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Cannabis: Drug of Abuse and Therapeutic Agent, Two Sides of the Same Coin

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ABSTRACT

The consumption of *Cannabis sativa* plant, known as marijuana in the Western world, for different purposes (therapeutic, intoxicating, and spiritual) due to its psychoactive effects, can be traced back to ancient times. *Cannabis* is the most used illicit drug worldwide; however, its legal status is changing rapidly. *Cannabis* regulation will allow a better understanding of its effects as a misused drug, including new challenges, such as the availability of highly potent *Cannabis extracts.* Furthermore, scientific research is making significant efforts to take advantage of the potential therapeutic uses of *Cannabis* active compounds. The science of *Cannabis* derivatives started with the identification of the phytocannabinoids Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), allowing the formal study of the complex set of effects triggered by *Cannabis* consumption and the deciphering of its pharmacology. Δ^9-THC is recognized as the compound responsible for the psychoactive and intoxicating effects of *Cannabis.* Its study led to the discovery of the endocannabinoid system, a neuromodulatory system widespread in the human body. CBD does not induce intoxication and for that reason, it is the focus of the search for cannabinoid potential clinical applications. This review examines the current state of knowledge about contrasting perspectives on the effects of *Cannabis,* Δ^9-THC, and CBD: their abuse liability and potential therapeutic use; two sides of the same coin. (REV INVEST CLIN. 2023;75(3):105-28)

Keywords: *Cannabis sativa.* Marijuana. Cannabinoids. Δ^9-tetrahydrocannabinol and cannabidiol. Endocannabinoid system. *Cannabis*-based treatments.

INTRODUCTION

Marijuana is a preparation of the *Cannabis sativa* herb consumed since ancient times with therapeutic purposes and as a misused drug. Cannabinoids are lipid compounds interacting with cannabinoid receptors. Plant-derived cannabinoids are termed phytocannabinoids and around 100 of them are recognized as exclusive of *C. sativa,* with Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) being the most abundant and studied[1]. The isolation of Δ^9-THC allowed its identification as the compound responsible for the psychoactive actions of *Cannabis,* the characterization of its intoxicating and therapeutic effects, and led to the discovery of the endocannabinoid system (ECS) in vertebrates. The phytocannabinoids Δ^9-THC and CBD exert their effects by interacting with the ECS[2].

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Cannabis preparations meet the criteria to be considered misused drugs, since they induce acute intoxication that can be rewarding and might lead to their repeated intake, producing tolerance to several of its effects and the development of physical dependence, expressed by a withdrawal syndrome. *Cannabis* use disorder (CUD) is recognized in the diagnostic and statistical manual (DSM-5)[3]. *Cannabis* consumption is worldwide spread; it is one of the most consumed drugs with abuse potential, only after alcohol and tobacco. Although considered as an illicit substance for decades, *Cannabis* legal status is changing to that of a regulated substance in several countries. Otherwise, the therapeutic application of cannabinoid-like compounds for distinct medical conditions is a relevant research field.

To date, the Food and Drug Administration of the United States (FDA) has approved three *Cannabis*-based pharmaceuticals as therapeutic agents, although with limited indications. These pharmaceuticals include two synthetic Δ^9-THC formulations, dronabinol (Marinol®, Syndros®) and nabilone (Cesamet™) and one CBD extract (Epidiolex®). This scenario urges the advance in the comprehensive understanding of the potential harmful consequences and therapeutic applications of *Cannabis,* Δ^9-THC, and CBD. This is highly relevant because evidence indicates that phytocannabinoid properties are complex. For instance, acute *Cannabis* produces dose-dependent, biphasic effects on anxiety reducing it at low doses but increasing anxiety levels at high doses[4,5]. Furthermore, although Δ^9-THC has a recognized antiemetic effect that resulted in one of the approved cannabinoid therapeutic uses, the chronic consumption of high *Cannabis* doses induces the *Cannabis* hyperemesis syndrome, characterized by persistent nausea and vomiting[6]. This complexity makes clear the need of continued research on the mechanisms of action underlying cannabinoid therapeutic effects to assure both their safety and effectiveness. This review examines the current state of knowledge about the opposed perspectives of the effects of *Cannabis* and its active principles, Δ^9-THC and CBD: Their abuse potential and therapeutic use, two sides of the same coin.

THE PLANT

Marijuana is a preparation from the plant *C. sativa*. Its origin appears to be Central Asia, with a later spread to Africa, followed by Europe and, finally to the Americas[7] (Fig. 1).

The genus *Cannabis* includes two main species: *Cannabis indica* and *C. sativa;* however, a morphological or chemical distinction between these species is difficult to make[8]. Therefore, the designation *C. sativa* is considered suitable for all plants of this genus.

C. sativa is an annual herbaceous flowering plant that can grow up to 5 m. It is a dioecious plant, meaning that there are male plants that create pollen sacs and female plants which develop inflorescences consisting of several individual bunches of flowers covered by trichome glands containing resin (Fig. 2). *C. sativa* grows better in template climates, although indoor-controlled cultivation is more common in recent times. It is a highly adaptable plant, explaining why its cultivation is widely expanded.

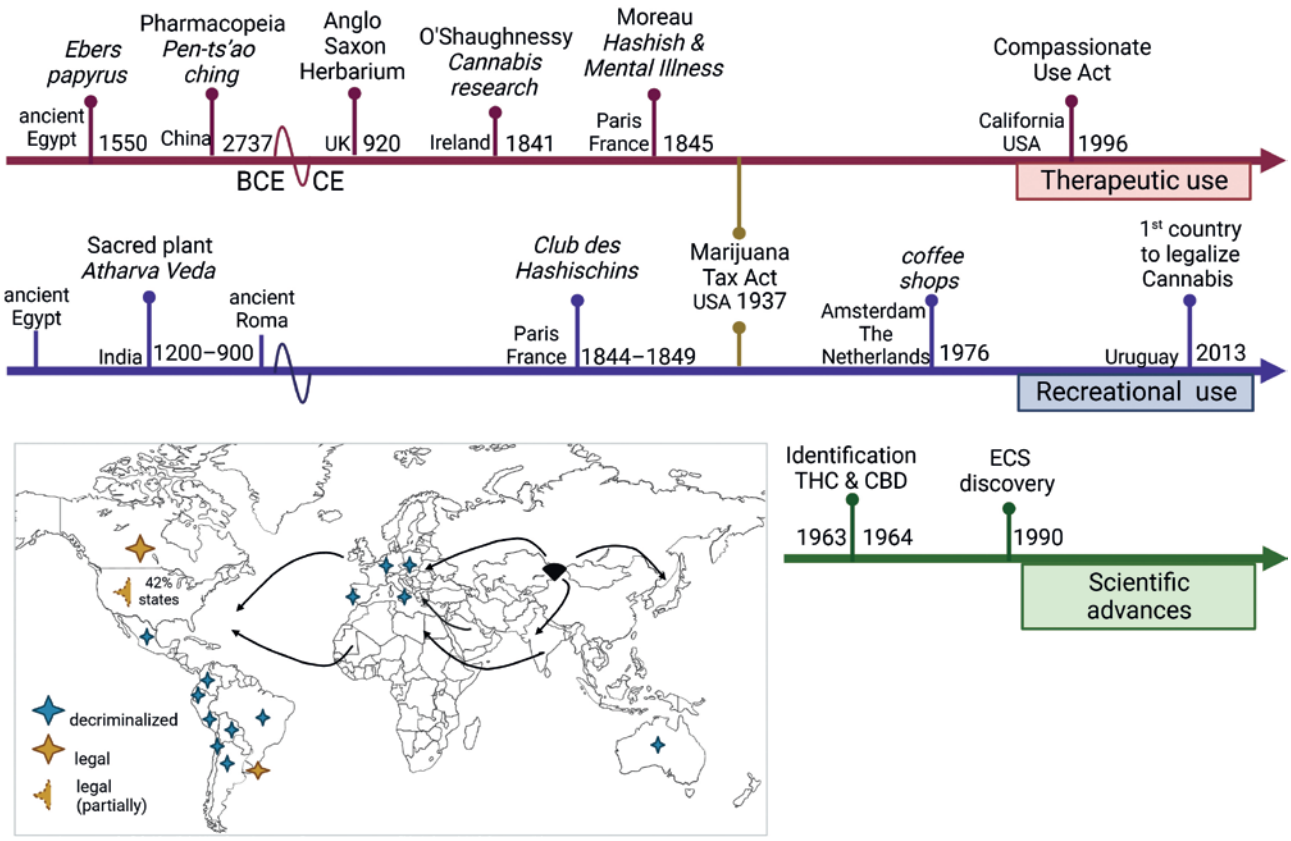
C. sativa contains approximately 500 compounds; around 100 are exclusive to the plant and are called phytocannabinoids, a term describing plant-derived cannabinoids. These compounds can be distinguished from synthetic cannabinoid molecules produced with therapeutic purposes (e.g., dronabinol). Synthetic cannabinoids also refers to the illicit molecules belonging to the new psychoactive substance group, recognized as a public health concern (e.g., "spice"). Phytocannabinoids are also distinct from those produced by living organisms known as endocannabinoids (eCBs) or endogenous cannabinoids (e.g., anandamide) (Fig. 3).

Δ^9-THC and CBD are the major components of *C. sativa,* and both modify brain and body functions. Δ^9-THC accounts for the intoxicating properties of *Cannabis* preparations, while CBD does not induce intoxication but exerts several psychoactive effects. The content of phytocannabinoids in the extracts of *C. sativa* is highly variable. The *Cannabis* plant has been semi-domesticated, and its Δ^9-THC content increased deliberately, making *Cannabis* preparations with a high Δ^9-THC content and a lower CBD content available[9]. Δ^9-THC interacts directly, while CBD interacts indirectly with the ECS to exert their effects.

THE ENDOCANNABINOID SYSTEM

Δ^9-THC effects are mediated by its ability to bind and activate cannabinoid receptors. These receptors are

Figure 1. *Cannabis* history. Timeline tracing some historical milestones about the therapeutical (red) and recreational (blue) use of marijuana; the years of the breakthrough that led to the scientific study of the plant are also depicted. In the map, the arrows represent how it is believed that the plant was distributed from Asia to the rest of the world, and the colored stars illustrate the countries that legalized and decriminalized medical and non-medical uses of the plant *(adapted from Pisanti and Bifulco[7]). Created with BioRender.com.*



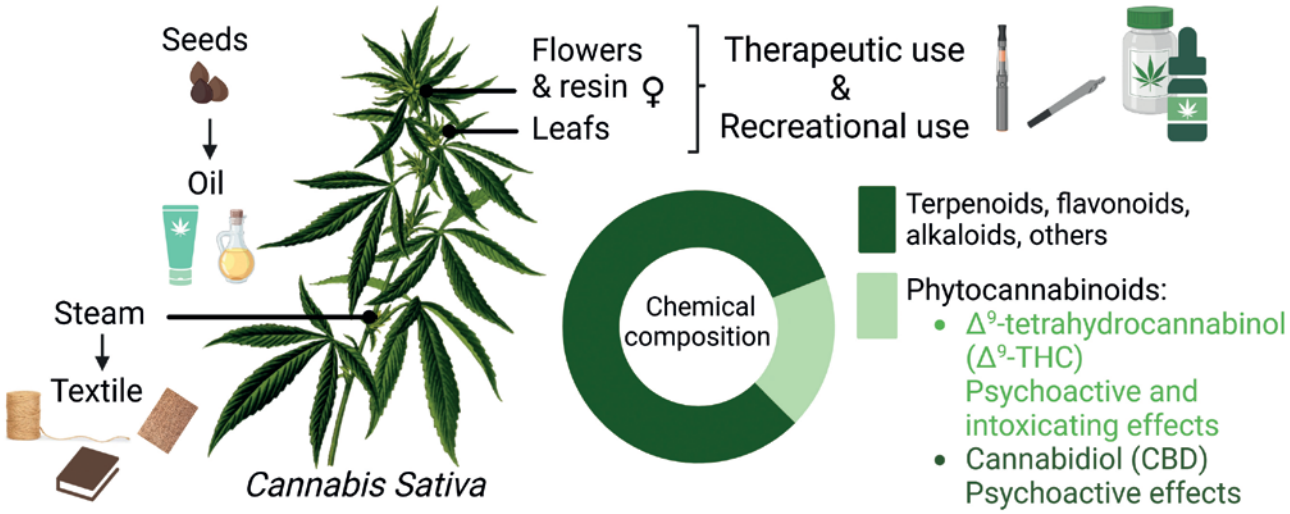
part of the ECS that encompasses cannabinoid receptors 1 and 2 (CB1R and CB2R), their endogenous ligands (eCBs), and the enzymes that participate in eCB biosynthesis and inactivation (Fig. 4). CB1R is expressed primarily in the brain[11] and moderately in peripheral tissues, whereas CB2R is mainly expressed in the periphery. In the brain, CB2R is mostly present in microglia, particularly following inflammation, or injury[12]. Although, CB2R has been recently identified in neurons in discrete brain areas[13]. The endogenous ligands of these receptors are the eCBs, of which AEA and 2-AG, both derivatives of arachidonic acid, are the most studied. The ECS also includes the enzymes responsible for the synthesis and metabolism of AEA and 2-AG (Fig. 4).

Unlike other neurotransmitters, eCBs are not stored in synaptic vesicles but are synthesized and released "on demand;" this means that specific stimuli, like increased neuronal activity, trigger their production. In the brain, eCBs act as retrograde transmitters, that is, they are synthesized and released from the postsynaptic neuron, travel backward through the synaptic cleft, and bind to CB1R located on presynaptic axon terminals. CB1Rs are metabotropic receptors coupled to inhibitory Gi/o proteins, which activation hyperpolarizes the neuron, inhibiting the release of other neurotransmitters (Fig. 5). The ECS seems to play a role in many physiological activities and pathological conditions[14], and it mediates the effects of *Cannabis* as a drug of abuse.

THE NON-MEDICAL USE OF *CANNABIS*

In 2020, the United Nations estimated that 209 million persons, or 4.2% of the global adult population, had consumed *Cannabis* in the previous year[15].

Figure 2. *Cannabis* sativa plant. From the family *Cannabaceae,* genus *Cannabis,* species *sativa* (Linnaeus, 1973). *C. sativa* is a versatile plant with multipurpose use. The fibers obtained from the stems, known as hemp, are durable and have been used in the textile and paper industry. The oil from the seeds is used in the cosmetic and food industry. The leaves, the flowers of the female plant, and the resin are used as preparations for its consumption. The plant's chemical composition can be divided into two main groups: phytocannabinoids, compounds exclusive of this plant including Δ^9 -tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD), and other constituents such as terpenoids and flavonoids, among others. Phytocannabinoids are more abundant in the plant's resin, flowers, and leaves. The table shows the main *Cannabis* preparations that are offered. Marijuana is also known as mota, weed, ganja, pot, dope, and Maryjane, among other street names. Hashish is also known as just hash. Oily Δ^9-THC, such as butane honey oil (BHO), can be obtained by different processes. The products derived from these highly efficient extractions receive a variety of names, such as shatter, wax, and dab[8-10]. *Created with BioRender.com.*



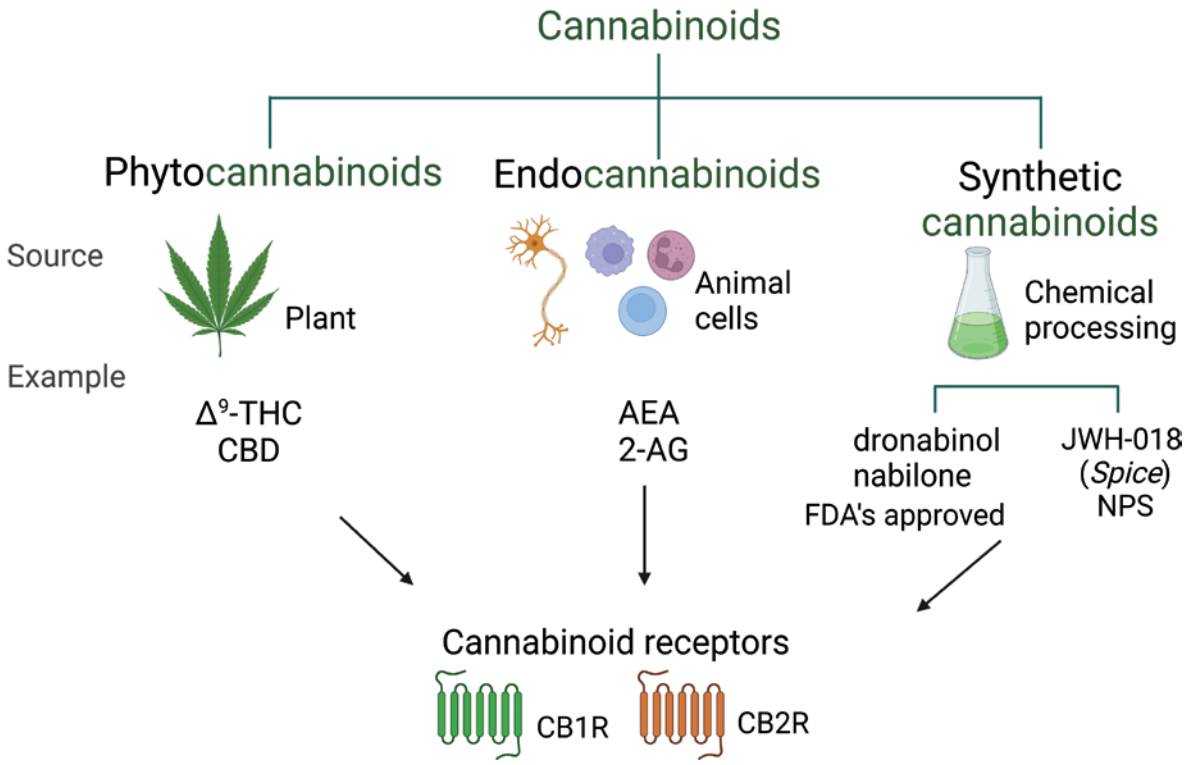
	Description	Route of administration	Δ⁹-THC : CBD ratio (ranges)
Marijuana	Dried flowers, leaves, resin and some tiny stems		≈12% : <0.15% (2014) ≈ 4% : ≈0.3-0.5% (≠1995)
Hashish	Blocks of dried resin (trichomes)		≈16-40% : <5%
Hash Oil	Solvent extraction from hashish		≈50-55% : Not detectable
Oily Δ⁹-THC extracts	Extracts, oils or capsules. Wide range of methods and products		≤ 80 % : Not detectable

Strictly, "marijuana" refers to the crude mixture of dried and crumbled leaves, small stems, and flowering tops usually smoked in hand-rolled cigarettes (joints), or water pipes ("bongs"). However, *Cannabis* can be offered in different preparations. Hashish is a pure resin preparation with high cannabinoid content. With even more potency, new preparations such as butane hash oil or wax are also available. Extracts of the plant *Cannabis* loaded into cartridges for vaping also exist[10]; some of the characteristics of the different preparations are specified in table of figure 2. Countries where *Cannabis* use is regulated, such as specific states from the United States, Canada, and Uruguay commercialize diverse *Cannabis* products classified according to their chemotype, that is, the proportion of different phytocannabinoids (mostly Δ^9-THC and CBD) contained.

Δ^9-THC pharmacokinetics

The two most common methods of Δ^9-THC administration are inhalation, through smoking or vaporization, and ingestion of edible *Cannabis* preparations. Smoking is the more efficient route to experience

Figure 3. Cannabinoids. The term cannabinoids refers to molecules that, regardless of their origin, have the ability to interact with the cannabinoid receptors (CB1R and CB2R). Phytocannabinoids allude to the constituents of the *C. sativa* plant, such as Δ^9-THC and CBD. Endocannabinoids is a term that designates those molecules synthetized by animal cells. Synthetic cannabinoids are those molecules produced in laboratories, as the name implies. For the synthetic cannabinoids, a distinction has to be made between those that are FDA approved to be used as therapeutic agents, such as dronabinol and nabilone, and those non-regulated due to its toxic effects that belong to the new psychoactive substances (NPSs) group of misused drugs, such as the JWH-018 found in products like *Spice*. *Created with BioRender.com.*



Δ^9-THC psychotropic effects, which start soon due the lungs' large and highly vascularized absorption surface and can last around 3 h. After reaching peak levels, plasma Δ^9-THC concentrations decline due to liver metabolism and drug accumulation in the body fat. When the preparation is consumed orally, its effects begin to be experienced at least half an hour later, due to the prolonged but poor Δ^9-THC absorption by the gastrointestinal tract, increasing the probability that the consumer takes a second dose and thus becoming exposed to high Δ^9-THC concentrations. These high concentrations often trigger adverse effects such as panic attacks.

Δ^9-THC is metabolized in the liver producing nearly 100 different metabolites, of which 11-OH-THC and THC-COOH are the major ones found in humans. Δ^9-THC accumulates largely in body fat, which serves as a long-term storage site for the drug. This characteristic explains Δ^9-THC large elimination half-life[16].

Details of Δ^9-THC pharmacokinetic parameters are shown in figure 6.

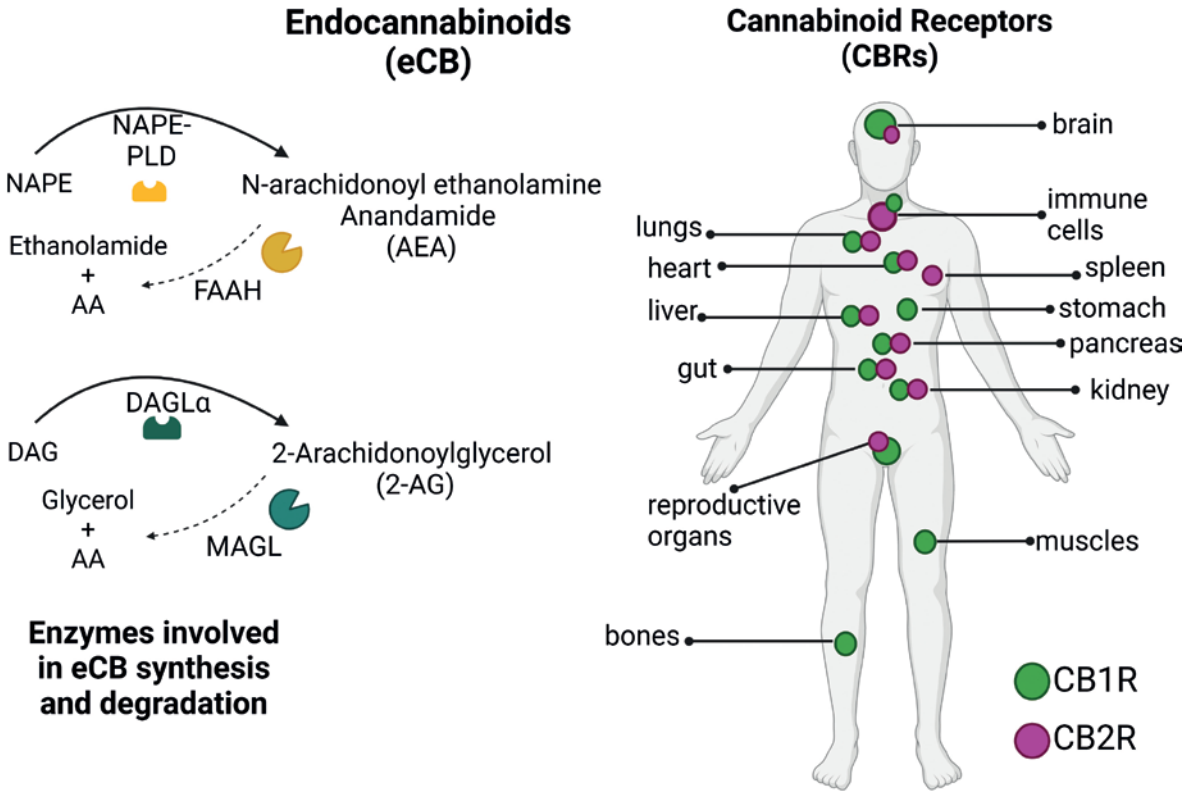
Δ^9-THC mechanism of action

Δ^9-THC is a partial agonist of CB1R and CB2R. Its effects have been described to be mediated by CB1R activation, though the participation of CB2R is beginning to be investigated. In the brain, CB1R is expressed in cortical areas involved in higher cognitive functions, in midbrain regions associated with motor control and reward, and in hindbrain regions controlling motor and sensory functions of the autonomic nervous system (Fig. 7).

Cannabis acute effects

In rodents, Δ^9-THC and cannabinoid receptor agonists typically induce a tetrad of effects: Analgesia, hypothermia, catalepsy (lack of voluntary movement), and

Figure 4. The endocannabinoid system. This system is present throughout the body and is composed of the cannabinoid receptors (CB1R and CB2R), their endogenous ligands (lipid-derived signaling molecules), of which the most studied and best characterized are N-arachidonoylethanolamine (anandamide, AEA) and 2-arachidonoylglycerol (2-AG), and the enzymes involved in AEA and 2-AG synthesis [N-acyl-phosphatidylethanolamine specific phospholipase D (NAPE-PLD) and diacylglycerol lipase α (DAGLα), respectively], and in their degradation [the fatty acid amide hydrolase (FAAH) and monoacylglycerol lipase (MAGL), respectively][2,14]. *Created with BioRender.com.*

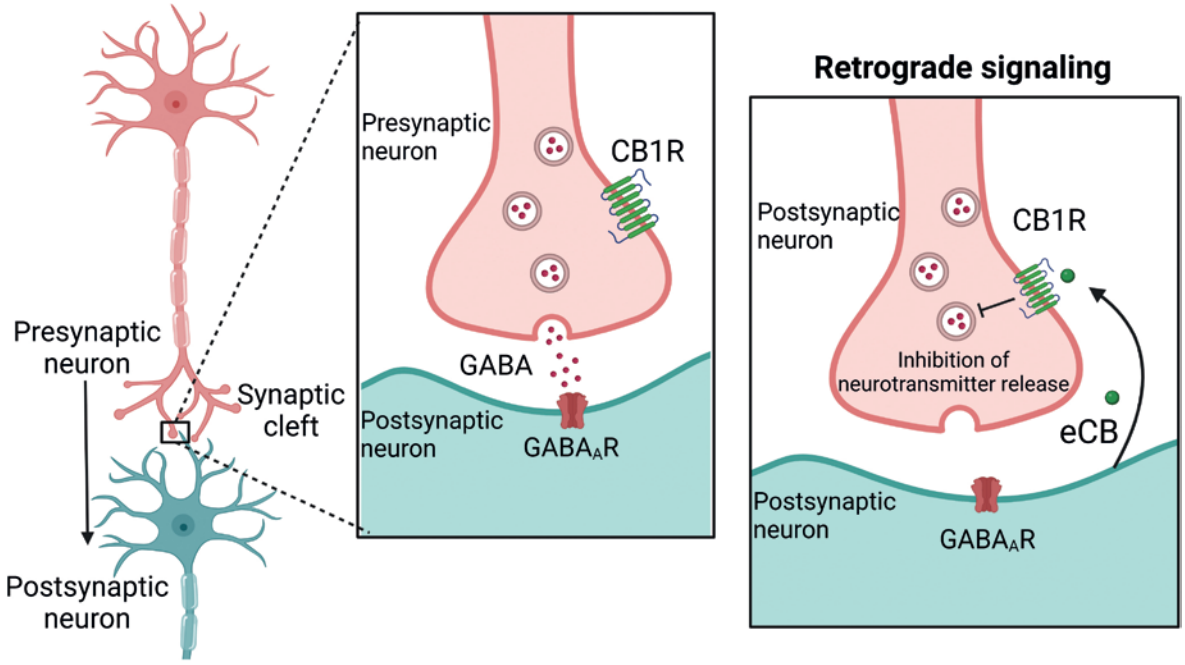


hypoactivity. This tetrad helps identifying the cannabimimetic activity of drugs. In humans, the effects of *Cannabis* depend on several factors, including the user's experience and possible tolerance, the expected effects and mental state, the environment (set and setting), and pharmacological factors like the administration route, which is highly relevant, especially in terms of the onset and duration of the effects. The Δ^9-THC content in *Cannabis* preparations, which is highly variable, is a determinant factor for its effects.

Cannabis causes, depending on the dose, complex significant effects on the human body and mind, altering sensory perceptions, mood, cognitive abilities, motor coordination, and the sense of self and time. Acute *Cannabis* use is associated with subjective symptoms of mild euphoria, relaxation, continuous laughter and talkativeness, sedation, lethargy, intensification of ordinary sensory experiences, and perceptual distortion, for example, time perception, social withdrawal, and increased appetite and food consumption known as "the munchies." Physical signs include conjunctival hyperemia (red eyes) and ptosis, dry mouth, increased heart rate, mild increase in blood pressure, and orthostatic hypotension. The cluster of subjective and physiological effects induced by *Cannabis* intake is known as the "high." Other central nervous system effects are alteration of psychomotor functioning and impairment of cognitive tasks. Table 1 summarizes the main effects of Δ^9-THC and their neurobiological bases, which are illustrated in figure 7.

The consumption of high Δ^9-THC doses may precipitate panic attacks or persistent paranoia as clinically significant adverse effects. Notwithstanding, a lethal Δ^9-THC dose or deaths due to *Cannabis* overdose have not been reported, which might be related to the absence of CB1R expression in the brainstem.

Figure 5. Retrograde signaling. In the brain, endocannabinoids (eCBs) are retrograde messengers, that is, they are synthesized and released by the postsynaptic neuron and act at CB1R located at the nerve endings of presynaptic neurons. CB1R activation leads to neuronal hyperpolarization and the inhibition of neurotransmitter release from the presynaptic terminal. This mechanism accounts for its neuromodulatory role at the synapsis[2,14]. *Created with BioRender.com.*



Remarkably, Δ^9-THC produces dose-dependent, biphasic effects, a feature shared by other phytocannabinoids such as CBD, eCBs, and synthetic cannabinoids. Thus, low and high doses of these compounds may exert opposite effects, or the effects of low doses get lost at higher doses[32]. The search for a state of mental relaxation and well-being is believed to be one of the factors driving the widespread consumption of *Cannabis*[5].

Cannabis rewarding effect

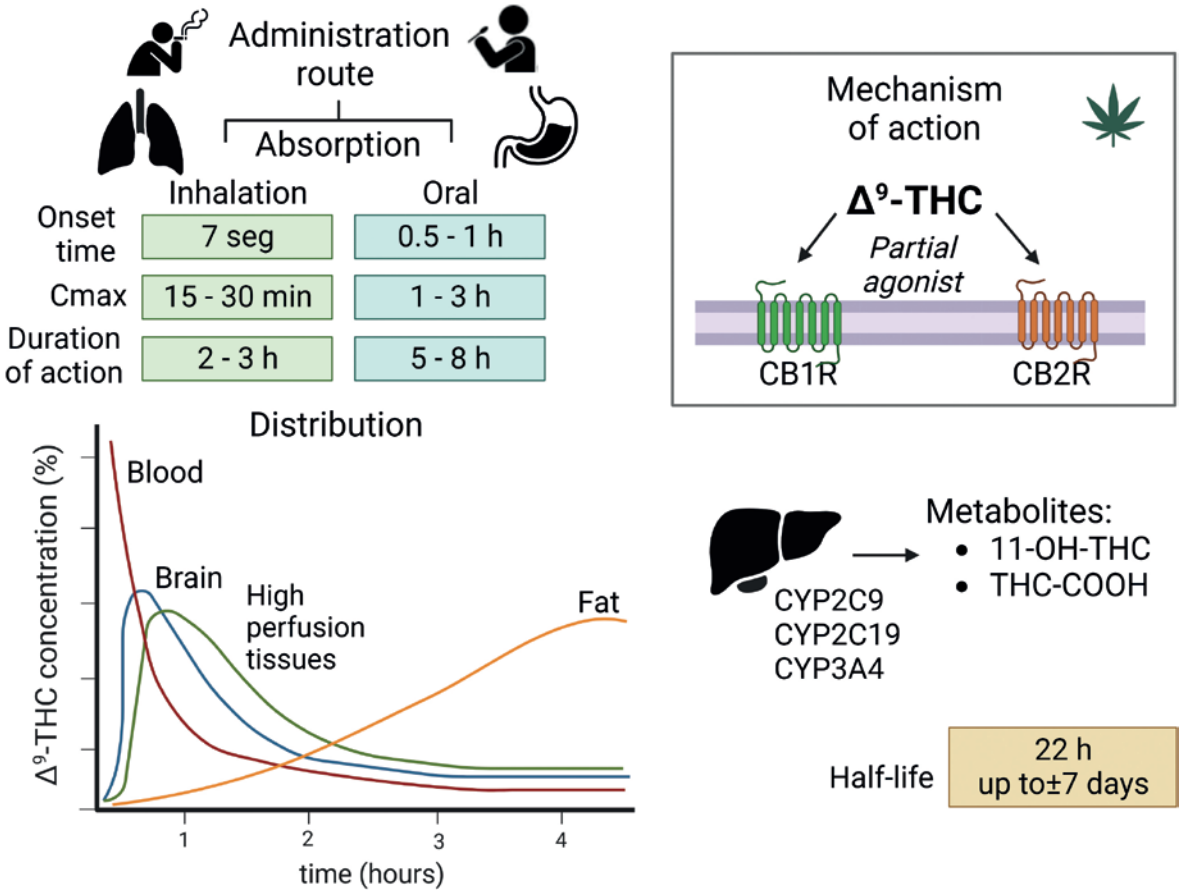
As with other misused drugs, the rewarding effects of acute Δ^9-THC intake are related to increases in dopaminergic neuron activity and dopamine release at the mesolimbic system (brain reward system)[33]. Since CB1Rs are not expressed on mesolimbic dopamine neurons, the Δ^9-THC-induced increase in dopaminergic activity is likely produced indirectly by interacting with the CB1R located on the axon terminals of GABAergic and glutamatergic inputs that modulate the activity of midbrain dopamine neurons[34] (Fig. 8). Neuroimage studies further demonstrated increased dopamine neuron activation in the human limbic striatum in response to acute Δ^9-THC[35]. In contrast, long-term use of Δ^9-THC is associated with a blunted dopamine system's activity, which is associated with reduced motivation and negative emotions[33].

Demonstrating the rewarding properties of Δ^9-THC using animal models has been challenging because animal responses to Δ^9-THC are less evident than those elicited by other misused drugs, such as cocaine or heroin. Thus, in the self-administration (SA) paradigm, Δ^9-THC induces a modest response, and this only in non-human primates. In the conditioned place preference model (CPP) and the intracranial self-stimulation (ICSS) protocol, Δ^9-THC exhibits a biphasic profile; whereas low doses induce CPP and decrease the ICSS threshold, high doses induce conditioned place aversion and increase the ICSS threshold. The table in figure 9 summarizes these results and briefly describes the models[36-38].

Effects of *Cannabis* use and *Cannabis* use disorder

Frequent *Cannabis* use has deleterious health effects (Table 2) and has been associated with several psychiatric conditions (Table 3). Two syndromes produced

Figure 6. Δ⁹-THC pharmacology. Pharmacokinetic parameters related to drug absorption vary according to the route of administration. The graph depicts the distribution of the Δ⁹-THC molecule in different tissues. As seen, tissues with high perfusion, including the brain, show an initial increase in Δ⁹-THC concentration followed by a decrease. By contrast, Δ⁹-THC concentration in the fat shows a constant increase, an effect associated with the lipophilic nature of Δ⁹-THC and contributing to its prolonged half-life[16]. Hepatic metabolism generates 11-hydroxy-Δ⁹-tetrahydrocannabinol (11-OH-THC) and 11-nor-9-carboxy-THC-Δ⁹-tetrahydrocannabinol (THC-COOH). 11-OH-COOH is a psychotropic metabolite that is equipotent to Δ⁹-THC. THC-COOH, in contrast, is a non-psychotropic metabolite. Δ⁹-THC is a partial agonist of CB1R and CB2R[16]. *Created with BioRender.com.*

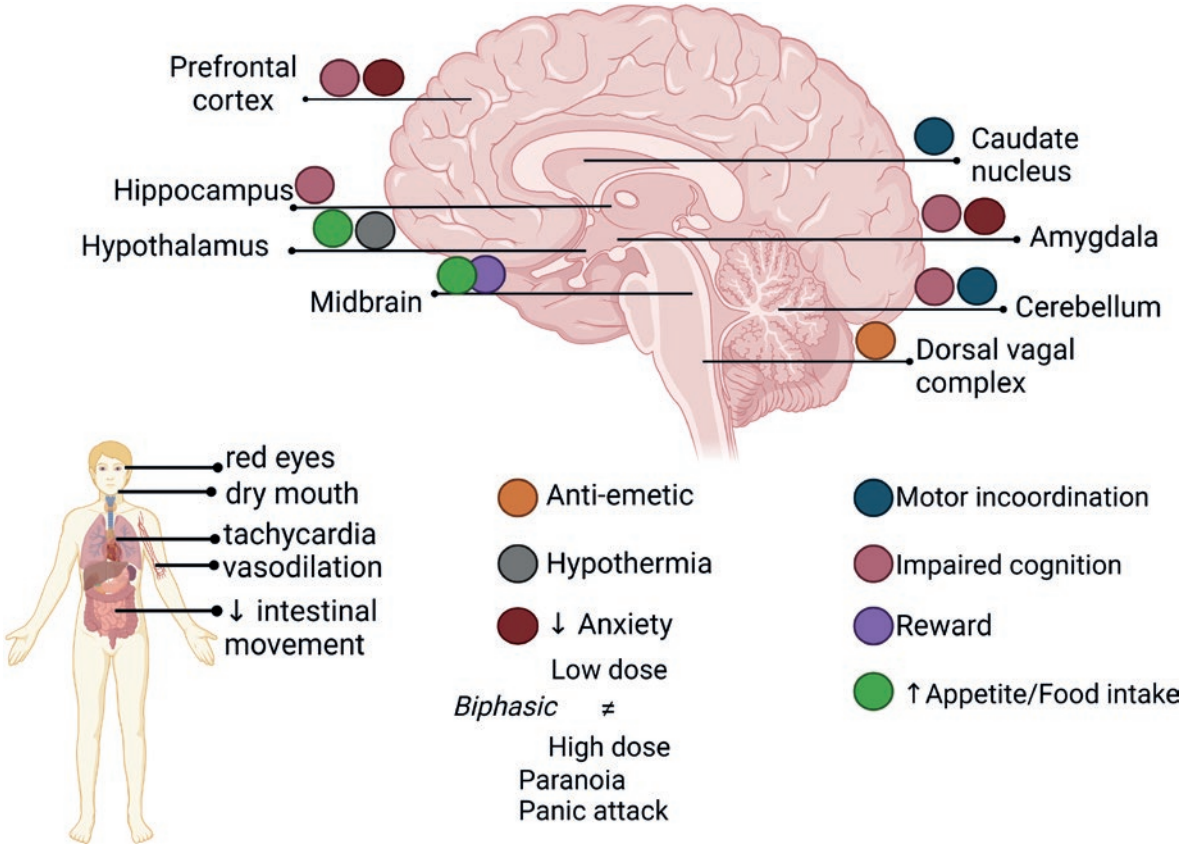


by heavy and chronic marijuana use have also been described: The *Cannabis* hyperemesis syndrome (Table 2) and the amotivational syndrome (Table 3). Although the latter has been a matter of debate, it is clear that the abuse of marijuana intake can lead to adverse consequences in cognitive areas and mental health, including the development of *Cannabis* Use Disorder (CUD).

It has been estimated that ≈ 9% of chronic *Cannabis* users will develop a severe CUD according to DSM 5 criteria[31], and this percentage increases when use begins before 18 years of age (≈ 16.6%). CUD is defined as the inability to stop consuming marijuana even when it is causing physical or psychological harm (ICD, WHO web). The DSM 5 criteria for CUD are presented in table 4. Pharmacological criteria for CUD are the appearance of tolerance to some of the Δ⁹-THC effects, including cardiovascular, cognitive, and physical effects[53].

Cannabis withdrawal (CW) is the manifestation of the development of physical dependence on Δ⁹-THC and emerges when a person stops its use. Because Δ⁹-THC accumulates in fat tissue and its clearance rate is slow, the CW signs and symptoms become evident not earlier than 1 week after interrupting marijuana consumption. CW can also be precipitated by CB1R antagonists. The CW syndrome includes anger, irritability, depression, restlessness, headache, loss of appetite, insomnia, and severe craving for marijuana. The complete list of symptoms of the CW syndrome is presented in table 4.

Figure 7. Δ^9-THC acute effects. Illustration of the complex cluster of effects induced by marijuana or any other preparation of the *C. sativa* plant. Δ^9-THC exerts its central effects by activating CB1R in different brain areas[31]. *Created with BioRender.com.*



CANNABINOID THERAPEUTIC POTENTIAL

The most ancient record of the use of *Cannabis* for therapeutic purposes is the world's oldest pharmacopeia, the Sheng-nung Pen-ts'ao Ching (China, 2737 BC)[54]. However, traditional use of *Cannabis* preparations for treating medical conditions does not constitute valid evidence for the modern medical use of the plant. High-quality pharmacological studies in large, well-controlled clinical trials are required to ensure the efficacy and safety of the therapeutic use of the phytocannabinoids, isolated, or combined.

The characterization of the most abundant phytocannabinoids in the *Cannabis* plant, Δ^9-THC and CBD, and the search for their mechanisms of action allowed the identification of the ECS. This system is distributed throughout the body and plays a key role in regulating many physiological processes and maintaining homeostatic balance. Therefore, the pharmacological modulation of physiological and pathological processes by cannabinoids appears therapeutically promising. The neuromodulatory role of the ECS is of particular interest since many neuropsychiatric conditions rely on neurochemical imbalances affecting the functioning of brain circuits.

Here, we review the available evidence for the suggested therapeutic applications of Δ^9-THC and CBD.

Cannabidiol pharmacokinetics

CBD is one of the most abundant phytocannabinoids of *C. sativa*. Its acute administration by distinct routes does not produce significant toxic effects in humans across a wide range of concentrations and is well tolerated at doses up to 1500 mg/day, as well as with chronic use[55]. In general, CBD has a favorable safety profile[56,57] and lacks abuse liability[58], two important features to consider when proposing it as a therapeutic agent for treating pathological conditions.

Table 1. Summary of the acute effects of Δ^9-THC

System or response	Human effect	Animal models	Neurobiology	References
Ocular	Conjunctival hyperemia (red eyed)	–	vasodilation → ↓ BP ↑ blood flow in the eyeball = red appearance	17
	↓ IOP /≈ 4 h THR: glaucoma	↓ IOP in rat model of glaucoma	CB1R ciliary processes: ↓formation of aqueous humor (↓ optic nerve damage)	18
CV	Biphasic effects: ▼doses → ↑ 20-50% HR /≈3 h ▲doses → bradycardia Variable changes in BP: Vasodilatation and ↓ BP, mostly diastolic	Anesthetized animals: ↓HR and ↓BP Conscious animals: Bradycardia, ↓HR and hypotension in some animals.	Complex hemodynamic effects CB1R-mediated ▼doses: ↑ sympathetic activation ↓vagal activity + reflex tachycardia (triggered by Δ^9-THC-induced vasodilation) ▲doses: ↑ parasympathetic stimulation	19
	Orthostatic hypotension ▲doses: dizziness		Postural (supine) hypotension→peripheral vasodilation and dysregulation of the baroreflex	20
GI	Biphasic effects: ▼doses → anti-emetic ▲doses → nausea and vomiting THR: anti-emetic	Dose-dependent suppression of Lithium induced vomiting in shrews.	Interaction with CB1R and 5-HT3 receptor (allosteric inhibition) at the dorsal vagal complex, specifically in the area postrema of the brainstem, which mediates emesis. ▲doses act peripherally. Activation of CB1R in GI and enteric nervous system could be involved as well.	21
	↓ salivation ↓ esophageal sphincter relaxation ↓ gastric acid secretion and motility ↓ peristalsis throughout the gut		Interaction with CB1R in nerve fibers and synapses throughout the gut wall and in the myenteric and submucosal plexuses of the enteric nervous system	22
Temperature	Hypothermia	Hypothermia	Thermoregulatory centers of the anterior hypothalamus	23
Analgesia	Limited (ethical issues) intradermal capsaicin-induced pain: ↓ with▲▼ MJ dose ↑ ▲MJ dose THR: Analgesic	↑ Of the pain threshold in models of thermal pain (hot plate/tail flick). Antinociceptive effect	CB1R in brain and spinal cord integrative sites; nociceptive sensory neurons of the dorsal root ganglion and trigeminal ganglion, and immune cells.	24
Anxiety	Biphasic effects: ▼doses → anxiolytic ▲doses → anxiogenic	Biphasic: ▼doses → anxiolytic-like ▲doses → anxiogenic-like CB1R KO mice: ↑increased anxiety-like behavior	Anxiolytic effect: CB1R on cortical glutamatergic neurons. Anxiogenic effect: CB1R on forebrain GABAergic neurons. ECS: modulates the response to stress (HPA & SNS), reward (MSL & PFC), and their interactions. Brain areas: hippocampus, PFC, amygdala, hypothalamus	4,5
Food intake	↑ feeding, even in a state of satiety emphasis on palatable-dependent appetite THR: Anorexigenic SR141716A (rimonabant): 1st approved drug but later removed from the market.	Bimodal feeding response: Activation of CB1R → ↑↑↑ feeding (despite satiety) Blockade of CB1R: ↓ food intake CB1R KO: lean phenotype, resistant to diet-induced obesity	Food intake is a complex behavior, CB1R are expressed in several brain regions and circuits regulating different aspects like feeding behavior, intake regulation, and satiety. Δ9-THC might act at: • olfactory bulbs (↑ food perception) • mesolimbic system (↑ food reward) • hypothalamus (↑ ghrelin release = ↑ hunger) The ECS has been recognized as critical for energy homeostasis and food intake regulation.	25,26

(Continues)

Table 1. Summary of the acute effects of Δ^9-THC *(continued)*

System or response	Human effect	Animal models	Neurobiology	References
Motor	7% Δ^9-THC: impairs complex psychomotor performance. 11% Δ^9-THC: alters movement speed and balance	↓spontaneous locomotor activity: catalepsy	High-density CBR in the caudate nucleus and cerebellum.	27
Cognitive	Mild-to-moderate performance impairment of several functions: ↑ Reaction time and ↓ speed processing ↓ Attentional control and ↓ working memory ↓ Executive functions: planning, reasoning, inhibitory control, problem solving. Learning and (episodic) memory,		CBRs expressed in brain areas involved in cognitive processes, such as PFC, hippocampus, and amygdala.	28
	Altered time perception: subjective perception of time = overestimation of the passage of time		Temporal estimation is processed in the cerebellum, a brain structure with high CB1R density.	29
	Driving abilities are significantly impaired, although modestly		Driving-related neurobehavioral skills and driving performance are integrated in diverse brain areas where CB1R is expressed.	30

BP: blood pressure; CBRs cannabinoid receptors; CNS: central nervous system; CV: cardiovascular; ECS: endocannabinoid system; GI: gastrointestinal; HPA hypothalamic–pituitary–adrenal axis; HR: heart rate; IOP: intraocular pressure; MJ: marijuana; MSL: mesolimbic system; PFC: prefrontal cortex; SNS: sympathetic nervous system; THR: Therapeutic relevance; Δ9-THC: Δ9-tetrahydrocannabinol.
▲: high dose ▼ low dose, ▼▲ medium dose. ↑ increased effect, ↓ decreased effect.

However, CBD is a potent inhibitor of hepatic drug metabolism and acts both as an inhibitor and an inducer of several cytochrome P450 isoforms, properties that might affect the metabolism of other drugs *in vivo* (for a review on drug-drug interactions, see[59]).

CBD is a highly lipophilic compound with poor oral bioavailability[15]. In human studies, maximum CBD concentration is achieved 3-5 h after its ingestion in healthy adults. CBD has a half-life of 14.4-16. Six hours after its oral administration and, in the presence of a high-fat meal, CBD exposure time significantly increases (4-fold)[60]. Following intravenous dosing, the average CBD half-life is 24 ± 6 h and 31 ± 4 h after its inhalation; these two administration routes present similar pharmacokinetics, reaching peak plasma concentrations in 3-10 min and an average bioavailability of 31%[15]. CBD intake by the oral route is subjected to first-pass metabolism and can therefore be transformed by liver enzymes before reaching the gut[61]. Hepatic hydroxylation of CBD produces 7-OH-CBD, which undergoes mainly fecal but also urinary excretion[16] (Fig. 9).

Cannabidiol mechanism of action

CBD has multiple molecular targets (Fig. 9) ([62] for a comprehensive review). It has a low affinity for CB1R and CB2R but can interact with them at 1 μM concentrations and acts as an inverse agonist at CB2R. CBD is also an antagonist at GPR55 receptors and an agonist at TRPV1, TRPV2, PPARγ, and 5-HT_{1A} receptors[63] (Glossary of CBD molecular targets in the box of Fig. 9).

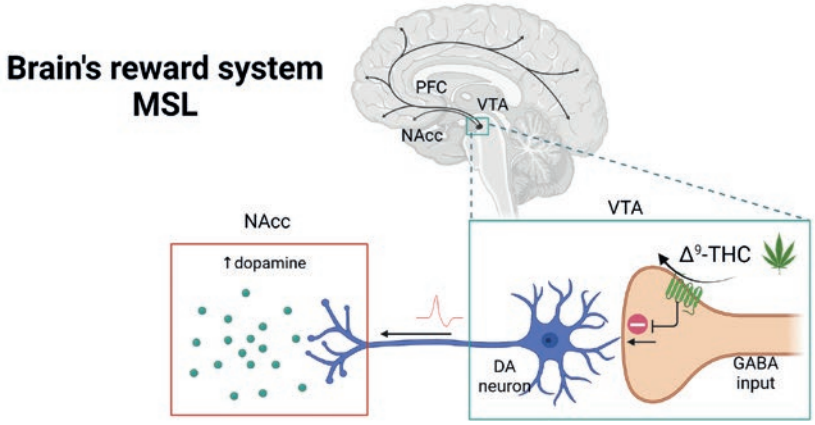
In addition, CBD blocks AEA uptake and inhibits its enzymatic hydrolysis, thereby increasing AEA concentrations[64], and antagonizes Δ^9-THC effects by interacting with non-cannabinoid receptors, like GPR55[65]. CBD can also increase Δ^9-THC potency through pharmacokinetic or pharmacodynamic interactions[66].

Cannabis-based prescription drugs

Among the prescription drugs derived from *Cannabis* approved for medical use, there is only one containing Δ^9-THC and CBD in a 1:1 ratio: Sativex®. Besides, two Δ^9-THC synthetic formulations, Marinol® and Cesamet®

Figure 8. Rewarding properties of Δ^9-THC. The table summarizes the animal models used to evaluate the rewarding properties of drugs of abuse. Like all other misused drugs, Δ^9-THC increases dopamine (DA) levels in the nucleus accumbens (NAcc) of the brain's reward system, constituted by the mesocortical and mesolimbic (MSL) dopaminergic pathways. Dopaminergic neurons' activity is under a tonic inhibitory control of GABAergic inputs. Δ^9-THC inhibits GABA release by activating the CB1R expressed on their nerve endings, thereby eliminating the inhibitory tone. As a result, DA neuron activity increases, augmenting DA release at the NAcc[34,36-38]. *Created with BioRender.com.*

TEST	MEASUREMENT	REWARDING PROPERTIES OF Δ^9-THC
Conditioned place preference (CPP)	Establishes whether an animal prefers an environment previously associated with the effects of the drug (CPP) or avoids it (CPA)	Biphasic, dose-dependent effects: Low doses → CPP High doses → CPA/NP Drug priming is one confounding factor
Self-administration (SA)	Animals press a lever to obtain a drug administration. ↑ reinforcing effects of the drug = ↑ lever pressing	Squirrel monkeys: show i.v. SA Rhesus monkeys: show modest SA by inhalation
Intracranial self-stimulation (ICSS)	Animals trained to press a lever to stimulate MSL through an electrode. ICSS reinforcement thresholds are ↓ by drug	Biphasic, dose-dependent effects: Low doses → ⇩ ICSS threshold High doses → ⇧ ICSS threshold

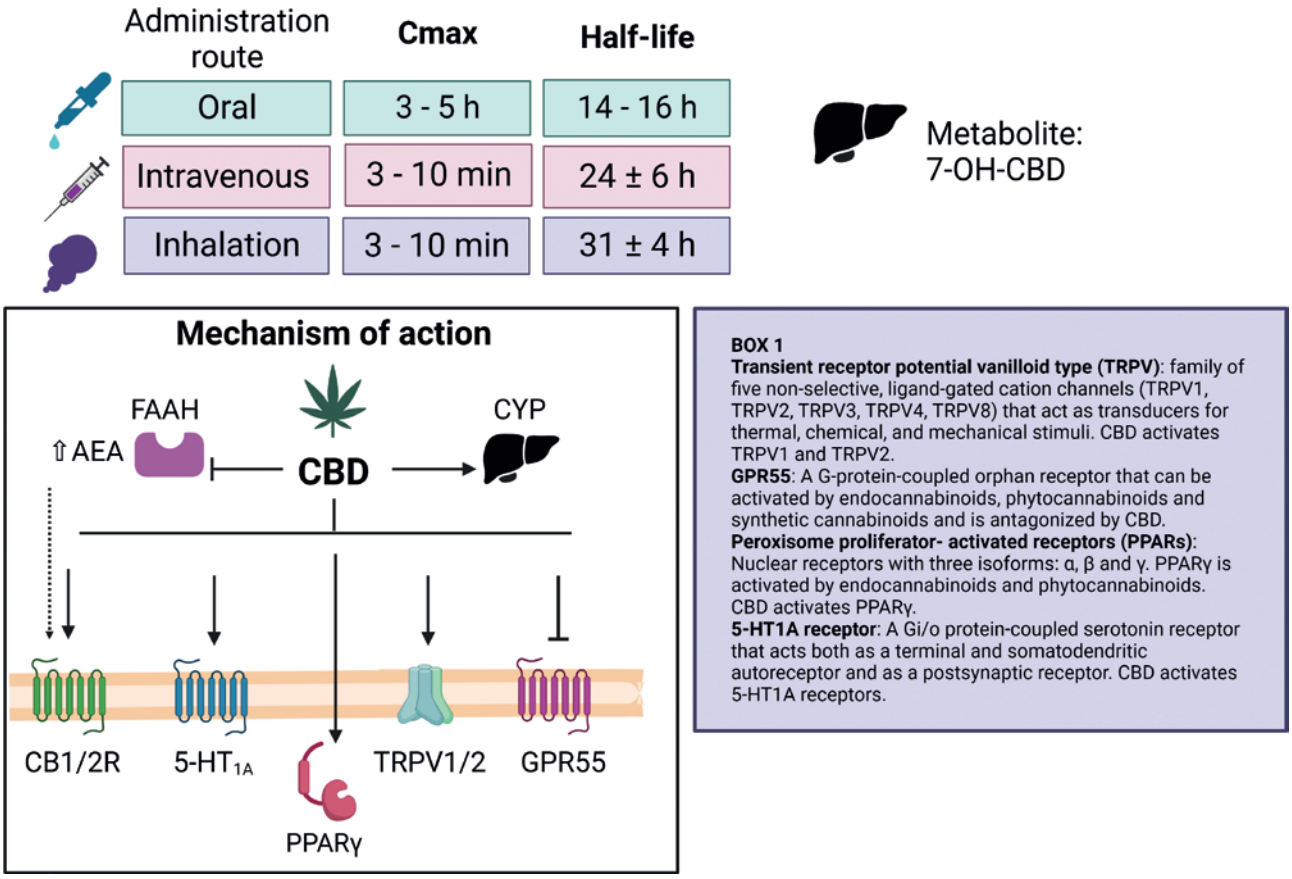


and one CBD extract, Epidiolex®, have also been approved and are currently available in the market. These formulations are being used in clinical trials aimed to support their putative therapeutic actions and there is continued search for new cannabinoid therapeutic uses.

It is important to highlight that a significant number of unregulated cannabinoid products are being offered in the market, mainly CBD, in different formulations (capsules, oils, tinctures, creams, e-liquids, wax for vaporization, and dietary supplements), in many of which the advertised CBD content and purity (some of them contaminated with Δ^9-THC) were found to be inaccurate when analyzed[67]. Still, CBD is consumed in a variety of over-the-counter products, various sold online, for the self-treatment of numerous conditions, for which clinical evidence is lacking or is not supported by robust controlled clinical trials. This makes it urgent to run high-quality clinical trials investigating the putative CBD usefulness for the treatment of those medical conditions that are advertised without sufficient scientific support.

Epidiolex® is a CBD product approved by the FDA for the treatment of seizures associated with Dravet syndrome, Lennox-Gastaut syndrome, and tuberous sclerosis complex. Evidence for all other CBD therapeutic effects is, at this moment, insufficient. Marinol® and Cesamet® prescription is strictly regulated for very specific medical conditions due to their abuse potential. The same occurs with Sativex®, but in this case,

Figure 9. CBD pharmacology. CBD pharmacokinetic parameters related to drug absorption vary according to the route of administration. Hepatic metabolism generates 7-OH-CBD. The main CBD molecular targets are CB1R and CB2R, 5-HT$_{1A}$ and GPR55 metabotropic receptors, TRPV1 and TRPV2 channels, and the PPARγ nuclear receptor. CBD can inhibit the AEA-degrading enzyme FAAH, thereby increasing its concentrations. CBD acts as an agonist (↓) or as an antagonist (⊥) on these targets. Box 1 includes a brief description of CBD molecular targets[16]. *Created with BioRender.com.*



the therapeutic applications could be wider because, as mentioned earlier, CBD has been found to counteract some of the unwanted Δ^9-THC-derived side effects and to complement its actions through molecular targets other than CB1R.

Δ^9-THC potential therapeutic actions

The study of the ECS highlighted that activation of central CB1R is the primary mechanism mediating Δ^9-THC psychoactive effects, as well as some of its potential therapeutic actions. However, the intoxicating properties of Δ^9-THC limit its therapeutic use as an isolated agent. Notwithstanding, the FDA approved two Δ^9-THC synthetic formulations (dronabinol and nabilone) as therapeutic agents to be used in specific conditions detailed in table 5[68-70].

Cannabidiol potential therapeutic actions

The majority of the therapeutic properties ascribed to CBD are based either on the results of preclinical studies, using cell and animal models, or on the involvement of the identified molecular targets of CBD in different pathologies. Only a few clinical trials validate those putative therapeutic properties. Here, we summarize those clinical trials (Table 6) and present an overview of preclinical studies, which support potential CBD therapeutic actions or point to novel putative clinical applications (Table 7).

Among the few therapeutic actions explored in well-controlled human trials are those related with CBD effects on psychosis, Parkinson's disease (PD),

Table 2. Summary of adverse effects of chronic *Cannabis* consumption

Adverse effect	Description	Reference
Respiratory symptoms	Smoking or vaping CN may lead to respiratory symptoms and lung injury due to the exposure to combustion products and/or other harmful chemicals.	39
	Smoking CN (> 1×/week for ≥ 1 year) is associated with respiratory symptoms: cough, sputum production, and wheezing.	
Cardiovascular	Smoking CN can be as harmful as tobacco smoke.	40
	Dysregulation of the ECS has been implicated in several CV pathologies. Activation of CB1R (CNS and CVS) facilitates the development of cardiometabolic disease.	
	Cessation of use → ↑BP and HR in heavy CN users.	
	Highly potent CN and synthetic cannabinoids: associated with more serious adverse CV events (↑ risk of cardiac arrhythmias, myocardial infarction, and angina)	
	Heavy CN users: ↓ cerebral blood flow (↑ on the cessation of use)	
Cannabinoid hyperemesis syndrome	Functional gut-brain axis disorder characterized by cyclic episodes of nausea and vomiting and frequent hot bathing (learned behavior to reduce the discomfort), worsened by *Cannabis* intake. The paroxysms are intense and incapacitating. Patients vomit profusely, often without warning (up to 5 times/h). Paradoxical effects on GI tract and CNS	6,21
Gynecological and obstetric complications, and adverse male sexual health effects	Chronic CN use: ↓ human reproductive potential	41
	♀ Fertility. Menstrual cycle disruption: ovulation delay and cyclicity inhibition. ♂ ejaculatory problems, sperm count and motility reduction, loss of libido and impotence	
	CN use in pregnancy → impairs embryo implantation.	
	Adverse neonatal outcomes: low birth weight, preterm birth, admission to neonatal intensive care, and small size for gestational age. Prenatal CN exposure influences brain development and may have long-lasting effects on cognitive functions.	
Cognitive consequences	Mixed results (difficulties related with quantification of the retrospective CN consumption).	42,43
	Mild residual cognition impairing effects: processing speed, attention, learning capabilities; short-term memory and verbal episodic memory. Impaired executive functions: working memory.	
	Cognitive deficits seem to be linked with the early onset of CN use. Preclinical data support the implication of CN use during important stages of neurodevelopment (adolescence).	

BP: blood pressure; CN: *Cannabis;* CNS: central nervous system; CV: cardiovascular; CVS: cardiovascular system; ECS: endocannabinoid system; GI: gastrointestinal; HR: heart rate.

Table 3. Summary of psychiatric disorders associated with *Cannabis* use and dual diagnoses with *Cannabis* use disorder

Syndrome	Characteristics	Reference
Amotivational syndrome	Heavy chronic CN users are more likely to experience apathy and passivity, leading to loss in productivity and diminution or absence of drive to engage in typically rewarding activities. The diagnosis remains uncertain.	44
Psychosis and schizophrenia	Daily and/or high potency CN use increases the odds (≈5 times) of psychotic disorder/episode (vs. no CN users).	
	CN use: risk factor for early onset of schizophrenia in people with predisposition and/or exacerbation of the psychotic symptoms already present.	45,46
Depression	Bidirectional relationship. CN use during adolescence and/or heavy CN use is associated with a moderately increased risk of developing MDD or other depressive disorders.	
	CN use is associated with a worse prognosis in individuals with MDD.	47,48
Anxiety	Bidirectional relationship. The odds of CUD among individuals with social anxiety disorder is higher (≈ 5 times) than among individuals without the disorder.	
	At low doses, CN use can enhance the extinction rate and reduce anxiety responses in PTSD.	49,50
ADHD	Childhood ADHD increases the chances of CN use and CUD. (Limited evidence).	51
BPD	Borderline traits contribute significantly to CN use and to develop CUD. (Limited evidence).	52

ADHD: attention-deficit/hyperactivity disorder; BPD: borderline personality disorder; CN: *Cannabis;* CUD: *Cannabis* use disorder; MDD: major depressive disorder; SUD: substance use disorders; PTSD: post-traumatic stress disorder.

epilepsy, and anxiety (Table 6). The main findings of these trials are as follows:

Epilepsy

The strongest evidence supporting CBD medical use is the one associated with the treatment of various types of epilepsy. Preclinical studies showed a decrease in the proportion of animals exhibiting seizures and reduced seizure-related mortality in several animal models of epilepsy (Table 7). Epidiolex®, the FDA-approved CBD preparation, has been reported to importantly decrease the median number of monthly seizure episodes in a number of clinical trials that included patients with severe, treatment-resistant, and childhood-onset seizures; Lennox-Gastaut patients, Dravet syndrome patients, patients with tuberous sclerosis complex, and adults and children with other types of epilepsy (reviewed in Britch et al.[60]) (Table 6).

Psychosis

CBD has been postulated as a potential treatment for psychosis (for review, see[75,76]). The antipsychotic potentiality of CBD was suggested by the detection of increased eCB circulating levels and changes in cannabinoid receptor expression in schizophrenic patients[77], as well as by preclinical evidence showing CBD-induced reduction of distinct psychotic-like symptoms in animal models (Table 7). At this moment, two trials with schizophrenic patients showing a reduction in psychotic symptoms and one trial with patients with PD, a neuropsychiatric disease that may

Table 4. DSM 5 criteria for CUD

Definition: A problematic pattern of *Cannabis* use leading to clinically significant impairment or distress, as manifested by at least two of the following criteria, occurring within a 12-month period:

1. *Cannabis* is often taken in larger amounts or over a longer period than intended.
2. There is a persistent desire or unsuccessful efforts to cut down or control *Cannabis* use.
3. A large amount of time is spent in activities necessary to obtain *Cannabis*, to use *Cannabis,* or to recover from its effects.
4. Craving, or a strong desire or urge to use *Cannabis*.
5. Recurrent *Cannabis* use resulting in a failure to fulfill major role obligations at work, school, or home.
6. Continued *Cannabis* use despite having persistent or recurrent social or interpersonal problems caused or exacerbated by the effects of *Cannabis.*
7. Important social, occupational, or recreational activities are given up or reduced due to *Cannabis* use.
8. Recurrent *Cannabis* use in situations in which it is physically hazardous.
9. *Cannabis* use is continued despite knowledge of having a persistent or recurrent physical or psychological problem that is likely to have been caused or exacerbated by *Cannabis.*
10. Tolerance, as defined by either of the following experiences:
    a. Need for markedly increased amounts of *Cannabis* to achieve intoxication or the desired effect.
    b. Markedly diminished effect with continued use of the same amount of *Cannabis.*
11. Withdrawal
    A. Cessation of *Cannabis* use that has been heavy and prolonged (i.e., usually daily or almost daily use over a period of at least a few months).
    B. Three (or more) of the following signs and symptoms develop within approximately 1 week after cessation (peak ≈10 days):
        a. Irritability, anger, or aggression
        b. Nervousness or anxiety
        c. Sleep difficulty (e.g., insomnia and disturbing dreams)
        d. Decreased appetite or weight loss
        e. Restlessness
        f. Depressed mood
        g. At least one of the following physical symptoms causing significant discomfort: abdominal pain, shakiness/tremors, sweating, fever, chills, or headache.

CUD severity: mild CUD (2-3 symptoms); moderate CUD (4 or 5 symptoms) or severe CUD (> 6 symptoms). CUD: *Cannabis* use disorder; DSM: diagnostic and statistical manual of mental disorders.

include psychotic symptoms, have been published. In this last case, the data of one clinical trial indicate that CBD reduced the psychotic symptoms related to PD and, in another, that it improved overall PD symptoms[60] (Table 6).

Likewise, the psychotic outcomes associated with Δ^9-THC exposure[91] can be prevented or reversed by CBD both in humans[92] and in animal models[93]. Moreover, the habitual use of *Cannabis* preparations with relatively high CBD concentrations produces fewer psychotic experiences than those with lower CBD content[94]. Notwithstanding, a recent controlled study found no evidence of CBD modulating Δ^9-THC-elicited effects[95].

Anxiety

Preclinical studies have reported CBD-mediated prevention of stress-induced anxiety-like responses in several animal models and reduction of already-induced anxiety-like behaviors (Table 7). Clinical investigations on the potential anxiolytic properties of CBD have been conducted in a couple of trials with healthy adults and two other studies were run in patients with anxiety disorders. The randomized, double-blind, and placebo-controlled studies mainly report on CBD-induced decreases in social anxiety in these two populations and in a trial with patients with fragile X syndrome, in which CBD produced what the authors called "meaningful clinical reduction" of social

Table 5. Summary of the therapeutic uses of Δ^9-THC for different conditions, according to the report of Health Effects of Marijuana (HEM)[69]

Condition	HEM	Approved Δ^9-THC-based medications	Reference
Chemotherapy-induced nausea and vomiting	Conclusive evidence as effective antiemetics	a. Dronabinol (Marinol®/Syndros®), approved by the FDA (1985) and EMA. Synthetic Δ^9-THC orally administered. Side effects include heart palpitations, asthenia, abdominal pain, and amnesia. A rare, but serious side effect is depersonalization. b. Nabilone (Cesamet™), approved by the FDA (1985, 2016). Synthetic cannabinoid similar to Δ^9-THC orally administered. Side effects are relatively minor and include orthostatic hypotension, dry mouth, drowsiness/ vertigo, euphoria, dyspnea, and headache. A rare, but serious side effect is psychosis.	69
Spasticity related with multiple sclerosis (MS)	Substantial evidence for improving patient-reported MS spasticity symptoms but limited evidence for an effect on clinician-measured spasticity	Nabiximols (Sativex®), approved by EMA (2010) and Canada. *Cannabis* sativa plant extract (containing Δ^9-THC and CBD in near-equal amounts) oromucosal spray. Side-effects include dizziness, fatigue, blurred vision, vertigo, constipation, either appetite decrease or increase, and depression. Rare, but serious side effects include palpitations, changes in blood pressure, and hallucinations.	68
Chronic pain	Modest to substantial evidence for adults' effective treatment. Complex effects of cannabinoids-induced analgesia	Recent meta-analysis: Nabilone elicits a significant pain reduction in patients with neuropathy. Examples of ongoing clinical trials: Dronabinol after arthroscopic surgery (NCT05335252); Treatment of chronic pain with cannabidiol (CBD) and Delta-9-tetrahydrocannabinol (THC) (NCT03215940). The synergism between THC and opioid medications is being explored, for example the clinical trial: Opioid-sparing effect of Dronabinol (NCT03766269)	70

Conditions with **moderate** evidence:
Sleep disorders: Improved short-term sleep outcomes in individuals with sleep disturbances associated with obstructive sleep apnea syndrome, fibromyalgia, chronic pain, and MS.

Conditions with **limited** evidence:
- Anorexia and weight loss: effective for. FDA approved Dronabinol-Marinol® for increasing appetite and decreasing weight loss associated with HIV/AIDS.
- Glaucoma (↓ intraocular pressure)
- Improvement of traumatic brain injury and intracranial hemorrhage outcome
- Posttraumatic stress disorder
- ↓ of depressive symptoms in individuals with chronic pain or MS
- ↓ of symptoms associated with dementia and Tourette syndrome (frequency and severity of motor and vocal tics)

Conditions with **insufficient** evidence:
Symptoms of irritable bowel syndrome, cancers, epilepsy, amyotrophic lateral sclerosis, Huntington's disease, Parkinson's disease, dystonia spasticity in patients with paralysis due to spinal cord injury, cancer-associated anorexia-cachexia syndrome, anorexia nervosa

(Continues)

Table 5. Summary of the therapeutic uses of Δ^9-THC for different conditions, according to the report of Health Effects of Marijuana (HEM)[69] *(continued)*

Condition	HEM	Approved Δ^9-THC-based medications	Reference
Examples of conditions tested in currently ongoing clinical trials (FDA):			
1. Neurodegenerative diseases: Effect of Medical *Cannabis* for Non-motor Symptoms of Parkinson's Disease (NCT05106504) Alzheimer's Disease: Trial of Dronabinol Adjunctive Treatment of Agitation in Alzheimer's Disease (NCT02792257)			
2. Mental disorders: Treating Nightmares in Posttraumatic Stress Disorder with Dronabinol (NCT04448808) Effects of Δ^9-tetrahydrocannabinol (THC) on Retention of Memory for Fear Extinction Learning in PTSD: R33 Study (NCT04080427)			

FDA: Federal Drug Administration (USA); EMA: *European Medicines Agency; HEM:* Health Effects OF Marijuana; MS: multiple sclerosis.

avoidance and of the anxiety component of this disease. Interestingly, trials with healthy adults found anxiolytic effects at a specific CBD oral dose (300 mg), while lower and higher CBD doses lacked effects on anxiety in this population[64]. Other studies employing CBD doses above 300 mg did not find anxiolytic effects in healthy subjects[96]. In contrast, studies in patients with anxiety disorders found anxiolytic effects at higher CBD doses (400 or 600 mg)[64] but also at lower doses (100-250 mg)[74] (Table 6). These data suggest that CBD might exert biphasic, dose-related effects on anxiety and that the basal anxiety level might modify the "therapeutic dose window." Notwithstanding, the evidence provided by the mentioned studies for the CBD management of anxiety disorders is weak since it is mainly centered on a specific type of anxiety, social anxiety. Therefore, high-quality studies supporting CBD's effects on other anxiety expressions are required.

Other potential therapeutic actions of cannabidiol

Other therapeutic applications endorsed to CBD include the relief of depressive symptoms, its usefulness as an antiemetic agent, and its ability to provide neuroprotective effects in Alzheimer's disease due to its antioxidant and anti-inflammatory properties[97]. However, the support for these effects relies only on preclinical studies (Table 7). Reduction of depressive-like behaviors and increases in motivation and hedonic behaviors in animal models of depression has been reported to result from CBD acute and chronic treatments. To date, there are no clinical trials that replicate these CBD properties.

CBD's reduction of nausea and vomiting has also been shown in animal models of conditioned and unconditioned nausea-like behavior. However, again, there are no clinical trials aimed at confirming this property in humans.

Due to its antioxidant and anti-inflammatory properties, CBD has been found to exert neuroprotective effects in animal models of Alzheimer's disease (AD), although no clinical trial has yet been conducted.

Overall, the potential therapeutic uses of cannabinoids are promising; however, the pharmacological manipulation of a neuromodulatory system like the ECS is challenging because the consequences of such manipulations may affect different neural functions that are difficult to foresee. An example is the experience with Rimonabant, a CB1R antagonist that was marketed in Europe from 2006 to 2009 as a treatment for overweight and type II diabetes management that had to be retired due to severe psychiatric side-effects, including depression and suicidal ideation, not detected during the clinical trials[68].

CONCLUSIONS

The evidence presented in this review allows us to conclude that Δ^9-THC and CBD produce biphasic, dose-dependent effects on several physiological responses. The biphasic nature of cannabinoid effects highlights the need for a careful analysis of the dose ranges separating therapeutic from unwanted effects. Besides, Δ^9-THC produces dependence and harmful effects, while CBD does not.

Table 6. Cannabidiol therapeutic effects

Disorder	Studied population	Dose and route of administration	Therapeutic effects	Reference
Schizophrenia	Adult schizophrenics (n = 42)	800 mg/day (4× 200 mg/day) for 4 weeks, oral (RDCT)	↓ of psychotic symptoms like amisulpride but with less side effects	71
	Schizophrenics (n = 88)	1000 mg/kg/day for 6 weeks, oral (RDCT)	↓ of positive psychotic symptoms	72
Parkinson disease (PD)	Adult PD patients with psychotic symptoms (n = 6) on L-DOPA treatment	150 – 400 mg/day for 4 weeks, oral (OLT)	Improvement of psychotic symptoms without affecting motor or cognitive functions	60
	Adult PD patients (n = 21)	75 or 300 mg/kg/day for 6 weeks, oral (RDCT)	300 mg/kg CBD dose improved well-being and quality of life without affecting motor and general symptoms	60
Refractory epilepsy	Patients aged 1-30 (n = 137), with severe, treatment-resistant childhood-onset seizures	from 2-5 mg/kg/day up to 25-50 mg/kg/day, oral (OLT)	↓ in monthly seizure frequency	60
	Children and young adults (n = 120) with Dravet syndrome	20 mg/kg/day, oral (RDCT)	↓ in monthly seizure frequency	60
	Patients aged 2-55 (n = 212) with Lennox-Gastaut syndrome	10 or 20 mg/kg/day, oral (RDCT)	↓ of drop seizures by both CBD doses	60
	Patients aged 2-55 (n = 171) with Lennox-Gastaut syndrome	20 mg/kg/day, oral (RDCT)	↓ in drop seizures	60
	Children (n = 77) and adults (n = 62) with various types of epilepsy	5-50 mg/kg/day, oral (OLT)	Reduction in seizure severity and ↓ frequency	60
	Patients (n = 18) with Tuberous sclerosis complex	50 mg/kg/day, oral (OLT)	↓ in monthly seizure frequency	60
Anxiety	Healthy adults (n = 47)	150, 300 or 600 mg, oral (RDCT)	↓ anxiety during simulated public speaking, only with the 300 mg dose	60
	Undergraduate students with social phobia (n = 24) and healthy subjects (n = 12)	single 600 mg dose, oral (RDCT)	↓ anxiety during simulated public speaking	60

(Continues)

Table 6. Cannabidiol therapeutic effects *(continued)*

Disorder	Studied population	Dose and route of administration	Therapeutic effects	Reference
Anxiety	Healthy adults (n = 60)	100, 300 and 900 mg, oral (RDCT)	↓ subjective anxiety ratings during public speaking only at the 300 mg dose	60
	Young adults aged 20-33 with generalized social anxiety (n = 10)	400 mg, oral (RDCT)	↓ anxiety on a Visual Analog Mood Scale	60
	Adolescents with social anxiety disorder (n = 37)	300 mg/day/4 weeks (RDCT)	Improved social anxiety	73
	Fragile X syndrome patients, aged 6–17 y (n = 20)	50 mg/day; 50 or 125 mg twice daily for 12 weeks, transdermal (OLT)	Clinical meaningful reductions in general anxiety and social avoidance	74

Note: Reference 60 is a review containing the specific citations for the different studies summarized. RDCT: randomized, double-blind, controlled trial; OLT: open-label trial.

Table 7. Preclinical evidence for cannabidiol potential therapeutic applications

Disorder	Evidence	Animal model	CBD dose	Effects	Reference
Schizophrenia	Reduction of psychotic-like symptoms	Apomorphine-induced stereotypy	15-60 mg/kg	↓ stereotyped behavior	78
		haloperidol-induced catalepsy	30-60 mg/kg	↓ catalepsy	79
		D-amphetamine- and ketamine-induced hyperlocomotion	30-60 mg/kg	↓ hyperlocomotion	80
		MK-801-induced PPI disruption	5 mg/kg	Reverses PPI disruption	81
Epilepsy	Anticonvulsant effects	Pentylenetetrazole model of generalized seizures	100 mg/kg	↓ incidence of severe seizures and mortality	82
		Acute pilocarpine model of temporal lobe seizure	1-100 mg/kg	↓ % of animals showing severe seizures	82
		Penicillin model of partial seizure	10-100 mg/kg	↑ seizure-induced mortality	
Anxiety	Prevention of anxiogenic effects	chronic unpredictable stress (14 days)	30 mg/kg/day after stress for 14 days	Blocked anxiogenic-like effects measured in the novelty suppression feeding and EPM; ↑ hippocampal neurogenesis and ↑ AEA levels	83

(Continues)

Table 7. Preclinical evidence for cannabidiol potential therapeutic applications *(continued)*

Disorder	Evidence	Animal model	CBD dose	Effects	Reference
Anxiety		foot shock stress applied 24 h before the light/ dark test	5 mg/kg acute and chronic administration (21 days)	Prevented anxiety-like responses (↓ time in the light box and ↑latency to enter the light box) to foot shock	84
	Anxiety reduction	EPM and novelty suppressed feeding	30 mg/kg for 14 days	anxiolytic-like effects (↑ entries and time in open arms; ↓ latency to feed) in stressed animals	85
Depression	Reduction of depression-like behavior	FST	200 mg/kg	↓ immobility but also ↓ locomotion	86
	Increases in hedonic behavior and motivation	Wistar-Kyoto rat, genetic model of depression	30 mg/kg	↑ saccharin preference	87
			45 mg/kg	↑ exploration in the novel object test and locomotion	
Emesis	Reduction of vomiting and nausea	Lithium chloride – nicotine- or cisplatin-induced conditioned gaping reactions	5 or 10 mg/kg	suppresses nausea-like (gaping) behavior	88
		Lithium chloride – conditioned and unconditioned rejection reaction	5 mg/kg	interferes with establishment of conditioned nausea-like behavior and attenuates the established conditioned nausea-like behavior	89
Alzheimer disease (AD)	suppression of neuroinflammation	Animal models of AD	2.5-100 mg/kg	memory improvement, prevention of cognitive deficits, ↓ Aβ plaques	90

PPI: prepulse inhibition; EPM: elevated plus maze tests; FST: forced swim test; AD: Alzheimer's disease.

The available pharmaceutical formulations of these phytocannabinoids and related molecules have clear therapeutic effects; however, more research is needed to assure their efficacy and safety since their effects are complex. Several additional potential therapeutic applications, mainly for CBD, are being proposed which, however, still lack sufficient clinical and preclinical support. For this reason, caution is advised when using or prescribing cannabinoids.

Additional consideration deserves the fact that the ECS participates in the development of the central nervous system[98]. Therefore, the use of cannabinoid-based formulations for the medical treatment of children and adolescents experiencing brain developmental changes must be carefully examined, balancing the pros and cons of prescribing cannabinoid-based medications in every single case. *Cannabis* research field is expanding with the identification of new molecular targets, the characterization of undescribed phytocannabinoids, and novel findings related to the ECS[99]. In addition, consumption of synthetic cannabinoids as drugs of abuse represents a new challenge in addiction research[100].

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