

CANNABIS & CBD

UNDER THE SCOPE

A simple guide to CBD



FOREWORD

Cannabis is an old plant that has been used in various industries for various purposes for centuries. Different varieties and parts of the plant are widely used in the construction, textile and automotive industries, as well as in the food industry as a healthy foodstuff rich in essential fatty acids and antioxidants. Additionally, thanks to naturally formed biomolecules in the *Cannabis* plant that are commonly referred to as (phyto)cannabinoids, it has numerous beneficial effects on the human body. Certain negative connotations related to the presence of psychoactive tetrahydrocannabinol (THC) in this plant are slowly disappearing thanks to the many advantages that this highly versatile plant has.

This guide describes the most important cannabinoid – cannabidiol (CBD), the history of *Cannabis* and CBD use, the characteristics of the plant and its further processing options. It also reveals the most important parameters that determine the quality of *Cannabis* and CBD-based products. And most importantly, it describes the endocannabinoid system (ECS) on a molecular level, along with the known pharmacological effects of the most investigated phytocannabinoid – CBD.



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WHAT IS CANNABIDIOL (CBD)?

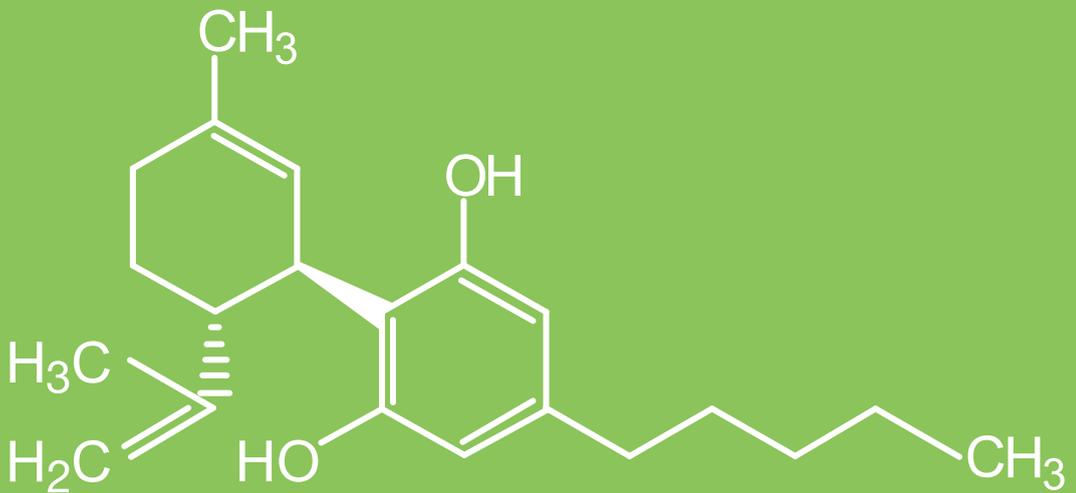


Figure 1: CBD chemical structure.

CBD is short for cannabidiol, a compound that is predominantly found in certain varieties of the plant *Cannabis sativa* L. It is a non-psychoactive compound with several beneficial effects on the human body that will be discussed below.

Chemically, CBD falls into the category of terpeno-phenolic compounds, which are produced abundantly in hair-like structures called glandular trichomes that are found on the surfaces of the Cannabis plants.

THE HISTORY OF CANNABIS AND CANNABINOID USE

The first known medicinal uses of *Cannabis* originate from China and other parts of Asia in ancient BC times. Its introduction into Western medicine occurred much later, in the 1830s (Figure 2; Reekie et al.). More than a century later, the *Cannabis* plant was included on the List of Drugs as a Schedule I drug. This list is a part of the Single Convention on Narcotic Drugs from 1961, which restricts the use of this plant with some exemptions: industrial, horticultural, research and medical purposes.

The research dedicated to this plant and its naturally occurring phytocannabinoids is indeed ongoing – one of the milestones was the structural identification of the psychoactive THC, which was confirmed back in 1964 (Gaoni and Mechoulam, 1964). Although CBD, the mostly recognised phytocannabinoid, was isolated from the plant for the first time in 1940, the complete structural identification was reported almost three decades later (Adams et al, 1940; Petrzilka et al, 1969).

With the discovery of the endocannabinoid system in the human body in the 1980s, the physiological effects of the *Cannabis* plant and phytocannabinoids are being continuously studied at an even higher level (Devane et al., 1988; Kinghorn et al., 2017). The proven beneficial effects in clinical studies lead to the registration of medicines such as Sativex[®], which was registered in Europe in 2010 and is currently the most prevalent cannabis-based medicinal product marketed in Europe (Bramness et al., 2018). Bedrocan, a Dutch company, became the world's first producer of medicinal *Cannabis* that was compliant with the European Medicines Agency's good manufacturing practice (GMP) standards in 2017.

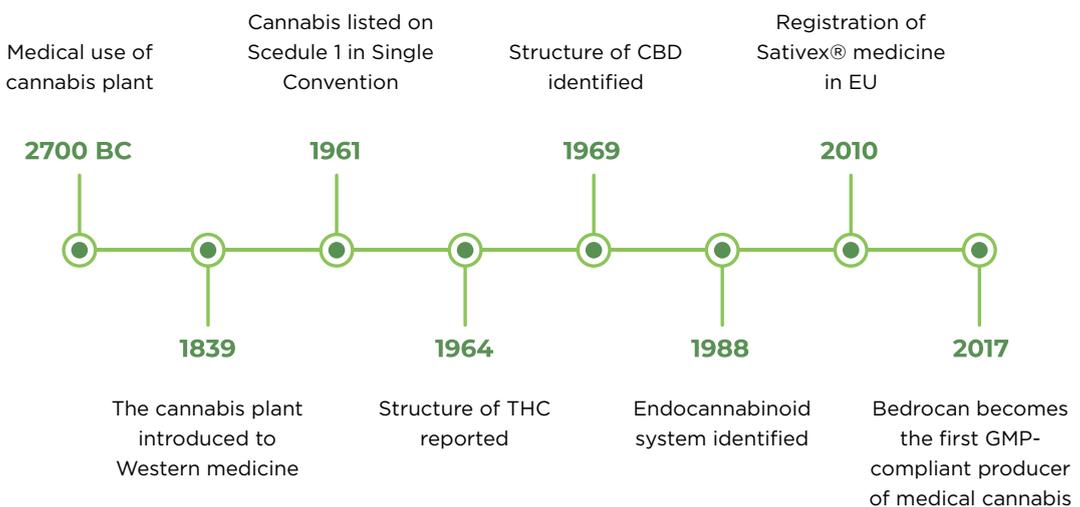


Figure 2: History of the Cannabis plant, cannabinoids and the endocannabinoid system.

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THE CANNABIS PLANT IS A SOURCE OF CBD AND OTHER PHYTOCANNABINOIDS

Cannabis is an annual herbaceous flowering plant with characteristic and well-recognisable leaves and smell (Figure 3). It can be grown under indoor or outdoor conditions, depending on the purpose and conditions that the specific variety of this plant requires. Indoor cultivation under controlled environmental conditions is essential for producing *Cannabis* in the pharmaceutical industry and results in a high-quantity biomass with a constant composition. On the other hand, outdoor production is more suitable for industrial purposes, including the foodstuff industry, as this is an economically more affordable yet still efficient option.

According to the taxonomists Schultes et al. (1974), there are three subspecies of *Cannabis*, more precisely named *Cannabis sativa* L.: *sativa*, *indica* and the less economically important and widespread *ruderalis*. Some varieties of *Sativa* include the well-known “industrial hemp” or “hemp” varieties that are legally used for foodstuff production and other industrial purposes. The main differences between *sativa* and *indica* are the cannabinoid profile and taxonomic differences. For example, the height of *sativa* ranges from 2.5 to 3.5m, while *indica* varieties are generally shorter (the average height is below 2m) and bushier with broader and darker green leaves. Additionally, *sativa* has fibres with a higher strength (Figure 3).

Sativa

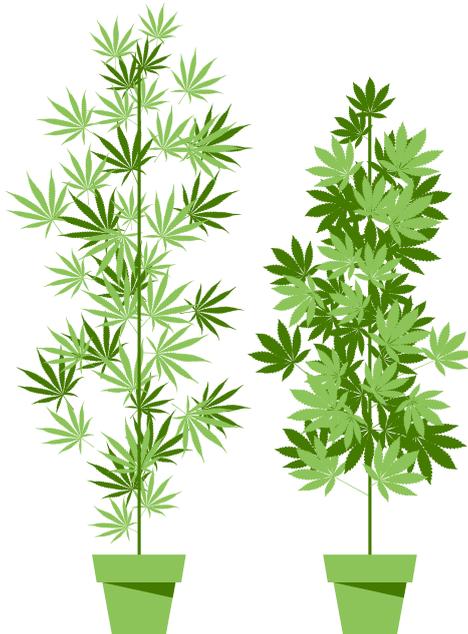
Tall in stature



Narrow leaves

Longer flowering cycles

Better suited for warm climates with a long season



Indica

Short in stature



Broad leaves

Shorter flowering cycles

Suitable for colder climates with a shorter season

Figure 3: Taxonomic differences between *Cannabis sativa* L. subsp. *sativa* and *Cannabis sativa* L. subsp. *indica*.

Over 560 natural compounds have already been identified or isolated from different varieties of *Cannabis*. Among them, there are more than 140 phytocannabinoids – substances that are formed via complex biochemical reactions in the tiny hairs (trichomes) of the plant. Trichomes are visible to the naked eye on the *Cannabis* flower but can also be found on the plant's leaves and stems (Figure 4). Another important group of naturally present substances formed in the trichomes are terpenes, which are associated with the characteristic *Cannabis*-like smell (Kinghorn et al., 2017). The amount of phytocannabinoids formed in *Cannabis* depends strongly on the variety and the environmental conditions during plant growth.

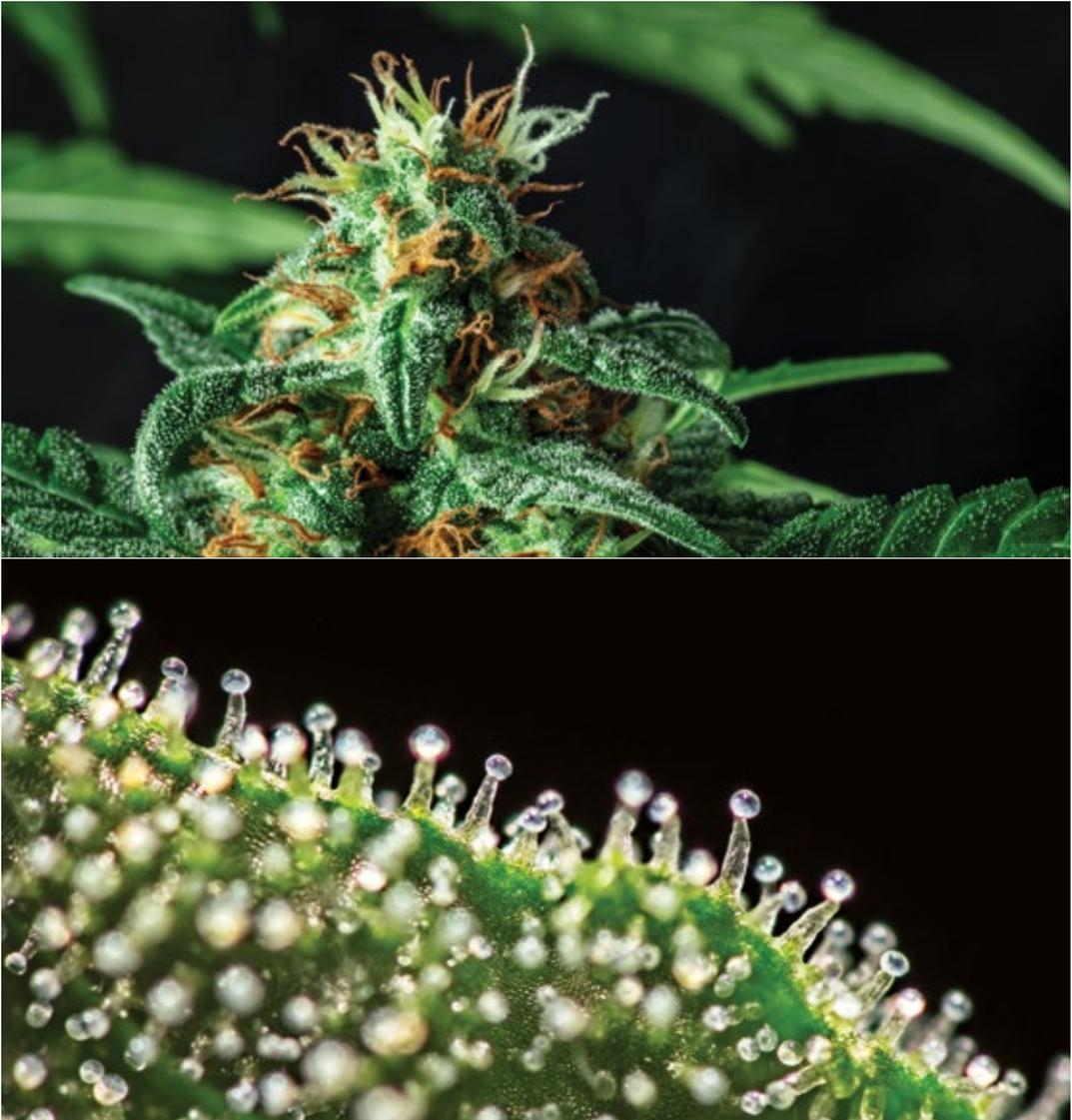


Figure 4: Trichomes – the “bio-factory” of phytocannabinoids and terpenes.

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HOW DO WE GET THE “FULL-SPECTRUM” EXTRACTS WITH LARGE AMOUNTS OF CBD?

Extraction is a separation process where one compound or a mixture is separated from a certain matrix. In the *Cannabis* world, this means the separation of phytocannabinoids like CBD, terpenes, fatty acids and other beneficial substances from the various parts of the plant (flowers, leaves, stems and seeds).

There are many types of extraction process that have been continuously used for decades in the food, cosmetic, pharmaceutical and other industries. For the extraction of *Cannabis*, three types are mainly used:

- cold-pressed extraction,
- organic solvent extraction and
- supercritical carbon dioxide (sCO₂) extraction.

Cold-pressing is used to extract oil from *Cannabis* seeds, which results in an oil rich in essential fatty acids that is suitable for your salad (Figure 5).

sCO₂ is mostly performed for the production of “full-spectrum” extract containing, besides CBD, other phytocannabinoids and terpenes (Figure 5). It is a green technique where the GRAS (“generally recognized as safe”) solvent CO₂ is used, which evaporates at the end of the process. This means that no dangerous solvent residues are present in the final product and that there is no impact on the environment from sCO₂ extraction (Cai et al., 2019).



Figure 5: Cold-pressed hempseed oil and full-spectrum extract rich in CBD and other phytocannabinoids.

TIPS FOR FINDING A HIGH-QUALITY CBD PRODUCT

Like every plant that is used in the cosmetic and/or food industries, products that contain CBD or “full-spectrum” *Cannabis* extracts must be checked for their quality and safety. And what are the most important parameters that determine the quality of a CBD product?

Besides the phytocannabinoid content, several other aspects such as the presence of pesticides, heavy metals and microorganisms together with mycotoxins are crucial to check and confirm the quality of the harvested biomass, “full-spectrum” extracts and final products (Brown et al., 2019).

Phytocannabinoid content analysis provides information about the concentration and consequently the potency of a certain product. Typically analyses determine the concentration of the 12 most relevant phytocannabinoids (Figure 6): CBD, THC, CBG (cannabigerol), CBN (cannabinol), CBC (cannabichromene), THCV (tetrahydrocannabivarin), CBDV (cannabidivarin), CBL (cannabicyclol) and 8-THC (Δ^8 -tetrahydrocannabinol) and acidic forms of CBD, THC and CBG, namely CBDA (cannabidiolic acid), THCA (tetrahydrocannabinolic acid) and CBGA (cannabigerolic acid).

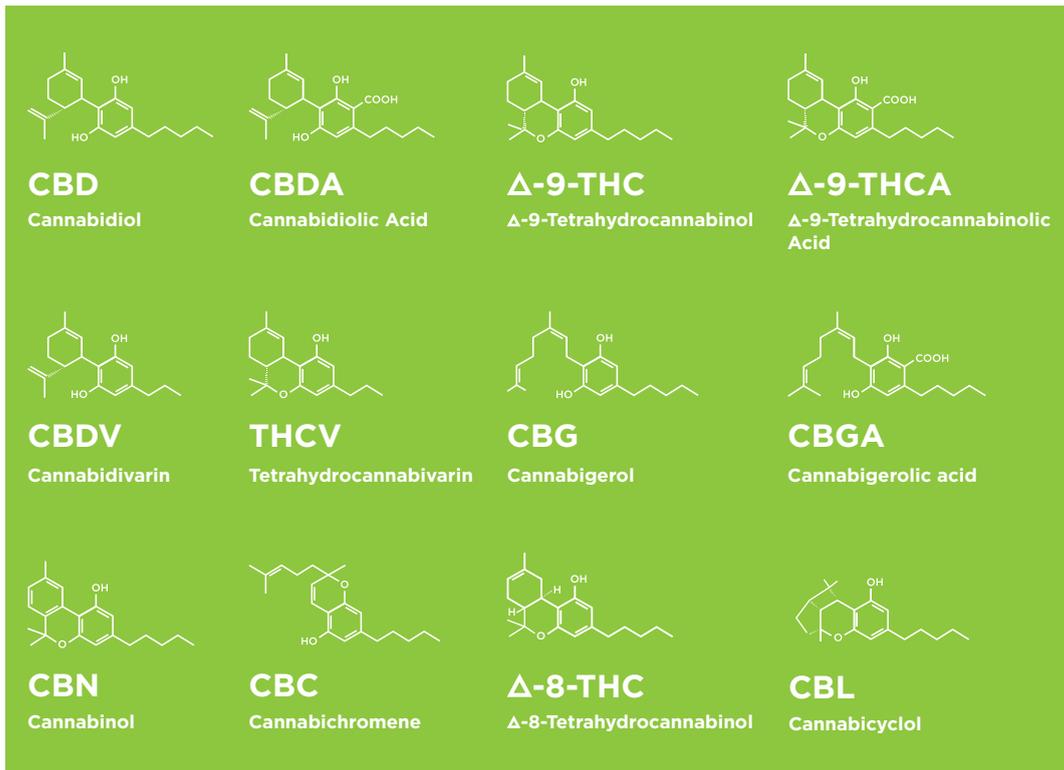


Figure 6: The 12 most relevant and abundant phytocannabinoids in *Cannabis* plants.

Pharmahemp Laboratories® (Figure 7) is an accredited analytical laboratory that provides the service of cannabinoid profiling under the ISO/IEC 17025 standard. The laboratory was also awarded by Emerald Scientific for excellence in cannabis testing for the potency of hemp buds and hemp oil. The analytical method used by Pharmahemp Laboratories® allows the determination of the exact concentration of 12 phytocannabinoids in:

- *harvested biomass material* – this information is important for growers/farmers,
- *various extracts from the Cannabis biomass* – this information is essential for the producers of the extracts and
- *the finished products* – this information is relevant for the producers and consumers of the finished products.



Figure 7: Pharmahemp Laboratories® is an accredited analytical laboratory that performs cannabinoid potency testing.

The Pharmahemp Laboratories® also represents part of an internal Quality Control for the PharmaHemp® company, which offers a variety of high-quality CBD-based products such as CBD oils, pastes, balms and other cosmetic and personal care products.

THE ENDOCANNABINOID SYSTEM AND HOW CBD INTERACTS WITH OUR BODY

Apart from phytocannabinoids derived from the plant, there is also another type of cannabinoid called endocannabinoids, which are formed in the human (or animal) body. In order to explain their roles, it is essential to first understand the basics of biochemistry.

In the human body, there are many proteins called enzymes that are capable of the synthesis and degradation of numerous biologically active substances (Figure 8).

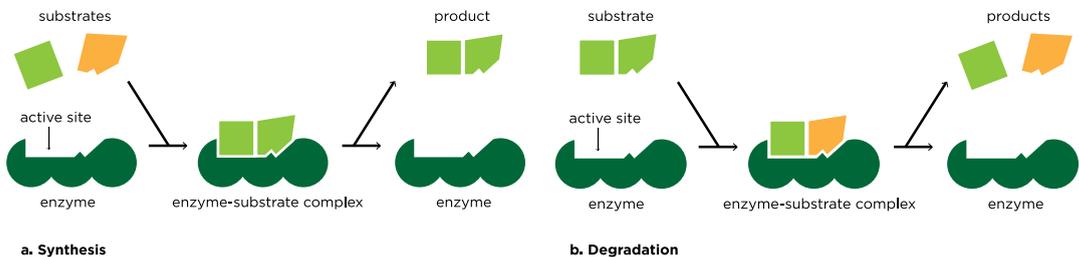


Figure 8: The synthesis and degradation of biologically active compounds.

These bioactive substances can also interact with another special group of protein molecules called receptors. (Figure 9). The interaction between a bioactive substance (or ligand) and a receptor results in a certain physiological effect. For example, endogenous endorphins as ligands interact with opioid receptors, which results in pain reduction. Alternatively, active substances can be exogenous, which means that they are not synthesized but rather introduced into the human body by their consumption. One example is the ingestion of the active pharmaceutical ingredient paracetamol, which interacts with a group of receptors called prostaglandins. This interaction again results in pain relief (Holden et al., 2005).

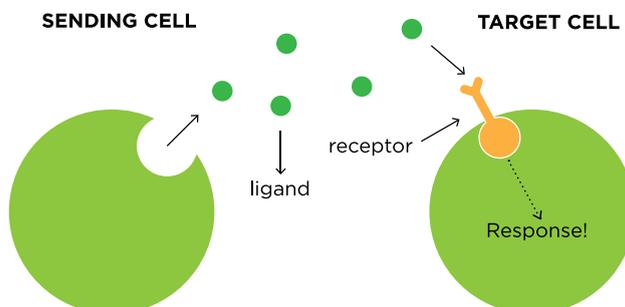


Figure 9: Process of a ligand binding to a receptor.

The endocannabinoid system (ECS), which is present in vertebrates (mammals, birds, reptiles and fish) and invertebrates (leeches, mussels, nematodes and others) is no exception – it consists of enzymes that synthesize and degrade cannabinoids, the cannabinoids as ligands and cannabinoid receptors (Silver, 2019). The term cannabinoids in this case refers to both endocannabinoids and phytocannabinoids. The primary purpose of the ECS is to provide homeostasis for many metabolic functions, such as neurotransmission, inflammation and energy modulation (Jarvis et al., 2017). There are two main cannabinoid receptors – CB1 and CB2 receptors – which differ in their location in the human body and in the effects that they trigger. CB1 receptors are primarily present in the brain and central nervous system but can also be found in lower amounts in other tissues. They modulate mood, appetite, memory, motivation and pain. CB2 receptors are more abundant in the peripheral tissues, especially in various immune cells, hence they are mainly associated with a role in immunity (Mackie, 2008; Reekie et al., 2018; Figure 10).

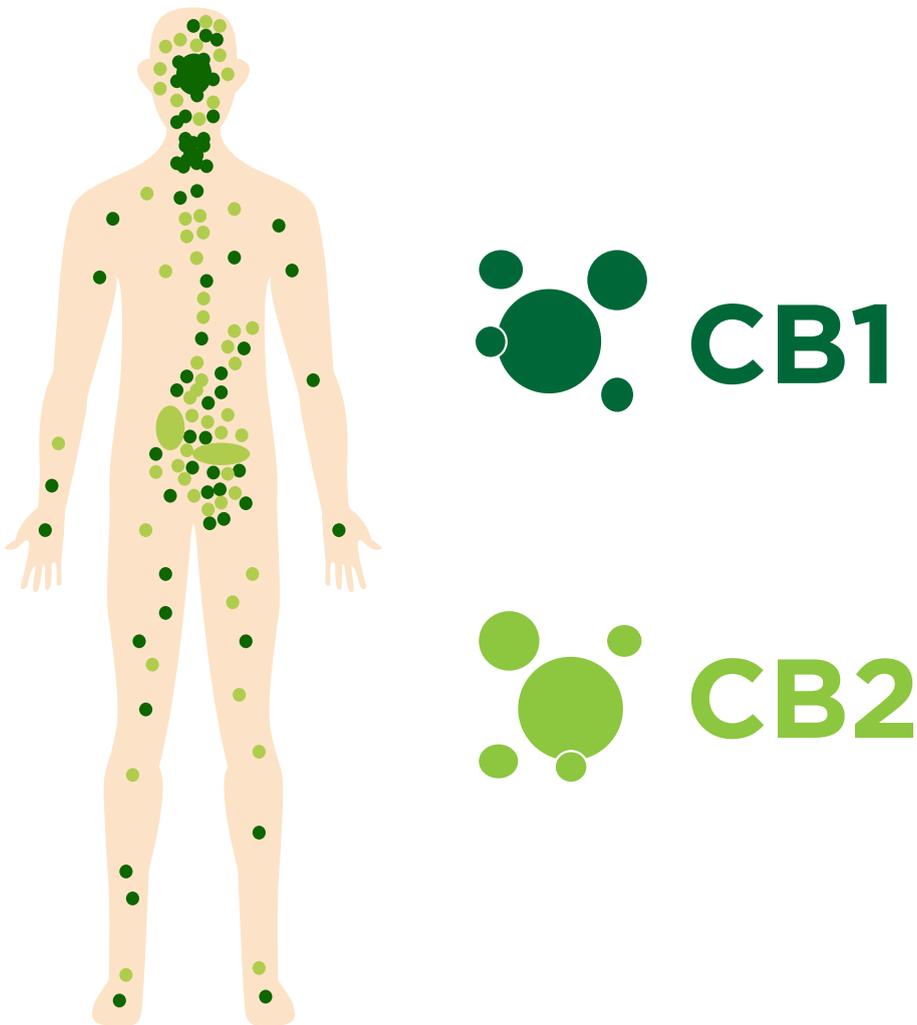


Figure 10: Locations of CB1 and CB2 receptors in the human body.

Endocannabinoids, CBD and THC – what’s the difference?

Endocannabinoids are bioactive substances that are formed and degraded in the human body by complex biochemical reactions with many enzymes involved. So far, there are several known endocannabinoids such as anandamide (AEA) and 2-archidonoyl glycerol (2-AG). Both AEA and 2-AG interact with the CB1 and CB2 receptors, though with a varying affinity towards each receptor. Due to certain similarities in the structure and spatial distribution of molecules between endocannabinoids and phytocannabinoids, the latter also interact with CB1 and/or CB2 receptors.

The affinity towards receptors also differs considerably among different phytocannabinoids, which results in varying physiological effects. For example, the psychotropic effect of THC is caused by an interaction with the CB1 receptor. On the contrary, CBD interacts with the CB2 receptor and does not result in any psychotropic effect, though it is related to several other beneficial effects, as will be revealed below. To make the story even more complex, CBD also affects the interaction between THC and the CB1 receptor, which results in decreased psychoactive effects of THC (Kinghorn et al., 2017).

The cannabinoids have also been shown to affect other systems in our body through interaction with opioid, serotonin and nuclear receptors and transient receptor potential (TRP) ion channels. Studies have confirmed that the control of the body temperature and the transfer of pain relief is partially related to the interaction of cannabinoids with TRP channels (Pacher et al., 2006). Based on all these interactions, the involvement of cannabinoids in physiological processes such as appetite and pain sensation, the control of chronic pain, metabolism, mood and the regulation of immune cell functions is continuously studied and to some extent already confirmed (Watkins, 2018). The most-studied cannabinoid (CBD) is discussed in detail in the next chapter.

THE EFFECTS OF THE “FIRST AND FINEST” – CBD

The discovery of the endocannabinoid system triggered an exponential growth in research studies investigating its physiological functions and the effects that endocannabinoids and phytocannabinoids trigger in humans and animals. In general, there are various types of studies for the assessment of such effects:

- studies conducted *in vitro* using cell lines;
- studies performed on animal models such as mice and rats;
- clinical studies, where the effects are studied on healthy volunteers and those with a certain condition, which is being targeted in the trial.

The vast number of *in vitro* and animal studies are oriented towards the most relevant phytocannabinoids with CBD taking the first place. CBD is the most abundant phytocannabinoid in the majority of Cannabis plant varieties and it has several beneficial effects, not only confirmed in the petri dish or on animals but also in clinical trials (studies on humans).

The confirmed effects of CBD are anti-inflammatory, anti-oxidative, anti-emetic, anti-psychotic, anti-convulsant and pain relief effects (Maurya et Velmurugan, 2018). In addition, Bhattacharyya et al. (2010) reported that pre-treatment with CBD and subsequent THC administration reduces the psychotic effects of the latter. The mechanism of reduced psychoactivity on a molecular level was explained in the previous section.

Furthermore, studies where CBD was used to treat psychotic symptoms of schizophrenia suggest an improvement of symptoms and fewer side effects caused by treatment with amisulprid, which is one of the most effective medicines for this disease. Promising results were also reported in a study by Chagas et al. (2014), where treatment with CBD resulted in an improved quality of life for patients with Parkinson's disease. The factors that were assessed in this study included mobility, activities of daily life, communication and similar.

The most-studied condition where CBD was used in clinical trials are various types of epilepsy such as Dravet syndrome, Lennox-Gastaut syndrome and others. Although reported studies differ in population size, the age of the patients, the dose of CBD and the combination of CBD with regular medications that patients received, the outcomes are similar. The seizure frequency was in general significantly reduced, by as much as 50% compared to the control groups (Iffland et Grotenhermen, 2017).

A special type of epilepsy is refractory epilepsy or drug-resistant epilepsy, which has been defined as the "failure of adequate trials of two tolerated, appropriately chosen and used antiepileptic drug schedules (whether as monotherapy or in combination) to achieve sustained seizure freedom" (Kwan et al., 2010). A recent study by Neubauer et al. (2018) revealed promising results for CBD as an add-on or adjuvant therapy for children with refractory epilepsies. Adjuvant therapy is a special type of therapy that is given in addition to the primary therapy with a certain medicine in order to maximize the overall treatment efficiency. About half of 66 patients receiving add-on therapy had a significant improvement in terms of seizure burden, among which 21% became seizure-free. Additional positive effects such as behaviour and better sleep (in 7), better motor functions and increased alertness (in 5), better cognitive functions, appetite, increased joyfulness and better speech (in 3), better communication and better eye-to-eye contact (in 2) were also observed.



CBD Dosing

In the European Union, CBD has the status of a novel food, while elsewhere dietary supplements with CBD are freely available on the market, for example, in some US states. Under certain conditions, CBD products can also be sold in shops in the UK, where the authorities have said that 70 mg of CBD is the recommended maximum daily intake for this versatile cannabinoid.

As an example, let's look at some general guidelines and how consumers use CBD in the UK, where CBD products are very popular.

Each and every one of us is different and therefore also the response of consumers to CBD products might vary. For example, if the user is extremely sensitive to any additives, foods, cosmetics or medicines, he/she is advised to start with low CBD doses – up to 10 mg per day. For those who are not so sensitive, the recommended starting daily dose is 20 to 30 mg. Actually, the dosage should be determined according to body weight, which in this case is approximately 0.5 mg CBD per kg of body weight per day. This value corresponds to a daily dose of 30 mg of CBD for a 60-kg person.

It is recommended that the user persists for at least 10 days with the initial daily dose. If he/she does not experience the desired effect, he/she can double the dose and continue with this amount for the next 10 days. The table below shows an example of the dosing of the most popular CBD drops. If the effect is still not felt by the user, continuing to increase the dose as shown in the table below (a higher dose every 10 days) is suggested. Daily doses can be used in any way: either as a single dose in the evening or the dose being evenly distributed throughout the day (morning, mid-day and evening).

Due to the different response of the human body to the use of CBD, the dose that solves the problem for an individual can be different. Some people successfully eliminate their problems by taking 25–30 mg of CBD per day, while some only get better at higher doses, e.g., 60 mg per day. The dose can always be increased or decreased during use, as the level of stress in our body and other symptoms fluctuate – this is a completely natural phenomenon. Therefore, when taking CBD products, it is recommended that users record the status and any observed changes in time. If CBD is used for general well-being, the user can monitor, e.g., changes in stress levels, mood, and sleep quality. It is necessary to take into account the fact that changes when taking CBD products are sometimes barely perceptible, which is especially common during the initial stages of use, when the user is trying to find the dose that will be most suitable and effective for him/her. For CBD products, it is also common that users experience changes in chronic problems such as anxiety, headaches, stress and problems with prolonged use.

Although many studies have already confirmed the safety of CBD, caution is important. For example, in the case of the concomitant use of medication, experts advise consulting a personal physician before using CBD products. Experts do not recommend taking daily doses of 70 mg CBD or more, or recommend that the user consults a personal physician before taking such high doses. Due to the lack of clinical studies, use is currently not recommended for pregnant women, nursing mothers and children unless the personal physician considers the benefit-risk assessment of CBD to be positive.

Table with examples of administration of CBD drops:

	3% DROPS 	5% DROPS 	10% DROPS 	12% DROPS 	15% DROPS 
CBD content in a 10 ml bottle	300 mg	500 mg	1000 mg	1200 mg	1500 mg
Product suitability	Sensitive initial users	Sensitive and less sensitive initial users	Less sensitive initial users and experienced users	Less sensitive initial users and experienced users	Experienced users
Starting dose	0.25 ml 1x daily (=7.5 mg CBD/day)	0.25 ml 1x daily (=12.5 mg CBD/day)	0.25 ml 1x daily (=25 mg CBD/day)	0.25 ml 1x daily (=30 mg CBD/day)	0.25 ml 1x daily (=37.5 mg CBD/day)
1st increase of the dose - after 10 days	0.25 ml 2x daily (=15 mg CBD/day)	0.25 ml 2x daily (=25 mg CBD/day)	0.25 ml 2x daily (=50 mg CBD/day)	0.25 ml 2x daily (=60 mg CBD/day)	0.25 ml 2x daily (=75 mg CBD/day)
2nd increase of the dose - after 10 days	0.25 ml 3x daily (=22.5 mg CBD/day)	0.25 ml 3x daily (=37.5 mg CBD/day)	0.25 ml 3x daily (=75 mg CBD/day)		
3rd increase of the dose - after 10 days	0.5 ml 2x daily (=30 mg CBD/day)	0.5 ml 2x daily (=50 mg CBD/day)			

CBD has no negative side effects

The review paper by Bergamaschi et al., (2011) reports on more than 20 clinical studies where CBD was administered to people in varying daily doses (from a few mg to as much as 1500 mg per day). No effects on the monitored psychomotor and physiological parameters such as blood pressure, heart rate and body temperature were reported in any of the reviewed studies. Even the chronic use of high CBD doses has been reported as well-tolerated. The good safety profile of CBD was also confirmed by the World Health Organisation in the WHO Critical report on CBD (2018). Regardless, CBD has the potential to cause some interactions with other drugs by interfering with hepatic drug metabolism. Therefore, consultation with a personal doctor about the combination of CBD with medicine is highly recommended for every patient.

CONCLUSIONS

CBD can be a part of our lives in many different ways. Products on the market that contain this precious cannabinoid are available in various forms – you can find CBD in cosmetics and personal care products, drinks, chocolates and even food supplements in the form of gummies. These products are highly popular among people facing various physiological and psychological problems, as well as those who want to maintain their well-being.

The use of CBD products is in general safe with no serious side effects expected. However, the producer and quality of the product should be always checked in order to avoid any potential unwanted events.

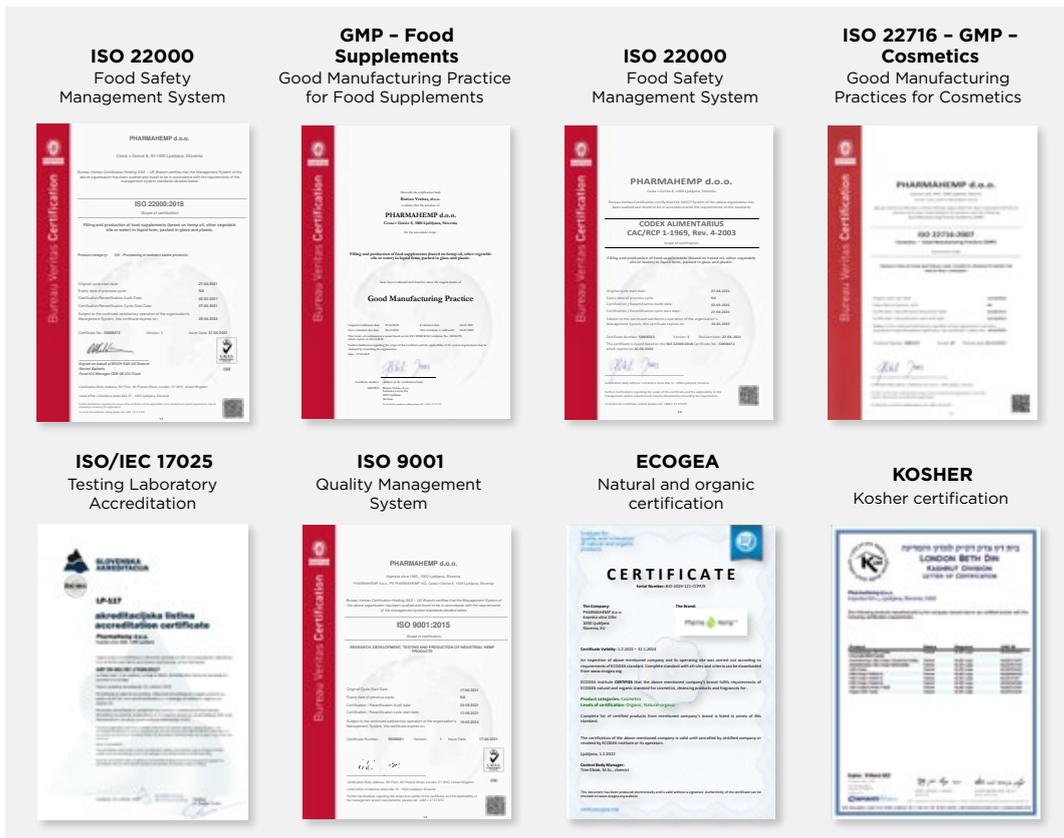
We hope that this guide has made the science behind the cannabis plant a little clearer and that it will help you find the right CBD product that will fulfil your expectations.

ABOUT THE PHARMAHEMP COMPANY AND THE AUTHOR

PHARMAHEMP® is a trusted European producer and supplier of superior full-spectrum CBD products providing a healthier everyday life for everyone.

The efficiency, safety and quality of our products and services are our main priority. We ensure the high quality of our products through continual analyses of the ingredients and finished products in an accredited in-house and 3rd party laboratories. We have proven the efficacy and safety of CBD through participation in several clinical and research studies. The collaboration with renowned national and international institutions is an ongoing process as we are fully aware that there are many potentials of CBD that are still out there to be discovered.

The reliability and trust in our work is also constantly monitored. We are being audited by independent certification agencies on a regular basis. PharmaHemp® holds several certificates related to the quality of production processes, the products themselves and the overall management system of the company.



Dr. Marjeta Česen, CHIEF REGULATORY AFFAIRS OFFICER



Marjeta graduated from the Faculty of Pharmacy at the University of Ljubljana and received a Ph.D. in Ecotechnology at the Jožef Stefan International Postgraduate School. After her Ph.D. studies, she worked as a postdoctoral student at the Department of Environmental Sciences at the Jožef Stefan Institute. During her career as a scientist in Slovenia and abroad, she has been involved in various national and EU projects, focusing on the chemical analyses and toxicity of environmental and food contaminants. She has published her work in a number of peer-reviewed scientific papers. In addition, she has a great track record of writing successful proposals for R&D projects. In 2018, she joined the PharmaHemp® company, where she primarily incorporates the knowledge from her

studies and working experiences into compliance with the legislation, new product development and various research project proposals. She has a wealth of expertise in navigating global regulations on *Cannabis*-related cosmetics, food supplements and medicinal products.

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Warning:

None of the information presented in this e-manual is intended to diagnose diseases. Readers use all the information at their own risk. Any errors or omissions are unintentional and the author is not responsible for them.

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