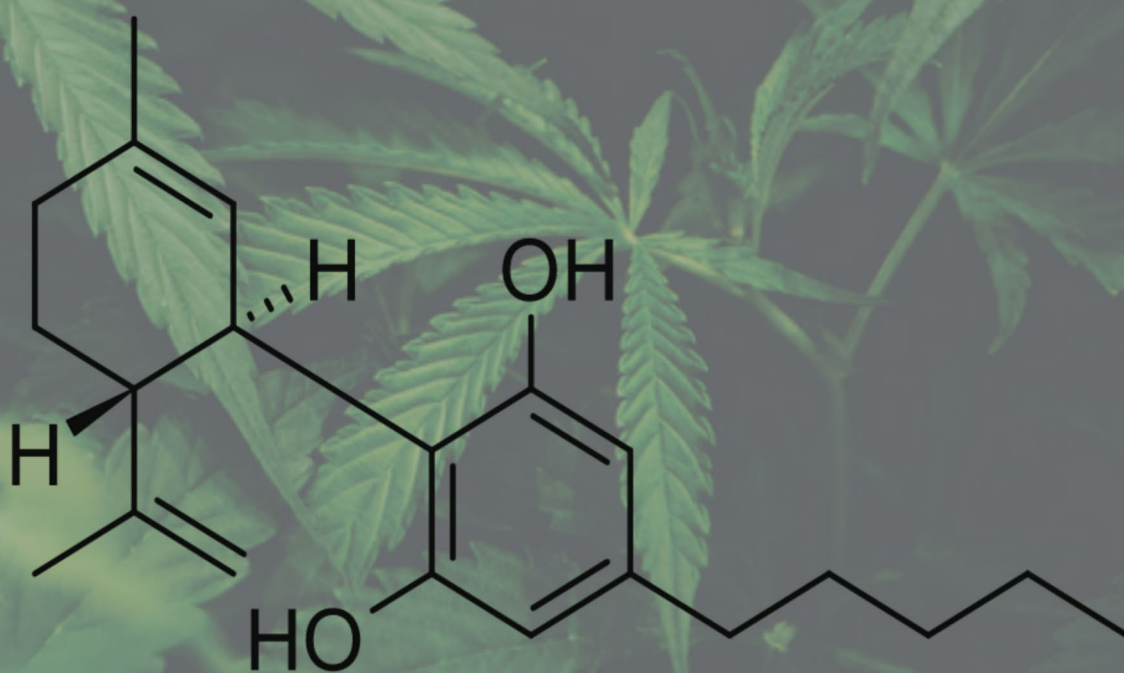


# REPORT ON CBD



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## CBD REPORT

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## INTRODUCTION

### CBD


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Plants appeared very soon after the origin of life and are the first manifestations of complex life to occur on the surface of our planet. The first living organisms were bacteria, which appeared about 3.5 billion years ago, a billion years after the Earth was formed. Bacteria, which are the most abundant form of life on our planet today, are unicellular beings, without a nucleus. About 1.5 billion years after the first form of life originated, that is, about 2 billion years ago, the first organisms appeared that protected their genetic information (called DNA) in a nucleus, separate from the rest of the components that make up a cell. The isolation of the nucleus inside the cell facilitated recombination in its replication process: this produced novelty and with it a biological diversity of which today we barely know a tiny fraction. The most optimistic estimates say that more than 80% of the species that exist are still unknown and, more chillingly, more than 99% of the species that have ever existed are extinct. On the other hand, the climate emergency in which we are currently immersed is exterminating species whose existence we will never know about.

*"Some eukaryotic cells [...] already contained cannabinoid substances, specifically an amino acid called FAAH (or fatty acid amide hydrolase)."*

The first cells without a nucleus are called prokaryotes, and those with a nucleus are called eukaryotes. Eukaryotic cells, in their recombination processes, gave rise to plants, which would appear about 500 million years after the first eukaryotic cell, and millions of years later to all the animals that would follow. The purpose of this biohistorical digression for the subject at hand, which is cannabidiol (henceforth CBD, for its chemical abbreviation), is that some eukaryotic cells, which later gave rise separately - as a consequence of the aforementioned replication mechanism - to every lineage of plants and animals, already contained cannabinoid substances, specifically an amino acid called FAAH (or fatty acid amide hydrolase). In the plant lineage, FAAH developed in a specific way in a specific plant called *Cannabis sativa*, leading to the generation of compounds called cannabinoids. Curiously, at least to date, of all the plants that have been searched, this type of compound has only been found in the cannabis plant. And yet, strangely, it is present in all the animals that have been searched, except in some insects.



The background of the page is a light green, semi-transparent image of cannabis leaves, showing the characteristic serrated edges and branching structure. The leaves are spread out across the page, creating a textured, organic backdrop for the text.

The fact that all animals contain cannabinoid compounds must surely play a crucial role in their survival. If this were not the case, they would not have been kept, conserved, and transmitted over the course of the millions of years that nature has needed to generate the quantity and diversity of living animals that we know of today. The implications of this phenomenon are just beginning to be understood by scientists today. But, without a doubt, one of them, and certainly the most important, is this: if these cannabinoid compounds are so important for the survival

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of animal organisms, they can be modulated using similar compounds present in the cannabis plant to treat a host of diseases. Of the hundreds of compounds present in the cannabis plant, of which more than a hundred are cannabinoids and, as I wrote above, are exclusive to it, there is one that in recent years has attracted the attention of scientists for its many potential medical applications. This compound is cannabidiol (or CBD). CBD, as we will discuss below, is a safe and effective compound for treating many diseases and physiological conditions in animals, hence the enormous success it has had in recent years in human and veterinary medicine.

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## THE CANNABIS PLANT

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Have you ever wondered how medicine came into being? Like all human processes, later perfected by science with its sophisticated methodologies, medicine was born from observation. Specifically, by observing animal behaviour. All animals use the plants present in their ecosystems not only to cure their diseases (which is known as "therapeutics"), but also to prevent them ("prophylaxis"). These are mainly parasitic diseases, which are the most common in the animal kingdom, including humans; but not only. Plants produce a plethora of substances that are used by animals for both prophylactic and therapeutic purposes. There are countless examples of this in the animal kingdom and there is a medical specialty, called zoopharmacognosy, which deals precisely with the study of this phenomenon.

*"Morphine, quinine, and cocaine are well-known examples that demonstrate, on the other hand, that the distinction between medicine, intoxicant, and drug does not exist in the natural world."*

The substances that plants produce and that are so useful to animals are called "secondary metabolites" and belong to chemical families known as sesquiterpenes, alkaloids, and

saponins. The secondary metabolites of plants are not directly involved in their growth, development, or reproduction: their function is to protect them from predators, as well as to use the animals present in their ecosystems to promote pollination and thus increase their chances of survival as a species. These secondary metabolites generated by plants also have no nutritional value for animals, but serve them as medicine and – for humans – also as condiments, pigments, flavourings, and various drugs with medical, but also intoxicating and recreational potential. Morphine, quinine, and cocaine are well-known examples that demonstrate, on the other hand, that the distinction between medicine, intoxicant, and drug does not exist in the natural world. That the secondary metabolites of plants are a source of medicines in the natural world should come as no surprise. As we explained in the introduction, animals and plants coexisted and, therefore, co-evolved for millions of years. In fact, it is estimated that approximately 20% of all known plants have some medicinal properties and today they are still the main source of food and therapeutics in the world, even though it may not seem so due to the growth of technology today. For example, approximately 70% of antibacterial, antifungal, and antiviral drugs come from or are derived from plant molecules; and 80% of anti-cancer treatments are also based on plant molecules or derivatives thereof.





## WHAT IS CBD AND WHY NOW?

CBD was the first cannabinoid to be isolated from the cannabis plant, although THC (isolated in 1964) preceded it in fame. In the 1940s two researchers independently isolated CBD from a Mexican marijuana plant and from Indian charas (hashish), respectively. Nobody seemed to be interested in the discovery, so it took almost twenty-five years before, in 1963, its chemical structure was perfectly described in the laboratory of Dr. Raphael Mechoulam, of the Hebrew University of Jerusalem (Israel), starting from Lebanese hashish. And it took another decade for pharmacological and clinical research to begin. What researchers were interested in was the psychotropic effect of the cannabis plant, because it was also the one that had medical properties. CBD, showing no effect on animals, did not arouse the interest of scientists. In fact, its medical properties were discovered largely by trial and error. In those years, research was carried out with samples of hashish and marijuana from the illicit market, which varied in composition and therefore produced different effects on animals, as they came from different batches and had different concentrations of cannabinoids. Once the chemical structures of THC and CBD were described, it was possible to attribute the differences in their effects to the variation in the concentrations of the two compounds present.

Scientists were then amazed at how CBD somehow counteracted and even behaved in animals in a way that was opposite to THC's: it reduced their seizures in epilepsy models, calmed them in anxiety models, and did not cause memory impairment in learning tests. Most of the medical effects of CBD, researched today as if they were a novelty, were actually already discovered in the 1970s and 1980s, such as the effects mentioned above, together with anti-inflammatory, antipsychotic, analgesic, anti-emetic, and many others that we will refer to below. The reasons why all these works went unnoticed is sobering in relation to the history of science: 1) the work was carried out on compounds belonging to a forbidden plant and which carried in its recent history the stigma of a dangerous drug, and 2) the researchers who signed the scientific articles, despite having been published in the most important journals of the field, belonged to Israeli and Brazilian universities (Dr. Mechoulam, Dr. Carlini, Dr. Zuardi, etc.), in a world dominated by Anglo-Saxon scientists. The science of CBD would be a few decades more advanced today had it not taken so long for those pioneering studies to be internationally recognised.

There are several reasons why CBD is finally positioning itself as one of the most interesting medicines for: 1) its versatility in treating a wide variety of conditions with different causes, 2) its very low toxicity, 3) its very high tolerability (its adverse effects, when they appear, are of a mild or moderate nature, never serious), 4) its reasonably simple clinical management in polymedicated patients, 5) its relatively easy production, and therefore, 6) its theoretically cheap and affordable accessibility for people who need it. This is not happening due to the lack of regulation, but it is something we will deal with in chapter 5.

But if these reasons have been known, as I wrote before, for decades, why is it that they are only being considered now? As with other medical breakthroughs, it is a combination of chance, ingenuity, and perseverance, not only from the scientific community, but also from civil society. Before controlled clinical trials with CBD were carried out at the industrial level, and although the cannabis trade, as well as its users, are persecuted, mankind never stopped using cannabis and neither did scientists,

TABLE 1

### IS CBD PSYCHOACTIVE?

Yes, CBD is psychoactive. Psychoactive means that it acts on the brain and, as a consequence, a psychological effect is experienced. The anxiolytic, anticonvulsant, and anti-inflammatory actions of CBD are due precisely to its action on the brain. CBD is sometimes said to be psychoactive, but not psychotropic, like THC is. It's a good way to illustrate the difference, but it's not entirely scientifically accurate either. The problem here is that pharmacological concepts are constantly being confused with legal concepts. For example, Spanish legislation confuses psychoactivity with toxicity, and thus prohibits THC and products that exceed a certain percentage of THC as psychoactive. But psychoactivity is not synonymous with toxicity. In pharmacology there is a difference between minimum active dose and toxic dose, and this difference is called therapeutic margin. Spanish legislation has eliminated the therapeutic margin



as we have seen, stop researching it, despite all the difficulties. In most scientific disciplines there is a gap between what scientists research in their laboratories and what reaches the general public. Except when it comes to very useful medicines that are prohibited, such as cannabis or hallucinogens like psilocybin or ayahuasca. The flow of information is then more fluid and there is a critical mass of people who are aware of scientific advances. With the technification of societies, in fact, this gap is becoming narrower and narrower. And in the world of cannabis, activism is pretty much up to date with scientific advances. So it was first the mothers and families of children with severe and incurable epilepsies who, of their own initiative, produced home-made oils as medicines for their children: as the numbers reached critical mass, pharmaceutical companies took notice and started to develop their own CBD-based medicines. At the same time, those pioneering studies were taken up again, and thanks to this feedback between science and civil society - and to the appearance of a new and no less important protagonist, business - the available scientific knowledge began to be popularised, new research was initiated, and the CBD trade soared to the point where it has often become propaganda, rather than evidence-based medicine. That's why it's time to put CBD in its rightful position as a therapeutic drug.



from its doctrine. Moreover, not all psychoactivity is necessarily toxic. Psychiatric drugs are psychoactive and are assumed to be beneficial, including hypnotosedatives, which are the third most consumed drug by Spaniards (after alcohol and tobacco and before cannabis). For its part, the term psychotropic is not a scientific term, but a legal one. Etymologically, it means something like "that moves the mind" (tropos=movement). Which doesn't mean anything. The term "psychotropic" was used to develop a list of drugs under international control. This list includes compounds such as THC, LSD (lysergic acid diethylamide), psilocybin, and MDMA (ecstasy). The problem with this list is that drugs were included in it not because of their possible toxicity, but because they were consumed by the population without medical guidance. Thus, while all

psychotropic substances are psychoactive, not all psychoactive substances are psychotropic, so they are not all prohibited. In order to draw up the list of psychotropic substances, in most cases technical reports were not carried out, so to say that CBD is psychoactive but not psychotropic is technically true: it is psychoactive, but not controlled. But this does not at all illustrate its psychological effects. The psychoactive effect that is of most concern to the legislator, and by which some psychoactive compounds may be added to the list of psychotropic substances, is euphoria. Thus, psychiatric drugs on the market must pass very stringent tests to show that they do not produce euphoria, and indeed most do not, whereas most psychotropic drugs do, and that is precisely why they are included in the list of psychotropic drugs. Drug addiction experts

equate euphoria with potential for abuse. Hence, psychoactive compounds that produce euphoria tend to be controlled because of their potential for abuse. We now know that many of psychotropic substances are medically useful, such as MDMA in the treatment of post-traumatic stress disorder or psilocybin for major depression, and we will soon see them marketed as drugs. Etymologically, euphoria means "feeling of well-being". So the confusion is huge: it is what produces well-being that is controlled. But CBD also produces wellbeing, doesn't it? What a mess! We'll leave the reader to puzzle it out and finish this explanation by saying that CBD does not produce euphoria (in the sense that psychotropic drugs are understood to do, whatever that may be) and therefore lacks the potential for abuse, dependence, and addiction.



## WHAT IS CBD'S MEDICAL POTENTIAL AND WHERE DOES THE EVIDENCE COME FROM?

The scientific community began to take cannabinoid medicine seriously as the endogenous cannabinoid system (ECS) became more widely known. Until the 1990s it was not known how THC, CBD, and other cannabinoids that were discovered in the plant as research progressed, produced their effect. The discovery that we have cannabinoids in our body, i.e. chemical compounds with the same structure as those unique compounds in the cannabis plant, and are therefore called endocannabinoids, revolutionized medicine.



There is a whole complex of chemical mechanisms inside our body that is in charge of producing cannabinoids, which bind to specific receptors, called cannabinoid receptors, and which form a complex system of cell signalling, mainly in charge of regulating the homeostasis (physiological balance) of the organism. And the same ECS was found in each of the animal species in which it was sought, except, as mentioned above, in some insects. Cannabinoid compounds were also found to interact with other receptors to which no endogenous substances are known to bind, as well as with receptors belonging to other chemical signalling systems (see Table 2 for known receptors onto which CBD binds). The reasons why these compounds have a therapeutic effect on so many diseases are finally beginning to be understood: the ECS is present in absolutely all tissues and organs of the body. After all, it is the earliest known signalling system, that the prokaryotic cell already shared with its direct cousin. The ECS is the first thing to be activated in the body when a disease occurs, to try to repair it. In fact, it activates on demand. So it is when the demands of the task exceed the capacity of action of the ECS that exogenous cannabinoids, found in the plant or synthesized in a laboratory, can be used to help the system return the organism to normality. Evolution has been working for many millions of years to perfect this sophisticated (and to this day still largely misunderstood)

system of homeostasis regulation in animals. It is said that it is not an essential system for survival, but that without it life would not be worth living, because of the suffering we would have to bear due to its role in the regulation of pain, mood, cellular protection and, as already mentioned, returning the body to normal when it has been disturbed by an external cause. Since the first parts of the ECS (endogenous receptors and ligands, or endocannabinoids) were discovered, research has only grown exponentially. In the specific case of CBD, there is already a drug on the market, called Epidiolex®, for the treatment of some childhood epilepsies, and others are being developed for other diseases, as we will explain later.

Thus, we already know that CBD has medical applications because it acts on the ECS, which is the first of an animal's systems to be activated to try to counteract a disease, an injury, or any other attack that endangers the organism, both physical and psychological (see table 3 for CBD's therapeutic potential). Nature, again, does not distinguish between them. We humans do, because we have consciousness and we make interpretations and assumptions about our environment and what happens to us. But for the organism it is the same thing. This is why CBD is said to be useful for the treatment of some mental disorders as well.



The versatility of CBD and other cannabinoids is explained precisely by the fact that, in the billions of years that have passed since the first eukaryotic cell – which carried with it almost the entire animal lineage up to now – synthesized a cannabinoid compound, the main physiological mechanism to contrast the adversities of the environment (the ECS also participates very actively in the physiological response to stress) and to fight diseases, was incorporated into the different organs, tissues, and functions that were emerging in the growing complexity of animal life. Other systems were, in turn, emerging and co-evolving with the ECS, which maintained its main role of cellular regulation, interaction with other systems, and has been present, as has been said, to this day, in every system, tissue and physiological function. The growing complexity of organisms made the ECS become more complicated as well, so that by affecting any other regulatory system, the ECS is also affected, and vice versa. In parallel, the cannabis plant was probably also gaining in complexity, until it became the unique natural factory of the chemical compounds described in Chapter 1.

This phenomenon is of utmost importance because it is the basis for understanding how diseases occur and how they can be cured, or attempted to be cured. The complexity of the ECS means that there are dozens of endogenous cannabinoid compounds, each acting at different sites in the system, often redundantly. The importance of this sophisticated mechanism is crucial, because it diversifies

actions. Diversifying the actions, acting in a redundant way (different compounds at the same time) and in different places (what is called "pharmacological promiscuity"), avoids pharmacological resistance, which is the main problem of selective drugs or medicines. Diseases can be understood as systems, with many interacting parts. If the system gets sick, it is a matter of detecting the part that has failed in order to act selectively to try to repair it pharmacologically. But systems, when they suffer a selective attack, reorganize themselves, and parts of the system take over the functions of the attacked parts. Thus resistance to the treatment occurs, and the treatment ceases to be effective; in addition, the system becomes resistant to drugs of the same family. This is what happens so often with viral and bacterial diseases, or rather, with the non-rational use of antibiotics. If however, when a disease occurs, instead of trying to attack the specific part that is failing in order to eliminate it, we act on the system as a whole, the treatment not only becomes more effective, but resistance is avoided. This is how cannabinoids in general, and CBD in particular, would act.

This means that CBD has a very complex mechanism of action, which has not yet been fully understood and which continues to offer surprises as it is explored in greater depth.

TABLE 2

## SOME OF THE MECHANISMS OF ACTION OF CBD

Target	Action	Target	Action	Target	Action
Glycine $\alpha 1/\beta 3$ receptors	Agonist/Positive allosteric modulator	COX activity	Inhibitor	PPAR- $\gamma$ Receptor	Agonist
Adenosine reuptake	Inhibitor	DA2 dopamine receptor	Partial agonist	Putative abnormal receptor-CBD	Antagonist
Adenosine A1/2A receptors	Modulator	Opioid- $\delta$ receptor	Positive allosteric modulator	$\sigma 1$ receptor	Antagonist
Anandamide reuptake	Inhibitor	FAAH	Inhibitor	Na <sup>+</sup> channels	Inhibitor
Ca <sup>2+</sup> (intracellular)	Regulator	Glutamate release	Inhibitor	TRPA1 channels	Agonist
Ca <sup>2+</sup> channel (T-type voltage-dependent)	Inhibitor	GPR55 receptor	Antagonist	TRPM8 channels	Antagonist
CB1 cannabinoid receptor	Non-competitive antagonist / Non-competitive negative allosteric modulator	Hydroperoxide-induced oxidative damage	Inhibitor	TRPV1-4 channels	Agonist
CB2 cannabinoid receptor	Inverse agonist	MTOR signal transmission pathway	Activator	TNF $\alpha$	Modulator
		Opioid- $\mu$ receptor	Ligand/Positive allosteric modulator	Tryptophan degradation	Inhibitor
		NO production	Inhibitor	VDAC1	Modulator
		PGE2 production	Inhibitor	5-HT1A	Agonist
				5-HT2A	Partial agonist
				5HT3A	Antagonist
				5- and 15-lipoxygenase	Inhibitor

The mechanism of action of CBD is very complex and although it is known to bind to a multitude of receptors – which is why it has so many different therapeutic effects – none of the individual mechanisms alone satisfactorily explain its medical potential. This box shows the mechanisms of action known to date. The list of targets/actions is not exhaustive. The targets/actions marked in blue seem to be the most relevant for the anxiolytic, antipsychotic, antiepileptic, and neuroprotective effects of CBD. Source: Dos Santos, R. G., Hallak, J. E. C., and Crippa, J. A. S. (2021). Neuropharmacological Effects of the Main Phytocannabinoids: A Narrative Review. *Advances in Experimental Medicine and Biology*, 1264, 29-45.



TABLE 3

## MAIN MEDICAL POTENTIALS OF CBD

Action	Condition	Level of evidence
Antiepileptic*	Dravet and Lennox-Gastaut syndromes.	Controlled clinical trials. Ample clinical evidence.
Anxiolytic	Every illness is accompanied by anxiety. Possible anxiogenic effects at high doses.	Limited evidence from controlled clinical trials. Ample clinical evidence.
Antipsychotic	Schizophrenia.	Controlled clinical trials. Limited clinical evidence.
Neuroprotection (anti-inflammatory, antioxidant)	Neonatal hypoxia, Alzheimer's, Parkinson's.	Extensive preclinical evidence. Limited clinical evidence. There are no controlled clinical trials.
Spasticity**	Multiple sclerosis. Spinal cord injuries.	Extensive clinical evidence from clinical trials in combination with THC.
Chronic pain	Mainly of neuropathic origin.	Ample clinical evidence. Limited evidence from controlled clinical trials. More effective in combination with THC.
Cancer	Different types of tumours (breast, testicles, brain, prostate, etc.).	Extensive preclinical evidence. Limited clinical evidence or evidence from controlled clinical trials.
Addictive disorders	Cravings, tobacco, harm reduction.	Limited evidence, both clinical and from clinical trials.
Skin diseases	Eczema, psoriasis, pruritus, and inflammatory conditions.	Ample evidence from preclinical research, limited evidence from clinical trials, ample clinical evidence.
Other	Autism and other developmental disorders.	Scarce evidence from clinical trials. Ample clinical evidence of improvement in behavioural problems associated with the disorder.

\* Authorized drug Epidiolex®, containing CBD.

\*\* Authorized drug Sativex®, containing THC and CBD (1:1).

## WHAT COULD EXPLAIN THE UNIQUENESS OF THE CANNABIS PLANT?

TABLE 4

How to explain the uniqueness of the cannabis plant in relation to the quantity and diversity of chemicals it produces in its flower? The secondary metabolites of plants, as we have explained above, are not strictly necessary for their survival. Plants can live perfectly well without them. They would be less noticeable, less firm, less colourful, attractive, and scented, animals would not be attracted to them and would not transmit their pollen through them, but they would not die. It is possible that, in the long run, many of them would die out as a species, as they would not attract any animals to spread their pollen. In a different logical order, the same can be said of animals. Without the ECS we would not tolerate pain, we would suffer from constant inflammation, we would be anxious and depressed, and we would have a myriad of medical illnesses and psychological disorders, but strictly speaking, we would survive. Not very well, but we would. In our case, it is obvious what our cannabinoids are for, but what about the cannabis plant? In the introduction we have explained that medicine arises by observing how animals make use of the plants present in their ecosystems, actively search for them, and culturally transmit their learning. And also that all animals, except insects, have an ECS. However, there is not a single known case of animals, other than humans, self-medicating with cannabis. Nor is any wild animal known to voluntarily intoxicate itself with cannabis. It seems that, despite having an ECS, almost no animals like the effects of cannabis, not even the laboratory animals on which experiments are done: scientists first have to teach the animals to self-administer it (by giving them rewards that do satisfy them when they do), but they do not do so voluntarily or actively. Only insects, which do not have ECS, are attracted to the plant, and not even all of them. One could think that the secondary metabolites are produced by a plant precisely to favour its reproduction, manipulating the behaviour of animals in its environment. But if a plant cannot use animals for its reproduction, why produce secondary metabolites? It doesn't seem a plausible explanation that its only purpose is the enjoyment and pleasure of humans, does it? Perhaps it is precisely because of the absence of predators that a plant can afford to be generous, profuse, and almost excessive in its expression of secondary metabolites. The sky is the limit, as the popular expression would say. Finally, there is only one known species of the cannabis plant, with different varieties. That is, since it separated from its lineage sister (*Humulus lupulus*) some 25 million years ago, it has hardly mutated at all. Cultural selection has also meant that there are thousands of varieties. But as a species, it has not mutated. And not having predators, its energy has, let's say, been used in an anthropocentric way, *enrich itself*. Then, by chance, the human being came across it and all this diversity of the plant connected with the complexity of the human ECS, and became one of our main sources of medicine, food (for its seeds) and fibre (to make clothes, for example). For this reason, since human beings discovered it, they took it wherever they went, and that is why today it is distributed all over the world, changing only its chemotypical composition, but not its genetic essence that characterizes it as a species.



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## AND IN HUMANS?

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Although the preclinical evidence, i.e. from research on cultured cells isolated in laboratory plates (see Table 1) and in animals, is overwhelming for many diseases (see Table 2), the evidence in humans is still relatively limited. With CBD, a relatively unusual phenomenon has occurred in medicine: popular use has overtaken clinical trials, which are scientific studies in which, under laboratory conditions, a drug is compared either to a placebo or to another drug that has already been shown to be safe and effective.

The legal status of cannabis (which I will discuss in the next chapter) has meant that research on its components has been conditioned by the stigma associated with prohibition and therefore the research on it, until recently, has been very limited. However, as CBD is not a controlled (prohibited) compound, it has been sold in specialised shops and, above all, on the Internet for some years now, while many countries and North American states have regulated its sale. This led countless millions of people, with and without illnesses, to start using CBD with or without medical supervision. In this regard, while the evidence from clinical trials for many medical conditions is sparse, the empirical evidence from the people who use it, and the clinical evidence from the physicians who oversee the treatments, are overwhelming.

The best described properties are anxiolytic ones, especially in people with anxiety disorders. Anxiety is a widespread problem in our society, and it can be found in all the people with a chronic illness. Many people use it as a substitute for addictive anxiolytics, such as benzodiazepines. The other highly interesting potential is as a neuroprotector in neuronal and neurodegenerative diseases. In these cases, apart from exerting possible neuroprotective and antioxidative effects, it improves psychiatric symptomatology, such as symptoms of depression or some associated behavioural problems. For other possible diseases, its efficacy is limited if it is not accompanied by THC, which is still the main therapeutic agent (for example, in spasticity, chronic pain, or some types of tumours). However, CBD counteracts the psychotropic effects of THC and the potentially associated cognitive and behavioural problems, so that combined THC and CBD treatments end up being the best therapeutic option. First, because CBD allows a good tolerability of THC, and second, because therapeutic effects are compounded.

The interest that CBD has aroused among the scientific community is so high that its applications are currently being investigated in diverse and complex areas (apart from those already mentioned) such as behavioural problems in children and adolescents with intellectual disabilities, post-traumatic stress disorder, and other psychological disorders such as depression, tinnitus, cardiomyopathies, or in the treatment of COVID-19.

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## IS IT LEGAL?

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Unlike THC, CBD is not considered psychotropic and is therefore not prohibited. In fact, in 2017 the WHO published a report concluding that CBD has no potential for abuse or dependence, is generally well tolerated, and has a good safety profile. However, its sale is only authorized as a food supplement, as a cosmetic, and as a medicine. With regard to CBD in flower form (buds), it is only authorised for sale as an air freshener, never for human consumption or above 0.2% THC, which is where, arbitrarily and unscientifically, the limit of non-psychoactivity has been established.

*"Unlike THC, CBD is not considered psychotropic and is therefore not prohibited."*

With regard to its marketing as a cosmetic, there are already countless products sold in pharmacies and beauty parlours. There are also several companies that have obtained permits from regulatory agencies to market CBD as a dietary supplement. There is also a drug, Epidiolex®, which is an oral solution approved only for the treatment of very severe childhood epilepsies, such as Dravet and Lennox-Gastaut syndromes. Sativex® is another drug that contains THC and CBD in a 1:1 ratio and is licensed for spasticity associated with multiple sclerosis.

In Spain, the cultivation of hemp for the purpose of CBD extraction requires a special permit from the Spanish Agency of Medicines and Health Products (AEMPS).





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## HOW TO USE IT?

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CBD can be found in the form of oils for sublingual use, flowers for inhaling or smoking, e-liquids for electronic cigarettes, and creams and ointments for topical use. Topical use, although sold as a cosmetic, is actually used for peripheral injuries (bruises, sprains, back pain...) and there is clinical evidence of efficacy for skin diseases such as psoriasis when applied locally. Obviously, it can also have a cosmetic use. The skin is densely populated with cannabinoid receptors, so topical uses, whether for medical or cosmetic purposes, are some of the most interesting uses of CBD.

The most common way to use CBD is sublingually in the form of oil, by placing the necessary drops under the tongue and keeping them as long as possible. The problem with the sublingual route is that the oil is not well absorbed, so some of it goes through the sublingual route and some of it goes through the oral route. This means that the absorption of CBD is reduced and, depending on the conditions to be treated, very high doses are needed, which, although not toxic, do make it very expensive to use. The effects of CBD administered sublingually are felt between 30 and 60 minutes later (the time varies depending on diet) and last for 6-8 hours. Therefore, this route is appropriate for the treatment of chronic diseases, as it allows a stable amount of CBD to be maintained in the body over time with 2 or 3 doses per day. Taking CBD together with high-fat foods (such as, for example, yoghurt - obviously not skimmed), can double absorption and therefore increase its effectiveness. For acute conditions (such as a pain peak, for example)

it is more advisable to inhale the substance (preferably using a vaporizer, thus avoiding combustion, or using electronic cigarettes, although the latter carry more health risks than vaporization), since its effect is immediate, although more limited in time (about two hours). Many patients use oils and only when acute worsening occurs do they resort to vaporization. This may occur in people with chronic pain or anxiety problems.

Finally, CBD oils are marketed in different content ratios: 1%, 5%, 10%, etc. Choosing one's percentage is more a question of price than a guarantee of effectiveness. The bioavailability (the amount of product that is absorbed once ingested) of CBD taken orally is very low, only 5%. It can be doubled when ingested with fatty foods. As some of it takes the sublingual route (which allows for greater absorption), combining all the factors can enhance absorption. The problem is that absorption is still very low and for many of the diseases for which there is evidence, doses must be very high, in the order of 400 mg. So, as the CBD market is currently a grey market from the point of view of regulation, you will need a whole bottle for a single dose, which is unaffordable for most budgets. As a result, we can say that the CBD market, as of today, is probably not doing any harm, but it is not doing any good either, simply because many people are under-dosed. When there is a regulated CBD market in Spain, then we will be able to recommend "consulting your doctor or pharmacist", because the dosage should be adjusted individually for each disease and for each person.



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## IS WHAT IS BEING SOLD **OUT THERE RELIABLE?**

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The fact that there is no regulated CBD market means that there is a lot of uncertainty about the quality of the products. In [a study conducted by Fundación Canna](#) in which fifteen samples of e-liquids were analysed, vitamin E acetate, a compound that may pose a risk to people with lung conditions, was found in one sample as a diluent. In relation to oils, different studies have been carried out, such as [this one by the Spanish Medical Cannabis Observatory](#), with which the Fundación Canna also collaborated, which found that they do not always contain what is written on the labels, but sometimes toxic compounds (such as heavy metals) or relatively high concentrations of THC (the psychotropic cannabinoid of the cannabis plant). Consequently, if you are going to buy CBD oils, you should inform yourself and try to check with the sources available to you how safe the product is, both in terms of the absence of toxic compounds and the accuracy of the label with respect to its content.





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## DOES IT HAVE RISKS? WHICH ONES?

### **DOES IT INTERACT WITH OTHER MEDICATIONS?**

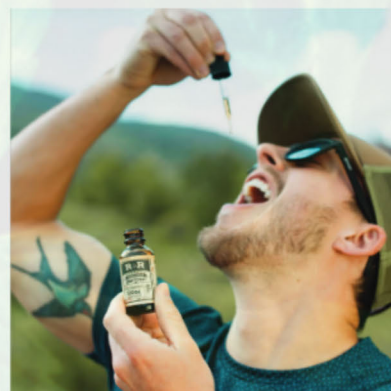
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Nothing that can be ingested is completely risk-free, not even water. However, of course, some products are safer than others. Water intoxication requires drinking many litres of water in a short space of time, while a few micrograms of some synthetic opiate is enough to kill someone. CBD is one of the safest products and medicines known to mankind. Death from overdose is exceptionally unlikely, even at very high doses. It does not generate dependence, addiction, or tolerance, so it is not necessary to increase the doses to achieve therapeutic effects in chronic treatments. Its organic toxicity, at therapeutic doses, at the level of knowledge we have today, can be said to be non-

existent. And, unlike THC, it does not adversely affect cognitive functions or produce psychological alterations. Rather, as already mentioned, its influence on the body is generally beneficial, functioning as an anti-inflammatory and neuroprotective.

However, depending on the dose, a number of non-severe adverse effects have been reported, mainly drowsiness, loss of appetite, diarrhoea, and fatigue.

The metabolism of CBD, when ingested orally (and, as mentioned above, some of the content taken sublingually actually goes



through the oral route) can interfere with the metabolism of other drugs. When this occurs, adverse effects can be more serious, including fever and vomiting. It is also possible to see increased blood levels of liver enzymes, which can lead to liver problems. Consult a specialist before using CBD oils if you are taking other medications. In clinical trials with Epidiolex®, in children with severe epilepsies, none of the adverse effects mentioned above have compromised the safety of the children, nor have there been any permanent sequelae, either hepatic or other. Simply reducing the doses of the various medications is enough to go back to normal. In chemotherapy treatments it is also important to bear in mind that CBD can interfere with the metabolism of chemotherapy drugs, and can lower or increase their concentrations and, therefore, their side effects. It is very important in these cases to consult a specialist.

Currently the biggest risk of CBD use is the proliferation of unregulated products, since many products, as we have already seen, may have pesticide residues, heavy metals, and other contaminants or labelling that does not match the real content of the product.

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"Currently the biggest risk of CBD use is the proliferation of unregulated products, since many products, as we have already seen, may have pesticide residues, heavy metals, and other contaminants or labelling that does not match the real content of the product."

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## WHAT ABOUT VULNERABLE POPULATIONS: **CHILDREN, THE ELDERLY, AND PREGNANT WOMEN?**

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**“*The decision to take it must be based on an appropriate risk/benefit balance, because nothing is harmless.*”**

As with any medical treatment or any use of a drug, medicine, or biologically active product, the decision to take it must be based on an appropriate risk/benefit balance, because, as has already been said, nothing is harmless and, at the same time, taking something can be more beneficial than taking nothing at all. It can be said that CBD, administered under medical supervision, is safe in children with refractory childhood epilepsies, that it is less toxic than authorised drugs, and that even its combination with these drugs allows the reduction of their dosage, thus gaining in safety. Thus, CBD in children does not seem to be problematic, which is not to say that it should be used to treat any minor problems. The decision must always be rational.

This extends to the elderly, especially since many of them are highly medicated. CBD, far from being a problem for them, can be a beneficial substance that

allows them to reduce other medications and, due to its anti-inflammatory and neuroprotective properties, can lead to an improvement in their quality of life. Controlling for potential drug interactions and liver markers, CBD may be a dietary supplement of clinical interest in the elderly.

With regard to pregnant women, there is no clinical evidence, although there is preclinical evidence of possible effects on the foetus. Just as evidence of efficacy from preclinical research is not always found in clinical trials, the same is true for adverse effects. In general, it is not recommended that pregnant or breastfeeding women take anything at all, unless the benefits of doing so outweigh the risks. It is up to them to make an informed decision about whether, when, how often, and for what purpose to take CBD, and to weigh up, preferably in conjunction with medical advice, the risk/benefit balance.



TABLE 5

## WHAT DO DOCTORS WHO USE IT SAY?

Between the months of July and August 2017, our team contacted six renowned physicians working with CBD and interviewed them regarding its clinical application. Four of the six doctors were Spanish, one was Canadian, and one was American. The main results of these interviews are presented below.

The basic criteria that doctors normally use to recommend one product or another to a patient are (in order of importance):

- The patient's **ability to access** the product.
- The **price** of the product.
- The **quality** of the product (laboratory analysis).
- The **"seriousness"** of the brand (availability/stability of stock).
- The **ease of dosing** (concentration).

Each doctor has preferred brands, but due to the variability of the market, we omit this information here.

Regarding the convenience of recommending a pure CBD product (produced by synthesis) or a CBD oil (produced by extraction), doctors unanimously recommend the extraction method due to the presence of traces of other cannabinoids, which, even in small doses, enhance the effects of CBD (known in medical jargon as the "entourage effect").

The major therapeutic potentials of CBD described by the interviewees are:

1. **Anticonvulsant or antiepileptic effect in severe and refractory childhood epilepsies**, both for its direct effect on the disease and on the well-being that it produces in the child's environment.
2. **Anti-inflammatory effect in inflammatory bowel diseases such as Crohn's disease, ulcerative colitis, irritable bowel, and functional digestive pathology**. In these cases and for these pathologies CBD works especially well, not only because of the anti-inflammatory effects itself, but also because of the lack of side effects that CBD produces.
3. According to the interviewees, **in the treatment of pain, the analgesic effect of CBD is quite effective in the first days of ingestion**. However, its effectiveness decreases with the passage of time (two weeks). While it is true that there are more powerful drugs available in pharmacies (such as opiates) to treat pain-related illnesses, cannabinoids, and in particular CBD, make lowering the dose of these drugs possible and thus reduce the side effects, some of which are quite serious, such as tolerance and its possible association with overdose, or dependence on these medications.
4. In terms of **anxiolytic and antipsychotic effects**, there are also drugs that are more effective and have a more immediate action than CBD, although the latter is valued for its lack of side effects, such as metabolic and psychoactive problems, which are present in prescription anxiolytic and antipsychotic drugs.
5. Other less common effects or indications of CBD that have appeared in the interviews are:
  - For **bone growth**.
  - As an **antioxidant**.
  - For **diabetes** (as a regulator of hyperglycemia).
  - **Hypotensive**.
  - **Constipation** (this effect does not appear in the Summary of Product Characteristics of Epidiolex®, while diarrhea does: perhaps the discrepancy may be due to the different effects that are sometimes found in the clinic (real world) compared to clinical trials (controlled context)).



In line with its effects, the indications for which the doctors interviewed usually recommend CBD (always, if possible, with a little THC) are as follows:

- **Refractory epilepsy:** this is where CBD shows the best and greatest results. The efficacy of CBD in this pathology is very high and so are the benefits for the patients and their environment.
- **Pain-related problems:** chronic pain, osteoarthritis, arthritis, rheumatoid arthritis, fibromyalgia, neuropathies, etc. "For these pathologies we can lower the doses of opiates by using a less toxic substance. Also, you get results with CBD in desperate patients for whom nothing else works."
- **Psychosis:** there are studies showing the same efficacy as other prescribed pharmaceuticals and with far fewer side effects.

When it comes to CBD dosing and cannabinoid dosing in general, there is a broad consensus among interviewees that it is necessary to listen to the patient's body. In this sense, some are aligned with the concept of "personalized medicine" and others are based on the model of shared decision-making between doctor and patient. Generally speaking, doctors adjust the dosage of CBD until a balance is found between therapeutic effects and unwanted effects. All agree to start with a small dose of about 0.5 mg per day and work up regularly. There is also agreement among interviewees that no maximum, or toxic, dose of CBD has been found, and the policy on the clinical prescription of CBD is that patients may take as much as they can afford financially.

Regarding the route of administration, it seems that the vaporized (inhaled) route is the best because it is direct and immediate, especially in acute conditions. The sublingual route is preferred for chronic situations.

There are few known interactions of CBD with other drugs. These interactions basically cause CBD to extend the life of other drugs (by altering their metabolic process), which can lead to greater toxicity. This is the case, for example, with oral chemotherapy medication, where it is obviously not in the interest of the body to extend the life of the drug. Interactions with clobazam, a drug for childhood epilepsy, are also described in the same terms: that CBD lengthens the life of the drug and makes the patient more drowsy. Knowing these mechanisms makes it possible, depending on clinical application, to combine different drugs with CBD but at lower doses, thereby reducing the toxicity of the former.

Finally, a 5% product concentration is not generally viewed badly by the professionals interviewed. Some point to the difficulty in designing the dosage, others add that a product with a medium range of concentration will be welcome in the market and many agree that the important thing will be the reliability of suppliers and the confidence that the product gives in terms of quality criteria.



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### Medical centres working with CBD

Kalapa Clinic. <https://www.kalapa-clinic.com/>  
Medcan. <https://medcan.es/>

### Scientific and clinical societies

Society of Clinical Endocannabinology. <https://www.endocannabinologia.es/>  
Spanish Society for Research on Cannabinoids. <https://www.seic.es/>  
International Association for Cannabinoid Medicine. <https://www.cannabis-med.org/>  
International Cannabinoid Research Society. <https://www.icrs.co/>

### Foundations and NGOs

Alchimia Solidaria. <https://alchimiaweb.org/es/>  
Asociación Dosemociones. <https://www.dosemociones.com>  
CANNABMED. <https://www.iceers.org/es/cannabmed/>  
Fundación CANNA: Scientific research and analysis of cannabis. <https://www.fundacion-canna.es>  
Fundación ICEERS - International Center for Ethnobotanical Education, Research, and Service. <https://www.iceers.org>  
Green House Medical. <https://ghmedical.com/>  
Observatorio Español de Cannabis Medicinal (Spanish Observatory of Medicinal Cannabis). <https://oedcm.com/>  
Patients' Union for the Regulation of Cannabis. <https://uniondepacientes.org/>



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