Vol. 17(1):85-98; May-June 2023

Cannabidiol, from Past to Present: a Review

Cannabidiolul, din trecut în prezent: O recenzie

Andra Popescu[1], Alexandra Dreanca[1], Orsolya Sarpataki[1], Mihai Cernea[1], Aurelia Jourdan[1], Ioan Marcus[1]

[1] University of Agricultural Sciences and Veterinary Medicine, Faculty of Veterinary Medicine, Cluj-Napoca, Romania

andra.popescu@usamvcluj.ro

Key words: Cannabidiol, CBD, chronic pain, epilepsy
Cuvinte cheie: Cannabidiol, CBD, durere cronica, epilepsie

Abstract

The cannabis plant contains the naturally occurring substance cannabidiol, also known as CBD. As opposed to its more widely known relative, tetrahydrocannabinol (THC), cannabidiol (CBD), does not possess any psychoactive or euphoria-inducing properties, and is widely regarded as harmless and non-addictive. Due to its alleged medicinal advantages, which are thought to include pain relief, anxiety reduction, epilepsy management and anti-inflammatory characteristics, CBD has attracted a lot of attention in recent years, in both human and veterinary medicine. The different kinds of CBD products available include oils, tinctures, capsules, lotions, and even edibles in the form of cookies and candy. In the field of veterinary medicine, the use of CBD has become more and more prevalent in recent years, and a formulation of treats for dogs and cats containing varying quantities of cannabidiol have been put on the market. Despite growing in popularity, CBD's legal status is still a little hazy in many nations, and more study is required to fully comprehend both its advantages and disadvantages. This article aims to review CBD's history, mechanisms of action, potential therapeutic roles as well as adverse effects that have been encountered thus far in clinical studies.

Rezumat

Planta de canabis conține substanța naturală canabidiol, cunoscută și sub numele de CBD. Spre deosebire de ruda sa mai cunoscută, tetrahidrocanabinolul (THC), canabidiolul (CBD), nu posedă proprietăți psihoactive sau care induc euforie și este considerat pe scară largă ca inofensiv și non-dependent. Datorită presupuselor sale avantaje medicinale, despre care se crede că includ ameliorarea durerii, reducerea anxietății, gestionarea epilepsiei și caracteristicile antiinflamatorii, CBD a atras multă atenție în ultimii ani, atât în medicina umană, cât și în cea veterinară. Diferitele tipuri de produse CBD disponibile includ uleiuri, tincturi, capsule, loțiuni și chiar comestibile sub formă de cookie-uri și bomboane. În domeniul medicinei veterinare, utilizarea CBD a fost din ce în ce mai răspândită în ultimii ani, iar o formulare de „treat-uri" pentru câini și pisici care conțin cantități diferite de canabidiol au fost introduse pe piață. În ciuda creșterii popularității, statutul juridic al CBD este încă puțin neclar în multe națiuni și este necesar un studiu mai aprofundat_pentru a înțelege pe deplin atât avantajele, cât și dezavantajele sale. Acest articol își propune să revizuiască istoria canabidiolului, mecanismele de acțiune, rolurile terapeutice potențiale, precum și efectele adverse care au fost întâlnite până acum în studiile clinice.

Introduction

The subject of cannabidiol (CBD) has gained much traction in the last two decades as an alternative or complementary treatment for quite a few pathologies, spanning over many organ systems.

The diversity of the localization of CBD receptors in the body give the product a unique edge over other medicinal plants, rendering it useful in acute and chronic inflammations, pain relief, anxiety and depression, oncological treatments, epilepsy and other neurological pathologies and much more, from both human and veterinary medicine standpoints.

CBD seems to be a "jack of all trades" in terms of its likely benefits for the body and various pathologies.

Cannabis sativa is an annual plant of the *Cannabinacea* family, the *Rosales* order of the Plantae reign. Its erect stem can reach, in some climatic and genetic contexts, up to 5 meters in height. The normal height is nevertheless between 1-2 meters. Its leaves are formed by 5 to 7 linear lanceolate leaflets with strongly toothed edges and tapered ends.

The plant of C. sativa is characterized by marked sexual dimorphism (dioecious plant, males and females are different and separate from one another). The fruit is unique, smooth, of light brownish coloration. Dissemination of seeds is usually by birds and/or by air.

In addition to the classic elements found in all kinds of plants, the characteristic of *C. sativa* lies in the presence of small elements on its surface called "trichomes" located at the height of the plant's aerial portion., in greater concentration at the level of the flower and leaves of the female plant (Bonini et al, 2018).

Trichomes correspond to epidermal protuberances present on the surface of the plant and are of two types: glandular or non-glandular (Happyana et al, 2013).

Glandular trichomes correspond to the place of production and storage of the secondary metabolites at the origin of phytocannabinoids and terpenes that we will define later (Andre et al., 2016).

The *Cannabis sativa* (Europe) and *Cannabis indica* (South Asia) plants have been documented as medicinal plants since the times of the ancient Greeks for various maladies such as fatigue and rheumatism. Many countries, such as China and Egypt, used the plants for the fabrication of textiles and papyrus (Crocq, 2020).

There is evidence from multiple sources, from ancient China and Iran, to the Greeks and Romans, that also stated the state of euphoria and intoxication that came about from burning the plant and inhaling the smoke produced, alongside other medicinal properties of the compound (Carod-Artal, 2013).

However, cannabidiol was discovered much later, in the first half of the 20th century, by Roger Adams in the USA. Adams isolated cannabidiol from wild *C. sativa* plants growing in the state of Minnesota and preliminarily deduced the chemical structure of the compound (Adams et al, 1940).

In 1946, Loewe and his team managed to perform an experiment with individual cannabinoids in rabbits in mice, and was the first to note the lack of catalepsy seen with the administration of CBD, an effect that was quite evident with THC (Pertwee, 1972). In the 1960s and 1970s, many studies concerning the pharmacological mechanisms of THC and CBD were conducted in both animal and human studies, with the main focus also being on the effects and mechanisms of THC (Paton and Pertwee, 1972; Pertwee 1972).

Research into cannabidiol was not as important at the time, however, was still mentioned. In the 1980s, evidence of cannabinoid receptors in the body was published, thus further elucidating the mechanism of action of phytocannabinoids derived from the *C. sativa* plant (Pertwee, 1988).

Over the next decade, further research on cannabinoids would lead to the discovery of the CB_1 and CB_2 receptors, as well as their ligands, discoveries made by Pertwee in 1997 and 1999. At the turn of the 21st century, along with a boom in the studies of cannabinoid receptors and their modulation, focus started shifting from psychoactive cannabinoids to cannabidiol and other non-psychotropic cannabinoids (Pertwee, 2004; Sim-Selley L.J., 2003; Robson, 2005).

In the last twenty or thirty years, major progress has been made in the research of the benefits of cannabidiol and other cannabinoids, especially in the application of the endocannabinoid system for potential therapeutic uses.

Synthesis Pathways

Canabis sativa plants are made up of many secondary metabolites – phytocannabinoids, alkaloids, terpenoids and flavonoids, each subgroup possessing different therapeutic activities.

Phytocannabinoids are, in fact, terpenoids that are considered to be bioactive and can only be found in the C. sativa plant (Govindarajan et al, 2023), and are implicated in many

physiological processes. Of the phytocannabinoid subgroup, CBD (cannabidiol), THC (tetrahydrocannabinol), CBG (cannabigerol) and CBN (cannabinol) appear to be of most interest to researchers (Khlan, 2020). Two different precursors seem to be at the origin of the formation of phytocannabinoids.

The main precursor of these syntheses are olivetolic acid ($C_{12}H_{16}O_4$), produced by the degradation of fatty acids and geranyl diphosphate, a known precursor of many terpenes produced by all kinds of plants (Lim et al., 2021).

Within the plant, enzymatic mechanisms allow the synthesis of the different phytocannabinoids. Hexanoyl-CoA is transformed, under enzymatic action of a TKS enzyme and olivetolic acid cyclase to olivetolic acid, which is then transformed into cannabigerolic acid (CBGA) under the action of cannabigerolic acid synthase and olivetolate geranyltransferase and geranyldiphosphate.

Thus, CBGA (*cannabigerolic acid*), under the enzymatic action of THCA synthase (*Tetrahydrocannabinolic acid synthase*) and CBDA synthase (*Cannabidiolic acid synthase*) gives rise to two distinct metabolites respectively THCA (*tetrahydrocannababolic* acid), CBDA (*cannabidiol acid*), which in turn undergo enzymatic decarboxylation, leading to the formation of the respective molecules of THC (*tetrahydrocannabinol*) and CBD (*cannabidiol*). This mechanism appears to apply to the synthesis of most phytocannabinoids (Figure 1) (Compton et al., 1993).

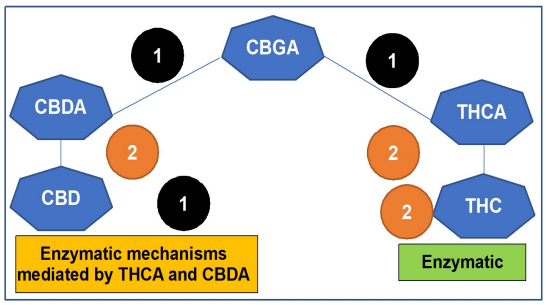

Figure 1. Synthesis of different phytocannabinoids, CBD and THC, from their main precursor, cannabigerolic acid and then from their respective precursors, cannabidiol acid and tetrahydrocannababolic acid.

Chemical Characterization

From a chemical point of view, there are no less than 540 components of interest within the *C. sativa* plant. Their structural classification makes it possible to determine different chemical classes whose biological effects are variable and often synergistic with each other (Hanus et al, 2016).

Phytocannabinoids

Phytocannabinoids are molecules with a pheno-terpene structure comprising an alkylresorcinol group and monoterpenes. From a chemical point of view, the phytocannabinoids produced by the plant react vis-à-vis the endocannabinoids, produced by the endocannabinoid system present within the neural system of many mammals (Hill et al, 2012).

They are essentially synthesized and stored by the female plant within the glandular trichomes or in the resin. Phytocannabinoids correspond to molecules composed of 21 to 22 carbon atoms.

The chemical group of phytocannabinoids are composed of no less than 90 molecules, divided into 10 distinct subclasses. Among these subclasses, some molecules seem to have a medical interest and have thusly been more widely documented (Bonini et al, 2018).

- **THCA / CBDA / CBGA**: precursor acids of phytocannabinoids undergoing de-carboxylation within the glandular appa-ratus of the trichome.
- **Cannabidiol (CBD):** Found as a major component in fiber-producing plants.
- Cannabichromene (CBC)
- Cannabigerol (CBG)
- **Tetra-hydrocannabidiol (THC)** – the only phytocannabinoid with psycho-tropic effects
- Cannabidivarin (CBDV)
- Tetra-hydro cannabimarin (THCV)

Terpenes

Terpenes or terpenoids correspond to a group containing more than 100 molecules highlighted today.

Their presence at the level of the plant is essentially reflected by the specific smell emitted by it. They evolve in terms of quantity and composition depending on the age of the plant and the different genetics of *C. Sativa* (Booth et al, 2017).

Classifications determine different groups of terpenes according to the number of repetitions of groups with 5 carbon atoms.

- **Monoterpenes** corresponding to molecules containing 10 carbon atoms. Monoterpenes are found in large quantities at the trichomes of the female plant.
- **Sesquiterpenes** include 15 carbon atoms, they are also found in high concentration at the trichomes of the plant.
- **Triterpenes** include 30 carbon atoms (Hanus and Hod, 2020).

Phenols

Molecules of phenylpropanoid, a molecular group composed of more than 10,000 elements of which phenolic acids seem to be the second most represented class.

Also found in this group are different subclasses of molecules whose therapeutic interests seem to be positive in various therapies. These are flavonoids and lignans.

These molecules, antioxidants, protect the plant from oxidative stress by acting on reactive oxygen species and binding to non-specific proteins (Radwan et al, 2021).

The Endocannabinoid System

The endocannabinoid system (ECS) corresponds to a network of receptors, molecules, proteins, and specific enzymes present in a large number of animal species.

The presence of the ECS within the body results in a regulation of different physiological functions, thus, it seems that this system intervenes in the regulation of the functions of perception of pain, learning, addiction, mood or anxiety.

Eating behaviour and cardiovascular function also appear to be modulated through the ECS. The endocannabinoid system is described in different specific components: endocannabinoid receptors, the endocannabinoids and the cannabinoid breakdown enzymes.

Anandamide (EDA) was first identified in swine in the brain of pigs (Devane et al., 1992). With this discovery, the number of studies that have contributed to the current state of knowledge on the endocannabinoid system (ECS) have increased significantly (Maccarrone et al., 2010).

Endocannabinoids (eCBs) are lipid mediators, isolated in both the brain and peripheral tissues. These are tiny molecules that are derived from arachidonic acid; in various biological processes, they mimic the action of Δ9-tetrahydrocannabinol (THC).

From the class of eCBs compounds, the most bioactive molecules are anandamide (arachidoniletanolamide; AEA) and 2-arachidoneylglycerol (2-AG) (Battista et al., 2012).

At the level of the central nervous system, CB_1 receptors are localized at the level of the presynaptic endings of both GABA-ergic and glutaminergic neurons alongside other tissues, thus is an important therapeutic target for neuropathic pain, multiple sclerosis, appetite modulation, combatting nausea in chemotherapy treatments, cardiovascular protection, inflammatory diseases and neurodegenerative diseases (McKenna and McDougall, 2020).

When coupled with the Gi/o proteins, CB_1 receptors are activated at the level of the presynaptic cleft. With the activation of receptors occurs an inhibition of adenylate cyclase, an increase in adenylate cyclase and a decrease in Ca^{2+} conductance. CB_1 is found and distributed in increased quantities in zones of the brain that coordinate cognition, motivation, emotions and homeostasis (Pagotto et al, 2006).

Outside of the brain and the ANS, the immune system can also be modulated by the endocannabinoid system. Endocannabinoids are not stored in vesicles unlike other classical neurotransmitters (Ralevic, 2003).

In periods of intense synaptic activity, through a receptor-dependent mechanism, endocannabinoids are released from precursor lipids and serve as retrograde signaling

messengers of glutaminergic and GABA-ergic synapses, in addition to modulating of post-synaptic transmission that interact with other neurotransmitters, including dopamine (Puente et al, 2011).

Endocannabinoids are transported into the cell by membrane transport and inactivated by two enzymes (fatty acid amide hydrolase and monoacylglycerol lipase).

Cannabinoid receptor agonists and antagonists, anandamide absorption blockers, and potent, selective inhibitors of endocannabinoid breakdown have all been created because of the preliminary pharmacological studies undertaken.

They allowed research into the physiological roles played by endocannabinoids and opened new approaches in the treatment of anxiety, pain, epilepsy, obesity, neurological disorders (including multiple sclerosis), or other psychiatric disorders such as drug addiction (Fonseca et al., 2004).

The body's endogenous cannabinoid system is widely dispersed. The distribution of different cell types and their locations (such as B lymphocytes in the spleen and lymph nodes) are reflected in the localization of endogenous cannabinoid system components in peripheral organs.

Contrarily, the nervous system's cell distribution is far more sophisticated and organized, which amply illustrates how crucial this system is for synaptic transmission.

There is a distribution of cannabinoid receptors, endocannabinoid transporters, and degradation enzymes in specific areas, such as the hippocampus. However, in other regions of the brain, such as the thalamus, there are differences in the distribution (such as transport activity and MAGL in the absence of a pertinent CB_1 receptor), which is indicative of our lack of information regarding the make-up of these regions and the endocannabinoid system itself (Fonseca et al, 2004).

The endocannabinoid system has been shown to be of major biochemical importance. It is involved in many physiological processes – in the nervous, digestive, reproductive, pulmonary and immune systems. Endocannabinoids increase appetite, reduce pain, act as neuroprotectors and regulators of cytokine production, and are somehow involved in the disappearance of memories – these are just some of their effects (Hillard, 2017).

Two major cannabinoid receptors were cloned, both belonging to the G protein superfamily – receptors coupled with the protein.

The first receptor described was called a CB_1 receptor and is located mainly in the neuron endings, in central and peripheral neurons and glial cells), some glandular systems and in the microcirculation and the reproductive system (i.e., the testicle (Devane et al., 1988).

The cannabinoid CB_2 receptor was then discovered, initially in several lymphoid organs, with the highest distribution detected in B lymphocytes, a moderate distribution in polymorphonuclear monocytes and neutrophils, and with the lowest distribution in T lymphocytes, although ensuing studies have also identified them in microglial cells (Munro et al., 1993).

A fascinating aspect of these receptors is their expression during brain development, where they control cell differentiation (Galve-Roperh et al., 2002) and their presence in tumor cells derived from glial cells (Galve-Roperh et al., 2000). Studies have exposed the existence of other target endocannabinoids, including the vanilloid receptor (Zygmunt et al., 1999) and at least two non-CB_1, non-CB_2 "CB-like" receptors, one in the vascular bed and the other in the terminals of the glutamatergic axon (Hajos et al., 2001).

Cannabinoid receptors, especially the CB_1 receptor, are displayed with unique properties. Their most relevant property is preservation throughout evolution: for example, humans, mice and rats' CB_1 receptors have 97-99% sequences of identical amino acids. The preservation of this ancient signaling system in vertebrates and in a series of invertebrates reflects the important functions that endocannabinoids play in cellular and systematic physiology.

A second remarkable feature of CB_1 receptors is their high distribution in the brain. The CB_1 receptor is most abundantly coupled with the G protein, with a density 10-50 times

higher than the classic emitters such as dopamine and opioid receptors (Herkenham et al., 1991).

Other receptors that do not correspond specifically to the endocannabinoid system, still seem to have functional importance (e.g. GPCR55, GPCR18, 5HT ...)

These receptors, coupled with G proteins, interact either by total or partial agonism, or by antagonism with endocannabinoid molecules, phytocannabinoids, ligands and flavonoids.

Since the discovery of anandamide almost 3 decades ago, the rising data on the main roles of endogenous cannabinoids and their influence on various pathologies have prompted this endocannabinoid system turning out to be more and more significant in the field of neurobiology (Fonseca et al., 2004).

Pharmacokinetics

The routes of administration of the CBD molecule are: oral, usually sublingual and respiratory by vaporization.

An intravenous parenteral route could be considered depending on the pharmaceutical form; however, it is very rarely utilized as such.

From a bioavailability point of view, the main routes of administration result in different bioavailabilities; oral bioavailability is fairly low, around 6-20% while respiratory and intravenous routes have a 25-26% bioavailability (Devinsky et al, 2014).

The low bioavailability may be due to both the first pass effect as well as poor absorption (Ohlsson et al, 1986).

Its highly fat-soluble nature allows it to pass the membrane barriers, however, it should be noted that the presence of terpenes would have a synergistic effect allowing an easier and faster passage of the blood-brain barrier (Harvey DJ., 1991).

Its half-life is somewhere between as little as 1 hour and up to 32 hours (Ujvary et al., 2016) depending on the route of administration (Guy and Flint, 2004; Stott et al, 2013; Millar et al, 2018).

The two routes of administration lead to two distinct metabolic pathways. By the oral route, rapid hepatic metabolism via cytochrome P450 enzymes will be noticed. It should be noted here that the concomitant administration of drugs activating the same liver degradation enzymes would seem to have a detrimental effect on the plasma bioavailability of the CBD molecule.

Through the respiratory tract, hepatic metabolism is delayed, since the molecule first passes into the blood by exchanges at the pulmonary level. It is distributed and finally metabolized at the hepatic level. This explains why the bioavailability is therefore greater by the respiratory route than by the oral route.

In addition, studies appear to support potentiation of the effect of opioids without increasing their bioavailability in patients who would have been administered CBD through the respiratory route. At the hepatic level, the molecule undergoes enzymatic degradation giving more than 8 distinct metabolites.

Excretion occurs through the fecal route and minimally through the kidneys (Chayasirisobhon, 2021).

Positive Effects of CBD

a. Anti-epileptic effects

The neurotransmitter with the main role of inhibiting the central nervous system (CNS) is GABA, which can couple with three different classes of type A γ-aminobutyric acid receptors (GABARs): GABAaRs, GABAbRs, GABAcRs. GABAaRs are chlorine-permeable ligand-dependent ion channels that induce neuronal hyperpolarization and a reduction in neuronal excitability from the CNS.

An insufficiency of GABAaRs seems to be involved in the pathogenesis of several neurodevelopmental diseases, epileptic syndromes and cognitive dysfunctions, conditions that can often coexist.

The class of drugs that comprise benzodiazepines and barbiturates also have GABAaRs as a specific target and are utilized for treating anxiety and seizures.

However, the use over a chronic period of these types of drugs leads over time to the development of tolerability and side effects.

For example, the use of phenobarbital over a longer period of time can induce liver failure.

Because of this, several compounds that have a safer profile are currently being investigated.

Among them, there is also the *Cannabis sativa* plant and its phytocannabinoid derivatives, which are receiving increasing attention, due to the vast therapeutic potentials involving GABA-ergic modulation (Morano et al, 2020).

Physiologically, the depolarization of synapses is given by the release of glutamate in the synaptic cleft, due to the increase of intracellular Ca^{2+} mediated by the opening of the voltage gated Ca^{2+} channels. In epileptic states, hyperexcitability occurs, in which a large quantity of NT is liberated from the presynaptic neuron. Glutamate, under basal conditions, binds to intra-synaptic ionotropic receptors. CBD regulates the amount of adenosine, which is a neuromodulator present in the CNS.

An increased amount of adenosine could activate presynaptic receptors of type A1 (A1Rs) leading to a reduction of the release of glutamate and prevention of its binding to specific receptors. Also, studies show that A1Rs interact with CB1 and would indirectly modulate glutamate inhibition (Barker-Haliski and White, 2015).

Other classes of molecules are involved in CBD signaling, namely the cationic channels of the transient receptor potential (TRP). TRP channels of vanilloid type 1 (TRPV1), which are activated by heat and capsaicin, in the case of neuronal activation are phosphorylated. CBD is a TRPV1 agonist and by activating this type of channel, it decreases calcium levels and neuronal excitability (Morano et al., 2020).

Studies have shown that CBD can be used with success in epileptic pathologies in human (Silvestro et al, 2019) as well as in companion animals (McGrath el al, 2019).

b. Neuroprotection

Among the actions of CBD is neuroprotection. This action is demonstrated by all cannabinoids that contain a phenolic group. Thus, through its anti-oxidant effect it can help neurons against oxidative stress. This activity is independent of CB_1 and CB_2 receptors (El-Remessy et al., 2003). In animal models of newborn hypoxic-ischemic damage, CBD prevented the decrease of viable neurons and also attenuated increases in inflammation and damage caused by oxidative stress (Ceprian et al, 2019).

In animal models of Alzheimer's disease, it was evidenced that CBD reduced beta-amyloid induced microglial activation (Campos et al., 2014).

Another interesting case of CBD conferring neuroprotection is in the case of chemotherapy-induced peripheral neuropathy (CIPN), which is an ongoing adverse effect in patients undergoing various types of chemotherapy. CBD has been shown to reduce or prevent the development of CIPN when given concurrently with the chemotherapeutic agent (Ward et al, 2014; Ward et al, 2011).

c. Antitumor and anti-inflammatory activity

CBD has potential benefits for fighting certain forms of cancer, including inhibiting the growth of tumors, angiogenesis and metastases in various types of cancer.

The molecular mechanism behind the anti-tumoral effect of CBD is not entirely understood, but most studies have shown that it prevents the proliferation of cancer cells by signaling apoptosis.

Moreover, one of the main benefits of CBD regarding its medicinal effects is the relief of pain caused by cancer.

Compared to the side effects of chemotherapeutic drugs, CBD can eliminate the feeling of nausea and vomiting caused by chemotherapy during treatment.

Therefore, CBD can have a double advantage in cancer therapy. (Yoon Young Go et al., 2020)

Additionally, CBD can control the homeostasis of calcium ions in immune and inflammatory cells, primarily through TRP channels, which is critical for the production and release of cytokines with pro-inflammatory properties.

Additionally, Ca^{2+} ions regulate the activation of a number of transcription factors (like NFAT) that control the expression of different cytokines, including IL-2, IL-4, and IFN, which influence cellular inflammatory responses (Atalay et al., 2019).

d. Cardioprotective effects

From a structural and pharmacological point of view, cannabinoids are compounds that bind naturally or synthetically to the constituents of the *Cannabis L. Sativa* plant or to the endogenous agonists of the CB_1 and CB_2 cannabinoid receptors. (Ronen Durst et al., 2007).

In a study conducted on rats, it was shown that anandamide, an endogenous cannabinoid, initially manifests an effect on the cardiovascular system through a slight decrease in heart rate and blood pressure and then a prominent decrease in heart rate and blood pressure is observed.

Also, the protective role of endocannabinoids against myocardial ischemia has been demonstrated and also helps to maintain endothelial function in coronary vessels during ischemia. This mechanism of action being mediated by receptors can be inhibited by specific blockers of CB_1 and CB_2 receptors. (Ronen Durst et al. 2007).

Cannabidiol has also shown a protective role against chemotherapy-induced cardiotoxicity, by improving cardiac dysfunction and reducing the levels of oxidative stress at the level of cardiac myocytes (Hao et al, 2015).

e. Anxiolytic Effects

The activity of the endogenous cannabinoid anandamide in the brain is a possible mechanism through which CBD can exerts anti-anxiety benefits (Crippa et al, 2010)

It has been demonstrated that CBD acts on endocannabinoid metabolism to raise endocannabinoid levels, which in turn increases cannabinoid receptor activation (Bisogno et al, 2001).

The anandamide-metabolizing enzyme FAAH is susceptible to inhibition by CBD, which raises anandamide levels and, in turn, indirectly increases CB_1 receptor activation. It has been proposed that CB_1 receptor activation mediates CBD's ability to control the long-term learnt fear processing (Papagianni and Stevenson, 2019).

Because FAAH activity is inhibited, anxiety-related symptoms may be lessened. Endocannabinoid signaling is a component of an endogenous anxiolytic neuromodulatory system (Patel and Hillard, 2006).

In veterinary medicine, preliminary studies have been conducted researching CBD's anxiolytic and fear reducing effects in companion animals, mainly canines, and have shown positive results (Hunt et al, 2023).

However, many more studies have been conducted on mice, rat and human models, therefore further research into this area is needed.

f. Analgesia in Different Pain Models

Studies in both preclinical and clinical settings point to a possible impact impact of CBD and CBD coupled with other drugs in a large quantity of disorders related to pain.

Depending on the dosage and route of drug administration, analgesic effects can change (Mlost et al, 2020).

CBD has shown promising analgesic effects in rat neuropathic pain models (Xiong et al, 2012; Costa et al, 2007), diabetes induced rodent neuropathic pain models (Toth et al, 2010), osteoarthritic pain models in dogs (Verrico et al, 2020), inflammatory pain models in rats (Britch et al, 2020) as well as other pain models (Wong and Cairns, 2019).

The results from these studies have demonstrated CBD's ability to mitigate pain, even in chronic conditions.

Adverse Effects of Cannabidiol

As with the vast majority of supplements and therapies currently on the market, cannabidiol is not a fully risk-free substance.

Adverse effects have been reported in both pre-clinical and clinical studies, however they do seem to be rare and the drug is generally well tolerated.

In clinical trials concerning refractory epilepsy in children, several clinical trials treating the conditions with cannabidiol noted various adverse effects, the most common being somnolence, fatigue and lethargy.

More serious side effects include status epilepticus, however, this has been attributed to the disease itself (Devinsky et al, 2016, Devinsky et al 2017).

More serious adverse effects appeared in children with Dravet syndrome in a 2018 study and included ataxia and abnormal behavior, however, they were concurrently taking clobazam, valproate, levetiracetam, topiramate, and stiripentol, therefore it is unknown if the adverse effects were due to the cannabidiol or the combination of medications (Devinsky et al, 2018).

In Devinsky's studies mentioned above, other non-neurological side effects were also reported and included decreased or loss of appetite, diarrhea, and more rarely, vomiting.

Respiratory symptoms were also noted in Devinsky's studies, with pneumonia being a rare adverse effect, alongside upper respiratory tract infections.

In clinical studies of schizophrenia, similar digestive adverse effects were reported, mainly diarrhea and nausea (McGuire et al, 2018).

Another phase 3 trial for refractive epilepsy noted hepatic adverse effects, with ALT, AST and GGT concentrations being higher than normal (Thiele et al, 2018).

In pre-clinical trials, rhesus monkeys were given very high doses of cannabidiol (150-300mg/kg), and reported hypopnea, bradycardia, and cardiac failure (Rosenkrantz, 1981). This study also reported organomegaly (liver and kidneys) in monkeys.

Furthermore, researchers found decreased testicular weights in the rhesus monkeys, which reflects potential in vitro decrease in reproductive capabilities, which is in line with another pre-clinical study conducted on rats by Rosenkrantz in 1979, which showed severe dose-related seminiferous tubule degeneration and spermatogenesis inhibition.

It should be noted that the doses given in Rosenkrantz's studies are much higher than the recommended doses given to humans, and very much higher than doses recommended for companion animals.

As stated above, no drug is without potential adverse reactions, however, there is sufficient data to conclude that cannabidiol appears to have a higher safety margin than certain medications given for various pathologies, especially epilepsy. Some of these adverse effects can be mitigated by giving a lower dose.

Conclusions

Since the discovery of the endocannabinoid system and the potential use of cannabidiol as a complementary treatment in various pathologies, many clinical studies have been conducted in order to elucidate both mechanisms of action as well as new opportunities in which CBD may be useful.

Many safety studies have also been conducted, leading to the discovery of relatively large safety margins for the drug, with the presence of a relatively small number of adverse effects compared to conventional therapies available on the market today, with growing applications in the fields of human and veterinary medicine.

With CBD's ability to aid in an impressive number of pathologies, it has emerged as a very exciting drug, especially in the field of veterinary medicine, where the use of CBD is still rather limited due to lack of studies concerning its dosing and benefits.

Bibliography

1. Adams, R., Hunt, M., & Clark, J. H. (1940). Structure of cannabidiol, a product isolated from the marihuana extract of Minnesota Wild hemp. I. *Journal of the American Chemical Society*, *62*(1), 196–200. https://doi.org/10.1021/ja01858a058
2. Andre, C. M., Hausman, J.-F., & Guerriero, G. (2016). Cannabis sativa: The plant of the thousand and one molecules. *Frontiers in Plant Science*, *7*. https://doi.org/10.3389/fpls.2016.00019
3. Atalay, S., Jarocka-Karpowicz, I., & Skrzydlewska, E. (2019). Antioxidative and anti-inflammatory properties of Cannabidiol. *Antioxidants*, *9*(1), 21. https://doi.org/10.3390/antiox9010021
4. Barker-Haliski, M., & White, H. S. (2015). Glutamatergic mechanisms associated with seizures and epilepsy. *Cold Spring Harbor Perspectives in Medicine*, *5*(8). https://doi.org/10.1101/cshperspect.a022863

5. Battista, N., Di Tommaso, M., Bari, M., & Maccarrone, M. (2012). The endocannabinoid system: An overview. *Frontiers in Behavioral Neuroscience*, *6*. https://doi.org/10.3389/fnbeh.2012.00009
6. Bisogno, T., Hanuš, L., De Petrocellis, L., Tchilibon, S., Ponde, D. E., Brandi, I., Moriello, A. S., Davis, J. B., Mechoulam, R., & Di Marzo, V. (2001). Molecular targets for Cannabidiol and its synthetic analogues: Effect on vanilloid VR1 receptors and on the cellular uptake and enzymatic hydrolysis of anandamide. *British Journal of Pharmacology*, *134*(4), 845–852. https://doi.org/10.1038/sj.bjp.0704327
7. Bonini, S. A., Premoli, M., Tambaro, S., Kumar, A., Maccarinelli, G., Memo, M., & Mastinu, A. (2018). Cannabis sativa: A comprehensive ethnopharmacological review of a medicinal plant with a long history. *Journal of Ethnopharmacology*, *227*, 300–315. https://doi.org/10.1016/j.jep.2018.09.004
8. Booth, J. K., Page, J. E., & Bohlmann, J. (2017). Terpene synthases from Cannabis Sativa. *PLOS ONE*, *12*(3). https://doi.org/10.1371/journal.pone.0173911
9. Britch, S. C., Goodman, A. G., Wiley, J. L., Pondelick, A. M., & Craft, R. M. (2020). Antinociceptive and immune effects of delta-9-tetrahydrocannabinol or cannabidiol in male versus female rats with persistent inflammatory pain. *Journal of Pharmacology and Experimental Therapeutics*, *373*(3), 416–428. https://doi.org/10.1124/jpet.119.263319
10. Carod-Artal, F. J. (2013). Psychoactive plants in ancient Greece. *Neurosciences and History*, *1*(1), 23–38.
11. Ceprián, M., Vargas, C., García-Toscano, L., Penna, F., Jiménez-Sánchez, L., Achicallende, S., Elezgarai, I., Grandes, P., Hind, W., Pazos, M. R., & Martínez-Orgado, J. (2019). Cannabidiol administration prevents hypoxia-ischemia-induced hypomyelination in newborn rats. *Frontiers in Pharmacology*, *10*. https://doi.org/10.3389/fphar.2019.01131
12. Chayasirisobhon, S. (2021). Mechanisms of action and pharmacokinetics of cannabis. *The Permanente Journal*, *25*(1), 1–3. https://doi.org/10.7812/tpp/19.200
13. Compton, D. R., Rice, K. C., De Costa, B. R., Melvin, L. S., Johnson, M. R., & Martin, B. R. (1993). Cannabinoid structure-activity relationships: Correlation of receptor binding and in vivo activities. *J. Pharmacol. Exp. Ther.*, *265*, 218–226.
14. Costa, B., Trovato, A. E., Comelli, F., Giagnoni, G., & Colleoni, M. (2007). The non-psychoactive cannabis constituent cannabidiol is an orally effective therapeutic agent in rat chronic inflammatory and neuropathic pain. *European Journal of Pharmacology*, *556*(1-3), 75–83. https://doi.org/10.1016/j.ejphar.2006.11.006
15. Crippa, J. A., Derenusson, G. N., Ferrari, T. B., Wichert-Ana, L., Duran, F. L. S., Martin-Santos, R., Simões, M. V., Bhattacharyya, S., Fusar-Poli, P., Atakan, Z., Filho, A. S., Freitas-Ferrari, M. C., McGuire, P. K., Zuardi, A. W., Busatto, G. F., & Hallak, J. E. (2010). Neural basis of anxiolytic effects of cannabidiol (CBD) in Generalized Social Anxiety Disorder: A preliminary report. *Journal of Psychopharmacology*, *25*(1), 121–130. https://doi.org/10.1177/0269881110379283
16. Crocq, M.-A. (2020). History of cannabis and the endocannabinoid system. *Dialogues Clin Neurosci*, *22*(3), 223–228. https://doi.org/10.31887/DCNS.2020.22.3/mcrocq
17. Devane, W. A., Dysarz, F. A., Johnson, M. R., Melvin, L. S., & Howlett, A. C. (1988). Determination and characterization of a cannabinoid receptor in rat brain. *Mol Pharmacol* ., *34*(5), 605–613.
18. Devane, W. A., Hanuš, L., Breuer, A., Pertwee, R. G., Stevenson, L. A., Griffin, G., Gibson, D., Mandelbaum, A., Etinger, A., & Mechoulam, R. (1992). Isolation and structure of a brain constituent that binds to the cannabinoid receptor. *Science*, *258*(5090), 1946–1949. https://doi.org/10.1126/science.1470919
19. Devinsky, O., Cilio, M. R., Cross, H., Fernandez-Ruiz, J., French, J., Hill, C., Katz, R., Di Marzo, V., Jutras-Aswad, D., Notcutt, W. G., Martinez-Orgado, J., Robson, P. J., Rohrback, B. G., Thiele, E., Whalley, B., & Friedman, D. (2014). Cannabidiol: Pharmacology and potential therapeutic role in epilepsy and other neuropsychiatric disorders. *Epilepsia*, *55*(6), 791–802. https://doi.org/10.1111/epi.12631
20. Devinsky, O., Cross, J. H., Laux, L., Marsh, E., Miller, I., Nabbout, R., Scheffer, I. E.,

Thiele, E. A., & Wright, S. (2017). Trial of cannabidiol for drug-resistant seizures in the Dravet syndrome. *New England Journal of Medicine*, *376*(21), 2011–2020. https://doi.org/10.1056/nejmoa1611618

21. Devinsky, O., Marsh, E., Friedman, D., Thiele, E., Laux, L., Sullivan, J., Miller, I., Flamini, R., Wilfong, A., Filloux, F., Wong, M., Tilton, N., Bruno, P., Bluvstein, J., Hedlund, J., Kamens, R., Maclean, J., Nangia, S., Singhal, N. S., … Cilio, M. R. (2016). Cannabidiol in patients with treatment-resistant epilepsy: An open-label Interventional Trial. *The Lancet Neurology*, *15*(3), 270–278. https://doi.org/10.1016/s1474-4422(15)00379-8

22. Devinsky, O., Patel, A. D., Thiele, E. A., Wong, M. H., Appleton, R., Harden, C. L., Greenwood, S., Morrison, G., & Sommerville, K. (2018). Randomized, dose-ranging safety trial of Cannabidiol in Dravet syndrome. *Neurology*, *90*(14). https://doi.org/10.1212/wnl.0000000000005254

23. Durst, R., Danenberg, H., Gallily, R., Mechoulam, R., Meir, K., Grad, E., Beeri, R., Pugatsch, T., Tarsish, E., & Lotan, C. (2007). Cannabidiol, a nonpsychoactive *cannabis* constituent, protects against myocardial ischemic reperfusion injury. *American Journal of Physiology-Heart and Circulatory Physiology*, *293*(6). https://doi.org/10.1152/ajpheart.00098.2007

24. El-Remessy, A. B., Khalil, I. E., Matragoon, S., Abou-Mohamed, G., Tsai, N.-J., Roon, P., Caldwell, R. B., Caldwell, R. W., Green, K., & Liou, G. I. (2003). Neuroprotective effect of(−)δ9-tetrahydrocannabinol and cannabidiol in N-methyl-D-aspartate-induced retinal neurotoxicity. *The American Journal of Pathology*, *163*(5), 1997–2008. https://doi.org/10.1016/s0002-9440(10)63558-4

25. Galve-Roperh, I., Rueda, D., Gómez del Pulgar, T., Velasco, G., & Guzmán, M. (2002). Mechanism of extracellular signal-regulated kinase activation by the CB1 cannabinoid receptor. *Molecular Pharmacology*, *62*(6), 1385–1392. https://doi.org/10.1124/mol.62.6.1385

26. Galve-Roperh, I., Sánchez, C., Cortés, M. L., del Pulgar, T. G., Izquierdo, M., & Guzmán, M. (2000). Anti-tumoral action of cannabinoids: Involvement of sustained ceramide accumulation and extracellular signal-regulated kinase activation. *Nature Medicine*, *6*(3), 313–319. https://doi.org/10.1038/73171

27. Go, Y. Y., Kim, S. R., Kim, D. Y., Chae, S.-W., & Song, J.-J. (2020). Cannabidiol enhances cytotoxicity of anti-cancer drugs in human head and neck squamous cell carcinoma. *Scientific Reports*, *10*(1). https://doi.org/10.1038/s41598-020-77674-y

28. Govindarajan, R. K., Mishra, A. K., Cho, K.-H., Kim, K.-H., Yoon, K. M., & Baek, K.-H. (2023). Biosynthesis of phytocannabinoids and structural insights: A Review. *Metabolites*, *13*(3), 442. https://doi.org/10.3390/metabo13030442

29. Guy, G. W., & Flint, M. E. (2004). A single centre, placebo-controlled, four period, crossover, tolerability study assessing, pharmacodynamic effects, pharmacokinetic characteristics and cognitive profiles of a single dose of three formulations of cannabis based medicine extracts (CBMEs) (GWPD9901), plus a two period tolerability study comparing pharmacodynamic effects and pharmacokinetic characteristics of a single dose of a cannabis based medicine extract given via two administration routes (GWPD9901 EXT). *Journal of Cannabis Therapeutics*, *3*(3), 35–77. https://doi.org/10.1300/j175v03n03_03

30. Hanuš, L. O., & Hod, Y. (2020). Terpenes/terpenoids in ***cannabis***: Are they important? *Medical Cannabis and Cannabinoids*, *3*(1), 25–60. https://doi.org/10.1159/000509733

31. Hanuš, L. O., Meyer, S. M., Muñoz, E., Taglialatela-Scafati, O., & Appendino, G. (2016). Phytocannabinoids: A unified critical inventory. *Natural Product Reports*, *33*(12), 1357–1392. https://doi.org/10.1039/c6np00074f

32. Hao, E., Mukhopadhyay, P., Cao, Z., Erdélyi, K., Holovac, E., Liaudet, L., Lee, W.-S., Haskó, G., Mechoulam, R., & Pacher, P. (2015). Cannabidiol protects against doxorubicin-induced cardiomyopathy by modulating mitochondrial function and biogenesis. *Molecular Medicine*, *21*(1), 38–45. https://doi.org/10.2119/molmed.2014.00261

33. Happyana, N., Agnolet, S., Muntendam, R., Van Dam, A., Schneider, B., & Kayser, O. (2013). Analysis of cannabinoids in laser-microdissected trichomes of medicinal cannabis sativa using LCMS and cryogenic NMR.

Phytochemistry, *87*, 51–59. https://doi.org/10.1016/j.phytochem.2012.11.001

34. Harvey, D. J. (1991). Metabolism and pharmacokinetics of the cannabinoids. *Biochemistry and Physiology of Substance Abuse*, 279–365.

35. Herkenham, M., Lynn, A. B., Johnson, M. R., Melvin, L. S., de Costa, B. R., & Rice, K. C. (1991). Characterization and localization of cannabinoid receptors in rat brain: A quantitative in vitro autoradiographic study. *The Journal of Neuroscience*, *11*(2), 563–583. https://doi.org/10.1523/jneurosci.11-02-00563.1991

36. Hill, A. J., Williams, C. M., Whalley, B. J., & Stephens, G. J. (2012). Phytocannabinoids as novel therapeutic agents in CNS disorders. *Pharmacology & Therapeutics*, *133*(1), 79–97. https://doi.org/10.1016/j.pharmthera.2011.09.002

37. Hillard, C. J. (2017). Circulating endocannabinoids: From whence do they come and where are they going? *Neuropsychopharmacology*, *43*(1), 155–172. https://doi.org/10.1038/npp.2017.130

38. Hunt, A. B., Flint, H. E., Logan, D. W., & King, T. (2023). A single dose of cannabidiol (CBD) positively influences measures of stress in dogs during separation and Car Travel. *Frontiers in Veterinary Science*, *10*. https://doi.org/10.3389/fvets.2023.1112604

39. Hájos, N., Ledent, C., & Freund, T. F. (2001). Novel cannabinoid-sensitive receptor mediates inhibition of glutamatergic synaptic transmission in the hippocampus. *Neuroscience*, *106*(1), 1–4. https://doi.org/10.1016/s0306-4522(01)00287-1

40. Kanabus, J., Bryła, M., Roszko, M., Modrzewska, M., & Pierzgalski, A. (2021). Cannabinoids—characteristics and potential for use in food production. *Molecules*, *26*(21), 6723. https://doi.org/10.3390/molecules26216723

41. Klahn, P. (2020). Cannabinoids-promising antimicrobial drugs or intoxicants with benefits? *Antibiotics*, *9*(6), 297. https://doi.org/10.3390/antibiotics9060297

42. Lim, K. J., Lim, Y. P., Hartono, Y. D., Go, M. K., Fan, H., & Yew, W. S. (2021). Biosynthesis of nature-inspired unnatural cannabinoids. *Molecules*, *26*(10), 2914. https://doi.org/10.3390/molecules26102914

43. Loewe, S. (1946). Studies on the pharmacology and acute toxicity of compounds with marihuana activityS. *J. Pharmacol. Exp. Ther.*, *88*, 154–161.

44. Maccarrone, M., Gasperi, V., Catani, M. V., Diep, T. A., Dainese, E., Hansen, H. S., & Avigliano, L. (2010). The endocannabinoid system and its relevance for nutrition. *Annual Review of Nutrition*, *30*(1), 423–440. https://doi.org/10.1146/annurev.nutr.012809.104701

45. McGrath, S., Bartner, L. R., Rao, S., Packer, R. A., & Gustafson, D. L. (2019). Randomized blinded controlled clinical trial to assess the effect of oral cannabidiol administration in addition to conventional antiepileptic treatment on seizure frequency in dogs with intractable idiopathic epilepsy. *Journal of the American Veterinary Medical Association*, *254*(11), 1301–1308. https://doi.org/10.2460/javma.254.11.1301

46. McGuire, P., Robson, P., Cubala, W. J., Vasile, D., Morrison, P. D., Barron, R., Taylor, A., & Wright, S. (2018). Cannabidiol (CBD) as an adjunctive therapy in schizophrenia: A multicenter randomized controlled trial. *American Journal of Psychiatry*, *175*(3), 225–231. https://doi.org/10.1176/appi.ajp.2017.17030325

47. McKenna, M., & McDougall, J. J. (2020). Cannabinoid control of neurogenic inflammation. *British Journal of Pharmacology*. https://doi.org/10.1111/bph.15208

48. Millar, S. A., Stone, N. L., Yates, A. S., & O'Sullivan, S. E. (2018). A systematic review on the pharmacokinetics of cannabidiol in humans. *Frontiers in Pharmacology*, *9*. https://doi.org/10.3389/fphar.2018.01365

49. Morano, A., Fanella, M., Albini, M., Cifelli, P., Palma, E., Giallonardo, A. T., & Di Bonaventura, C. (2020). cannabinoids in the treatment of epilepsy: Current status and future prospects. *Neuropsychiatric Disease and Treatment*, *Volume 16*, 381–396. https://doi.org/10.2147/ndt.s203782

50. Munro, S., Thomas, K. L., & Abu-Shaar, M. (1993). Molecular characterization of a peripheral receptor for cannabinoids. *Nature*,

365(6441), 61–65. https://doi.org/10.1038/365061a0

51. Pagotto, U., Marsicano, G., Cota, D., Lutz, B., & Pasquali, R. (2005). The emerging role of the endocannabinoid system in endocrine regulation and Energy Balance. *Endocrine Reviews*, *27*(1), 73–100. https://doi.org/10.1210/er.2005-0009

52. Papagianni, E. P., & Stevenson, C. W. (2019). Cannabinoid regulation of fear and anxiety: An update. *Current Psychiatry Reports*, *21*(6). https://doi.org/10.1007/s11920-019-1026-z

53. Patel, S., & Hillard, C. J. (2006). Pharmacological evaluation of cannabinoid receptor ligands in a mouse model of anxiety: Further evidence for an anxiolytic role for endogenous cannabinoid signaling. *Journal of Pharmacology and Experimental Therapeutics*, *318*(1), 304–311. https://doi.org/10.1124/jpet.106.101287

54. Paton, W. D. M., & Pertwee, R. G. (1972). Effect of cannabis and certain of its constituents on pentobarbitone sleeping time and phenazone metabolism. *Br. J. Pharmacol*, *44*, 250–261.

55. Pertwee, R. G. (1972). The ring test: A quantitative method for assessing the 'cataleptic' effect of cannabis in mice. *British Journal of Pharmacology*, *46*(4), 753–763. https://doi.org/10.1111/j.1476-5381.1972.tb06900.x

56. Pertwee, R. G. (1988). The Central Neuropharmcology of psychotropic cannabinoids. *Pharmacology & Therapeutics*, *36*(2-3), 189–261. https://doi.org/10.1016/0163-7258(88)90106-4

57. Pertwee, R. G. (1997). Pharmacology of cannabinoid CB1 and CB2 receptors. *Pharmacology & Therapeutics*, *74*(2), 129–180. https://doi.org/10.1016/s0163-7258(97)82001-3

58. Pertwee, R. G. (1999). Pharmacology of cannabinoid receptor ligands. *Current Medicinal Chemistry*, *6*(8), 635–664. https://doi.org/10.2174/0929867306666220401124036

59. Pertwee, R. G. (2004). The pharmacology and therapeutic potential of cannabidiol. *Cannabinoids*, 32–83.

60. Puente, N., Cui, Y., Lassalle, O., Lafourcade, M., Georges, F., Venance, L., Grandes, P., & Manzoni, O. J. (2011). Polymodal activation of the endocannabinoid system in the extended amygdala. *Nature Neuroscience*, *14*(12), 1542–1547. https://doi.org/10.1038/nn.2974

61. Radwan, M. M., Chandra, S., Gul, S., & El-Sohly, M. A. (2021). Cannabinoids, phenolics, terpenes and alkaloids of cannabis. *Molecules*, *26*(9), 2774. https://doi.org/10.3390/molecules26092774

62. Ralevic, V. (2003). Cannabinoid modulation of peripheral autonomic and sensory neurotransmission. *European Journal of Pharmacology*, *472*(1-2), 1–21. https://doi.org/10.1016/s0014-2999(03)01813-2

63. Robson, P. (2005). Human studies of cannabinoids and medicinal cannabis. *Handbook of Experimental Pharmacology*, *168*, 719–756. https://doi.org/10.1007/3-540-26573-2_25

64. Rodriguez de Fonseca, F., Del Arco, I., Bermudez-Silva, F. J., Bilbao, A., Cippitelli, A., & Navarro, M. (2004). The endocannabinoid system: Physiology and pharmacology. *Alcohol and Alcoholism*, *40*(1), 2–14. https://doi.org/10.1093/alcalc/agh110

65. Rosenkrantz, H., & Hayden, D. W. (1979). Acute and subacute inhalation toxicity of Turkish marihuana, cannabichromene, and cannabidiol in rats. *Toxicology and Applied Pharmacology*, *48*(3), 375–386. https://doi.org/10.1016/0041-008x(79)90421-6

66. Rosenkrantz, H., Fleischman, R. W., & Grant, R. J. (1981). Toxicity of short-term administration of cannabinoids to Rhesus Monkeys. *Toxicology and Applied Pharmacology*, *58*(1), 118–131. https://doi.org/10.1016/0041-008x(81)90122-8

67. Silvestro, S., Mammana, S., Cavalli, E., Bramanti, P., & Mazzon, E. (2019). Use of cannabidiol in the treatment of epilepsy: Efficacy and security in clinical trials. *Molecules*, *24*(8), 1459. https://doi.org/10.3390/molecules24081459

68. Sim-Selley, L. J. (2003). Regulation of cannabinoid CB1 receptors in the central nervous system by chronic cannabinoids. *Critical Reviews in Neurobiology*, *15*(2), 91–119. https://doi.org/10.1615/critrevneurobiol.v15.i2.10

69. Stott, C. G., White, L., Wright, S., Wilbraham, D., & Guy, G. W. (2012). A phase I study to

assess the single and multiple dose pharmacokinetics of THC/CBD oromucosal spray. *European Journal of Clinical Pharmacology*, *69*(5), 1135–1147. https://doi.org/10.1007/s00228-012-1441-0

70. Thiele, E. A., Marsh, E. D., French, J. A., Mazurkiewicz-Beldzinska, M., Benbadis, S. R., Joshi, C., Lyons, P. D., Taylor, A., Roberts, C., Sommerville, K., Gunning, B., Gawlowicz, J., Lisewski, P., Mazurkiewicz Beldzinska, M., Mitosek Szewczyk, K., Steinborn, B., Zolnowska, M., Hughes, E., McLellan, A., … Wilfong, A. (2018). Cannabidiol in patients with seizures associated with Lennox-Gastaut syndrome (GWPCARE4): A randomised, double-blind, placebo-controlled phase 3 trial. *The Lancet*, *391*(10125), 1085–1096. https://doi.org/10.1016/s0140-6736(18)30136-3

71. Toth, C. C., Jedrzejewski, N. M., Ellis, C. L., & Frey, W. H. (2010). Cannabinoid-mediated modulation of neuropathic pain and microglial accumulation in a model of murine type I diabetic peripheral neuropathic pain. *Molecular Pain*, *6*. https://doi.org/10.1186/1744-8069-6-16

72. Ujváry, I., & Hanuš, L. (2016). Human metabolites of Cannabidiol: A review on their formation, biological activity, and relevance in therapy. *Cannabis and Cannabinoid Research*, *1*(1), 90–101. https://doi.org/10.1089/can.2015.0012

73. Verrico, C. D., Wesson, S., Konduri, V., Hofferek, C. J., Vazquez-Perez, J., Blair, E., Dunner, K., Salimpour, P., Decker, W. K., & Halpert, M. M. (2020). A randomized, double-blind, placebo-controlled study of daily cannabidiol for the treatment of canine osteoarthritis pain. *Pain*, *161*(9), 2191–2202. https://doi.org/10.1097/j.pain.0000000000001896

74. Ward, S. J., McAllister, S. D., Kawamura, R., Murase, R., Neelakantan, H., & Walker, E. A. (2014). Cannabidiol inhibits paclitaxel-induced neuropathic pain through 5- HT 1a receptors without diminishing nervous system function or chemotherapy efficacy. *British Journal of Pharmacology*, *171*(3), 636–645. https://doi.org/10.1111/bph.12439

75. Ward, S. J., Ramirez, M. D., Neelakantan, H., & Walker, E. A. (2011). Cannabidiol prevents the development of cold and mechanical allodynia in paclitaxel-treated female c57bl6 mice. *Anesthesia & Analgesia*, *113*(4), 947–950. https://doi.org/10.1213/ane.0b013e3182283486

76. Wong, H., & Cairns, B. E. (2019). Cannabidiol, Cannabinol and their combinations act as peripheral analgesics in a rat model of myofascial pain. *Archives of Oral Biology*, *104*, 33–39. https://doi.org/10.1016/j.archoralbio.2019.05.028

77. Xiong, W., Cui, T., Cheng, K., Yang, F., Chen, S.-R., Willenbring, D., Guan, Y., Pan, H.-L., Ren, K., Xu, Y., & Zhang, L. (2012). Cannabinoids suppress inflammatory and neuropathic pain by targeting α3 glycine receptors. *Journal of Experimental Medicine*, *209*(6), 1121–1134. https://doi.org/10.1084/jem.20120242