECA ACADEMY, 2020).

The European Pharmacopoeia (Ph. Eur.) is currently working on a Monograph on *Cannabis*, however, some specific challenges (e.g. inclusion of preparations, sample availability) are still under discussion (ECA ACADEMY, 2020)

10 PHARMACOLOGY

N-arachidonoylethanolamine (AEA) and 2-arachidonoylglycerol (2-AG) are the main endocannabinoid ligands present in the animal kingdom (McPartland, 2004). AEA and 2-AG are produced from cell membrane phospholipids, which contain arachidonate, and are immediately released. Fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL) are degradation enzymes of AEA and 2-AG, respectively, which through their hydrolysis regulate cannabinoid tone. The two main endocannabinoid receptors are cannabinoid receptor type 1 (CB1) and cannabinoid receptor type 2 (CB2) (Mechoulam et al., 1998).

The endocannabinoid system (ECS) appears in the most primitive animals with a nerve network and in mammals, birds, amphibians, fish, and various echinoderms and mollusks (Salzet et al., 2000). However, the presence of ECS has not been identified in all terrestrial invertebrates. Few studies have reported cannabinoid receptors and/or enzymes in insects. It is known, however, that *C. sativa* is able to evoke neurological and behavioral changes in insects, as a result, agronomists use its extracts as insect repellents (McPartland et al., 2001).

In mammals, the ECS exerts a significant neuromodulatory effect (Mechoulam et al., 1998). Mice with a targeted deletion of CB1 receptors exhibit altered nociceptive responses, extreme hypomobility, and significantly increased mortality (Zimmer et al., 1999).

The human brain contains very high levels of cannabinoid receptors, about 10 times higher than opioid receptors (Sim et al., 1996). In particular, CB1 receptors are widely expressed in the hippocampus, basal ganglia, amygdala, cortical areas, and cerebellum, all regions that are involved in mood, cognitive functions, and motor control (Tsou et al., 1998). Lower expressions have been found in other areas of the brain, for example, in the brain stem, where the regulatory centers of respiration and cardiac function are located (Akerman et al., 2013). CB1 receptors have also been located in peripheral areas such as the gut, liver, adipose tissue, and immune cells (Jourdan et al., 2010). The brain expression of CB2 receptors in physiological condition is much lower compared to CB1 receptors; however, during inflammation, CB2 receptor levels increase dramatically in microglia and other glial cells (Savonenko et al., 2015). (Thompson et al., 2003). In recent decades, a large number of cannabinoid compounds capable of modulating CB1, CB2 receptors and endocannabinoid metabolism, AEA and 2-AG, have been developed and characterized (Rampa et al., 2012, Giacoppo et al., 2014).

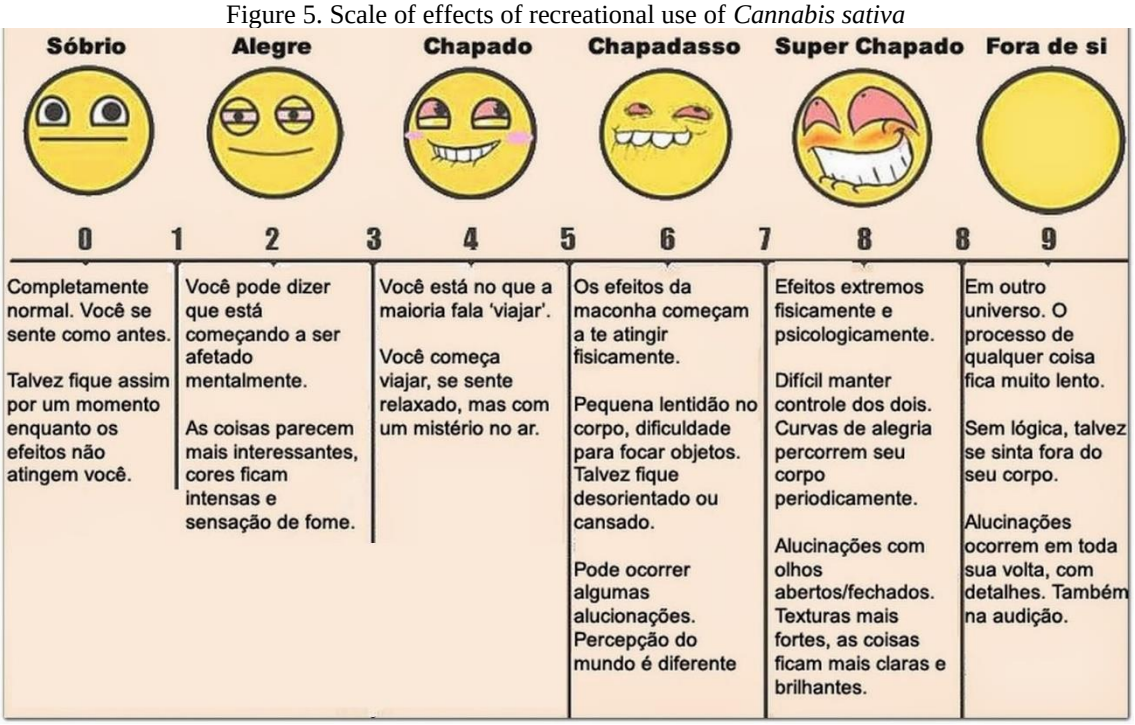
The use of different C. *sativa* preparations (natural and synthetic) is associated with therapeutic strategies for many diseases. Certainly, due to the diffuse presence of the ECS in the brain and periphery, its activation or inhibition regulates several pathophysiological phenomena (Mastinu et al., 2018).

ECS is involved in various disorders, including metabolic and neuroinflammatory pathologies. Especially, in the brain, cannabinoids modulate hunger/satiety and neuroinflammation, and in the periphery, they are involved in the peripheral metabolic reactions of liver, fat, muscles, and anti-inflammatory response in blood cells (Mastinu et al., 2018).

11 SIDE EFFECT, CONTRAINDICATION, ADVERSE REACTION AND PRECAUTION

Cannabinoid use is associated with an increased risk of short-term adverse events such as asthenia, balance problems, confusion, dizziness, disorientation, diarrhea, euphoria, drowsiness, dry mouth, fatigue, hallucination, nausea, drowsiness, vomiting (Lim et al., 2017), and anxiety (Whiting et al., 2015). Many of the adverse effects of *C. sativa* are associated with addiction and recreational use. Such effects depend on the dose and route of administration and are illustrated in the figure below.

Figure 5. Scale of effects of recreational use of *Cannabis sativa*



Source: Google Images

12 FORMULATIONS

In Brazil, several artisanal extraction oils of *C. sativa* can be found, produced individually or in patient associations, with judicial authorization. Such products are conceptually herbal medicines, but are difficult to register due to the lack of standardization of production and, therefore, quality control, which ensures constancy of efficacy and safety (CANNABIS & SAÚDE, 2020).

In countries where the medicinal use of *Cannabis derivatives* has been regulated for a longer time, there are several formulations, generally in the form of CBD, THC and the so-called *full spectrum* oils. In addition to herbal and medicinal plant presentations, phytopharmaceuticals are also on the international market, which are also considered plant biodiversity medicines, but differ from herbal medicines because they are purified substances isolated from plant raw materials with a defined chemical structure (CANNABIS & SAÚDE, 2020).

Imports of medicinal products derived from *Cannabis*, such as cannabidiol, are authorized in accordance with Collegiate Board Resolution (RDC) 335/2020. To request this authorization, it is necessary to access the Federal Government's services page and fill out the electronic form to request authorization for exceptional importation of cannabidiol (ANVISA, 2020).

Figure 6. Miscellaneous presentations of products derived from *Cannabis* available in the market

Source: Google Images

In December 2019, the National Health Surveillance Agency (Anvisa) approved the creation of a new category of cannabis-derived products. The Resolution of the Collegiate Board of Directors - RDC No. 327, of December 9, 2019, entered into force on March 10, 2020. This regulation provides that the trade will be carried out exclusively upon medical prescription of special control. The rules vary according to the concentration of tetrahydrocannabinol (THC). In formulations with a THC concentration of up to 0.2%, the product must be prescribed through a type B prescription, with a number provided by the local Health Surveillance and prescription renewal within 60 days (ANVISA, 2019).

On the other hand, products with THC concentrations higher than 0.2% can only be prescribed to terminally ill patients or those who have exhausted therapeutic treatment alternatives. In this case, the prescription will be type A, valid for 30 days, provided by the local Health Surveillance, a standard similar to that of morphine, for example (ANVISA, 2019).

At the end of April 2020, Anvisa approved the first authorization for a Brazilian company to produce a cannabis-derived product. It is an oral solution of cannabidiol manufactured by Prati-Donaduzzi, from Paraná. According to the authorization published in the Official Gazette of the Union (D.O.U.), the product is a phytopharmaceutical, with a THC concentration of up to 0.2% and, therefore, must be prescribed through a type B prescription.

The indication and form of use of *cannabis-based* products are the responsibility of the attending physician, and patients must be informed about the use of the products in question. The information provided should include: the health risks involved; the regulatory condition of the product regarding the proof of safety and efficacy, informing that the *Cannabis* product is not a medicine; the possible adverse effects, taking as an example, but not limited to, sedation and cognitive impairment, which may impact work, the act of driving and operating machinery or other activities that imply risks to oneself or others; and care in use. In addition, the patient or, if this is not possible, his/her legal representative must sign a Free and Informed Consent Form (ICF) on the use of the *Cannabis product* (CRF-TO, 2020).

Figure 7. First derivative product of *Cannabis* registered in Brazil

Source: Google Images

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