

Next generation pharmaceuticals

Explore the therapeutic
potential of cannabinoids

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with confidence





Executive summary

Early-stage drug development plays a critical role in expanding therapeutic possibilities for patients globally, especially for conditions that are difficult to manage or treat. To address unmet patient needs and develop next generation drug products, pharmaceutical manufacturers are increasingly exploring novel molecules, like cannabinoids.

Cannabinoid actives – such as cannabidiol (CBD) – hold huge potential in pharmaceutical research and development. Powered by a favorably evolving regulatory landscape and promising scientific findings indicating their therapeutic potential in central nervous system (CNS) diseases, pain disorders, cancer and more, cannabinoids are anticipated to break new boundaries in drug innovation.

This whitepaper explores the latest science-based benefits behind cannabinoids – with a focus on CBD – and new opportunities for innovation in the pharmaceutical space. It will then cover how DSM is supporting early-stage drug development in this groundbreaking field of research as a science-led, co-innovation partner to the pharmaceutical industry. The paper does not imply the administration of cannabinoids without in-depth clinical research demonstrating the safety and therapeutic benefits of these molecules or local regulatory clearance.

What are cannabinoids?

Cannabinoids are a group of bioactive compounds found in the *Cannabis sativa* plant. The cannabis plant naturally produces an estimated 80-100 cannabinoids; however, CBD and tetrahydrocannabinol (THC) are the two major cannabinoids and present in the plant in much higher quantities than other cannabinoids.

While THC produces the “high” associated with marijuana use, CBD does not induce any psychoactive effects – this means less risk of addiction and misuse of CBD and also less potential side effects, making it an attractive candidate for innovation across the pharmaceutical space.

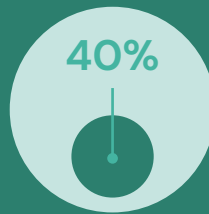
CBD is generally extracted from industrial hemp due to its high CBD concentrations and low THC content; however, it can be produced via synthetic and biosynthetic routes too. To date though, most approved CBD-based drug products have been developed using natural, plant-based CBD, which is supported by significant safety data.



The rising relevance of rare cannabinoids

Rare cannabinoids – also referred to as minor cannabinoids or CBx – are revealing new therapeutic avenues that offer great potential for patients too. Rare cannabinoids make up less than 1% of the hemp biomass and because they are present in much lower concentrations than the other major molecules, CBD and THC, it can be technically and commercially challenging to extract them. For this reason, and also because they are generally less well-known, research has been more limited in this field, until recently.

200 million
people use cannabis globally



of users do so for medical reasons¹

CBD and the endocannabinoid system

Renewed interest in cannabinoids follows the discovery of the endocannabinoid system (ECS) in the early 1990s. The ECS is a complex cell signaling network present throughout the body that helps to regulate and balance critical bodily functions, including metabolism and appetite, mood and anxiety, immunity, and pain perception. CBD is thought to bind to cannabinoid receptors in the ECS – via which it exerts its multiple effects. This makes the ECS one of the most promising targets for new therapeutics and is the reason why research in the field of CBD is increasing rapidly.

The history of CBD

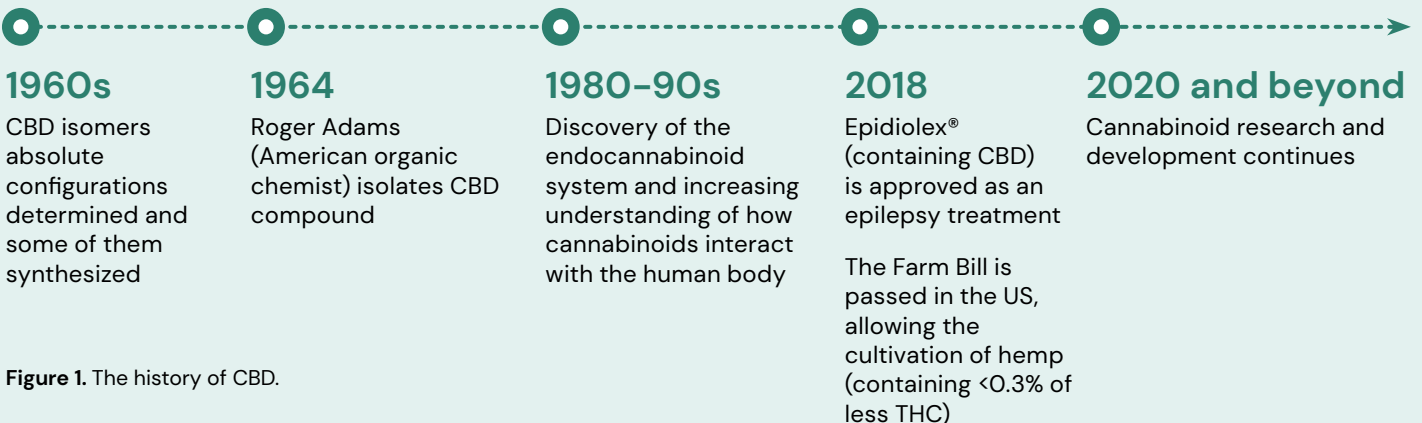


Figure 1. The history of CBD.

The therapeutic potential of CBD

There are a myriad of opportunities to expand treatment options and better support patients through CBD-based drug discovery and development. The science behind CBD is growing rapidly, with 200+ clinical trials (including 30+ late-stage clinical trials) currently exploring the therapeutic capacity of this molecule.²

In the US and Europe, the three most widely used cannabinoid pharmaceuticals are Sativex®, Epidiolex® and Dronabinol (including brand name formats). The way the market is moving, the approval of new cannabinoid therapeutics is expected across the world.

An increasing bank of evidence demonstrates the promising potential of CBD in areas including CNS diseases (mainly epilepsy), pain disorders, anxiety, cancer and more. There is a major opportunity to advance CBD science and developments in prevalent conditions where the molecule is thought to have significant therapeutic value, like pain, anxiety and sleep disturbances. These conditions affect tens of millions of people globally each year but there are still no approved cannabinoid-based pharmaceuticals for their treatment.

Additionally, research and development related to rare cannabinoids – such as cannabigerol (CBG) and cannabichromene (CBC) – is just beginning and is expected to be a growing focus for innovation in the coming years.

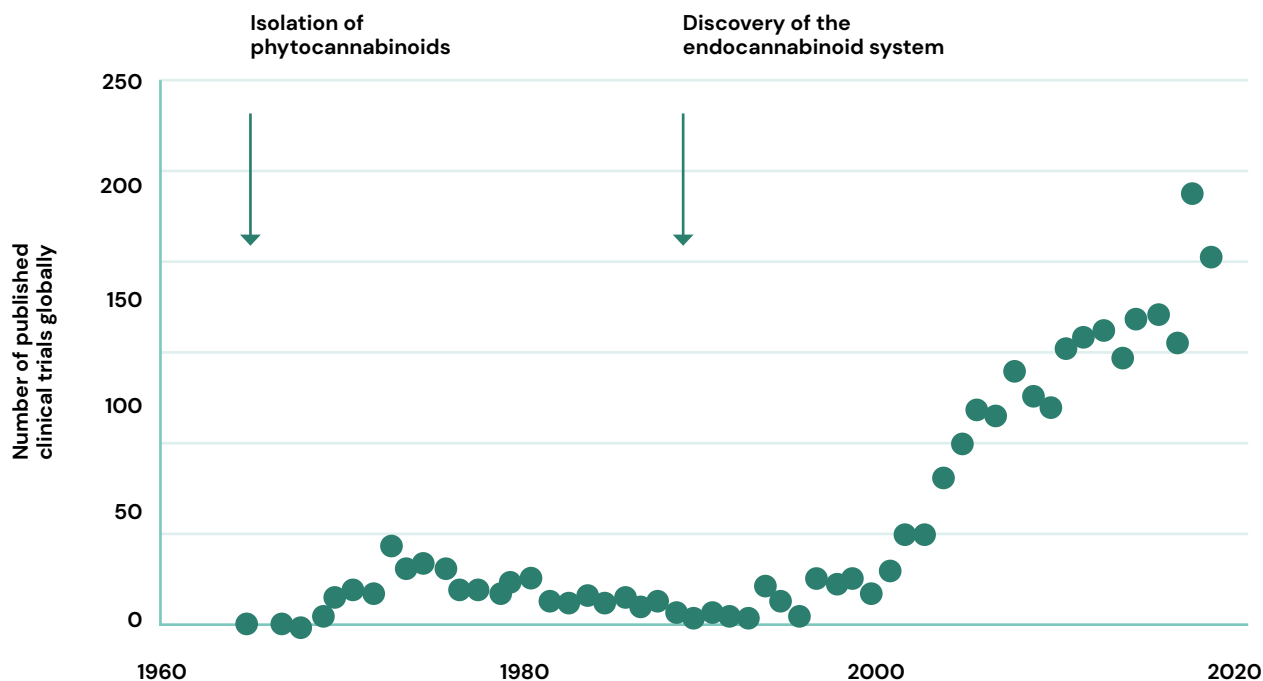


Figure 2. Trends in the clinical research of cannabinoids.²¹

Expert view



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1 Why is CBD an attractive therapeutic candidate?

Many conditions, like chronic pain and mood disorders, are difficult to treat because symptoms are unique to each individual or the treatment itself has unpleasant side effects – nausea and vomiting are common side effects of cancer therapies, for instance. This is creating demand for novel treatment approaches that address patient needs without majorly affecting their quality of life.

In recent years, the scientific community has shown interest in CBD due to its promising therapeutic efficacy and favorable safety and tolerability profile in humans. One example of where CBD could bring benefits is in pain management, where healthcare professionals often rely on prescribing opioids as a relief for chronic pain. Although opioids are considered safe for the short-term treatment of acute pain, individuals who require longer-term therapy are at high risk of developing an opioid dependence (or addiction), which can lead to negative physical and mental effects. For these reasons, doctors and patients alike are increasingly searching for innovative solutions that will help to manage chronic pain more safely.

2 How can pharmaceutical manufacturers turn insights into purpose-led drug products?

The market for pharmaceutical products that leverage the ECS remains largely untapped. There are still just a handful of approved pharmaceuticals on the market which target the ECS, despite its emerging potential in many physiological functions and role in a vast number of common illnesses. One of the main reasons for this was restrictions related to research in this specific field, which have now been mostly lifted.

The first step in creating purpose-led drug products is generating supporting science. Investment in early-stage drug development is critical in the cannabinoid space, to uncover new pharmaceuticals that will expand treatment options and benefit patient health. This will involve the launch of clinical trials to establish which cannabinoids (at which dosages and ratios) work safely and effectively for different conditions and patients.

3 What is the pipeline for future CBD research specifically?

The next approved CBD pharmaceuticals are likely to be for indications like pain management, cancer, mood disorders and spasticity. Pain is the most common condition of those treated with cannabis. However, no single cannabinoid drug has received widespread approval for the treatment of pain. When an approved drug does become available, this will have a large impact on the global market for pain medications.

Sativex® (CBD + THC) – which is marketed in over 30 countries in Europe – is currently undergoing phase III trials for symptomatic release of spasticity in multiple sclerosis in individuals who have not responded to other therapy. The latest evidence could enable FDA approval and subsequent marketing of the drug to patients in the US too – reaching as many as 450,000 individuals a year. Research shows that Sativex® is also beneficial in patients suffering from chemotherapy-induced nausea and vomiting.³

Other ongoing late-phase clinical trials are focused on conditions where cannabis is not currently widely used, including ocular, dermal and behavioral conditions (like Tourette's syndrome). As research continues and expands, there is a large likelihood that clinical trials will reveal new therapeutic uses for CBD which have not been considered and explored to date.

The science-based benefits of CBD: clinical evidence

1 Epilepsy and CBD

CBD science is strongest and most established in CNS disorders, with 50% of cannabinoid research focusing on this area.² CNS disorders encompass a broad category of neurological conditions including epilepsy, Alzheimer's disease, Parkinson's disease and mental illnesses. In recent years, the scientific community has shown growing interest in CBD in this field due to its good safety profile, anti-convulsant effects^{4,5} and neuroprotective properties⁶ in several neurodegenerative diseases, including epilepsy, Parkinson's^{7,8} and Alzheimer's.^{9,10,11} The molecule's neuroprotective activity appears to be linked to its anti-inflammatory and antioxidant properties.^{12,13}

There has been significant research into the potential of CBD as an epilepsy treatment – especially in patients that do not respond to conventional anti-epileptic drugs. Epilepsy is the most common

neurological disorder – affecting more than 50 million people worldwide.¹⁴ It is characterized by recurrent seizures, but up to 70% of people diagnosed with epilepsy could live seizure-free if properly diagnosed and treated.¹⁵ CBD has been investigated for its anti-convulsant effects in this field.^{16,17,18} Several studies have confirmed its efficacy in the management of epileptic seizures, especially in children^{19,20} – leading to the launch of Epidiolex® for the treatment of severe, orphan, early-onset, treatment-resistant epilepsy syndromes.

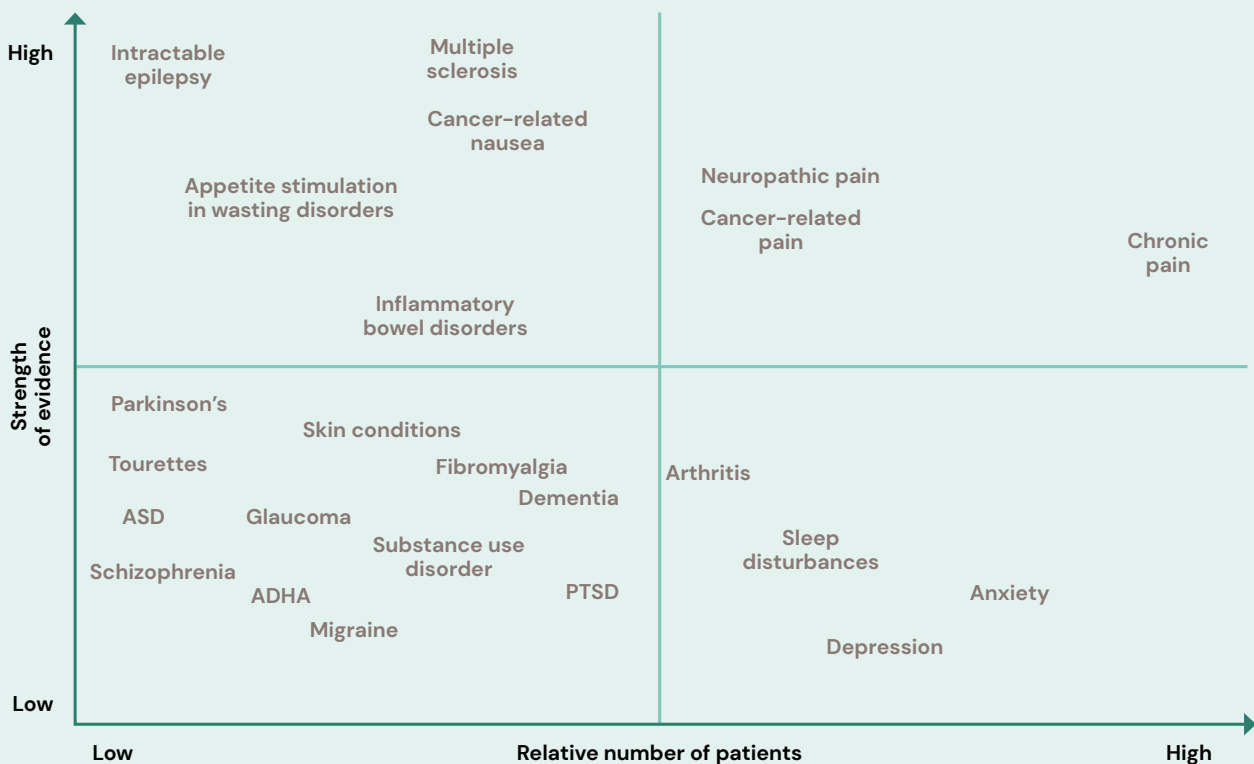
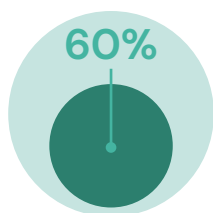


Figure 3. Evidence supporting cannabinoid efficacy* in a number of therapeutic areas – the strength of evidence is strongest in CNS disorders, like epilepsy.²¹

* Summary of the strength of the current evidence relative to the estimated number of patients using cannabis-based medical products for a certain condition. Includes real world evidence, observational studies and RCTs. For some of the therapeutic applications, such as intractable epilepsy, CBD has been used as an intervention, whilst for others, such as cancer-related nausea and chronic pain, current evidence might derive from studies exploring medical marijuana or CBD+THC combinations.

2 Pain disorders and CBD

Globally, 1 in 10 people develop chronic pain every year and its prevalence is as high as 20–25% in some countries and regions.²² Aside from the pain itself, chronic pain significantly impacts quality of life due to disruptions to sleep and mood. 60% of CBD consumers in the nutraceutical space already use CBD to manage pain.²³ However, pain disorders are predicted to be a big focus for future CBD innovation in the pharmaceutical market too, with a number of ongoing studies examining the effects of the molecule in a variety of pain-related indications, including cancer-related pain, musculoskeletal pain and fibromyalgia.



60% of CBD consumers in the nutraceutical space already use CBD to manage pain.²³

Explore the promising potential of CBD in the management of chronic pain.



Watch the video

3 Cancer and CBD

Cancer is a complex disease influenced by genetics and environmental and lifestyle factors. This makes most forms of cancer difficult to treat and despite advancements in medical care, patients diagnosed with cancer still experience many unwanted and distressing symptoms, both from the disease itself and its treatment. Nausea and vomiting, loss of appetite and pain are common side effects of cancer and cancer treatments, like chemotherapy and radiation, and remain an ongoing challenge to manage and significant burden for many patients.

There are no studies to date confirming that CBD alone eases the side effects of cancer or cancer therapy, but the molecule is thought to have some potential in this field and there are already some cannabinoid-based drugs on the market prescribed to help relieve symptoms caused by chemotherapy. Nabilone – sold under the brand name Cesamet® – is a synthetic cannabinoid that mimics THC. It is FDA-approved and licensed for the treatment of severe sickness and nausea from chemotherapy if other anti-sickness drugs are unable to control it. Whereas Nabiximols – also marketed as Sativex® – is a THC and CBD spray showing promise in treating cancer pain and subject to ongoing research.^{24,25}

CBD is demonstrating potential as a cancer drug too. A number of pre-clinical *in vitro* and *in vivo* studies suggest that CBD may have anti-cancer activity in a wide variety of cancer types – including a role in cancer cell death and blocking cancer cell growth. In a mouse model of breast cancer, CBD shows pro-apoptotic and anti-proliferative activity in many breast cancer cells.²⁶ Similar effects have been demonstrated in glioma (a common brain malignancy), pancreas, prostate, colorectal and lymphoma cancers too.^{27,28,29,30} It is also suggested that CBD affects the tumor environment by stopping the development of blood cells that feed the cancer, preventing its ability to spread and reducing inflammation.^{31,32} The effect of CBD appears to be milder on normal cells in the same tissues or organs as the cancer too, which has attractive therapeutic potential.^{33,34,35}

4 Mood disorders and CBD

Approximately 5-10% of the global population suffer from anxiety-related disorders.³⁶ Depression is another common illness, estimated to affect 280 million people worldwide.³⁷ CBD is generating interest in this space due to its potential anti-depressant, anti-psychotic^{38,39} and anxiety-relieving^{40,41,42} properties. Recent research indicates that CBD might significantly reduce the severity of two important types of anxiety disorder – obsessive-compulsive disorder (OCD)⁴³ and post-traumatic stress disorder (PTSD).^{44,45} Preclinical trials have also highlighted antidepressant-like effects of the molecule in several animal models of depression.^{46,47,48,49} Additionally, CBD is already used by patients to manage their psychiatric symptoms, despite up to 50% of them not reporting this to their doctors.⁵⁰

Considering that evidence from preclinical studies suggests anti-depressant effects and well-conducted randomized-controlled trials in other health conditions have demonstrated anti-psychotic and anxiety-reducing effects, as well as being generally safe and well-tolerated with limited abuse liability, multiple reviews conclude that CBD may have an important role in the treatment of mood disorders in the future.^{51,52}



Novel therapeutic avenues for CBD innovation: immune modulatory agent

As well as having a potential positive role in a number of health conditions, CBD has capacity as a novel immune modulatory therapeutic agent too, i.e. it can regulate immune responses.⁵³ The normal immune system is modulated and regulated by antigens, which induce the production and secretion of proteins, including cytokines (like interleukin-1) and chemokines, from immune and non-immune cells. In addition to antigens, mediators of the brain-immune axis, like CBD, are also capable of controlling the immune response.

In recent years, CBD has become one of the most widely studied cannabinoids due to its possible immunomodulatory properties, with existing data demonstrating it as an immuno-suppressive and anti-inflammatory API.^{54,55,56} Research shows that CBD helps to modulate a variety of immune cell functions in humans and animals – ranging from suppression of resistance to infection to enhancement of cytokine production by macrophages.^{57,58,59,60,61}

These potential immunomodulatory and anti-inflammatory properties have made CBD an attractive therapeutic compound for a number of diseases where excessive inflammation is a challenge.^{62,63} As such, further research and development of CBD as a state-of-the-art immunomodulatory therapy is anticipated.

- 1 Immunomodulators** are agents that are used to regulate or normalize the immune system. CBD regulates the immune response.
- 2 Immunosuppressants** suppress or reduce the strength of the body's immune system. CBD is demonstrated to modulate the production and function of pro-inflammatory cytokines, T cells and chemokines.
- 3 Anti-inflammatories** help to reduce inflammation in the body by blocking the agents that cause it. CBD has shown anti-inflammatory effects in several conditions, including arthritis.^{64,65}



Expert view



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1 How does CBD modulate the immune system?

Inflammation is a normal response by the immune system triggered by factors including pathogens, damaged cells and toxic compounds. Usually, acute inflammatory responses are eventually resolved (via the coordinated actions of various immune and non-immune cells) and tissue homeostasis returns. However, uncontrolled inflammation can become chronic – contributing to a number of diseases.

CB1 and CB2 receptors are found throughout the body and immune system.⁶⁶ The immune-suppressive effects of CBD occur due to the molecule's ability to directly inhibit target cells in the immune system, such as T cells, microglial cells and innate cells. Through such actions, CBD reduces the levels of pro-inflammatory cytokines, inhibits T cell proliferation, induces T cell apoptosis and decreases the migration and adhesion of immune cells.⁶⁷

For example, IL-6 is a proinflammatory cytokine produced by many cell types, predominantly innate cells. Many studies have shown that circulating IL-6 is readily inhibited by CBD in inflammatory models, including diabetes⁶⁸, asthma⁶⁹ and pancreatitis⁷⁰ – thus reducing proinflammatory signaling.

In addition, CBD anti-inflammatory activity has been shown to be antagonized by both a selective CB2 antagonist and arachidonoyl-ethanolamide (AEA), an endogenous CB2 receptor agonist – confirming its anti-inflammatory effects.⁷¹

2 What does this mean for innovation in the pharmaceutical space?

Growing evidence for the role of the ECS in immune regulation predicts that the components of this system will be explored in the future for the treatment of chronic diseases and inflammatory conditions.

For example, CBD may be a promising immunomodulatory therapy for the treatment of autoimmune conditions, like multiple sclerosis, type 1 diabetes or rheumatoid arthritis, due to its immunosuppressant properties. In these conditions, CBD may help to stop the body's hyperimmune response against healthy organs and tissues.

CBD bioavailability: the challenge

Due to its therapeutic potential, CBD is being pursued as a treatment for multiple conditions, usually by oral delivery. Oral drug delivery is the most common route for drug administration and preferred by patients and formulators alike. However, many cannabinoids – including CBD – have low and variable oral bioavailability, making the formulation of CBD drugs challenging.

Low oral bioavailability

Oral bioavailability is a measure of the quantity of drug absorbed into the systemic (blood) circulation following oral administration of the drug. The oral bioavailability of CBD has been shown to be very low in humans (6%)⁷² as a result of incomplete absorption in the gut and significant pre-systemic elimination by the liver.

1 Incomplete gastrointestinal absorption

Cannabinoids, including CBD, have very low solubility in water and high lipophilicity, meaning a significant fraction of the dose may be lost in the gut due to incomplete absorption.

2 Extensive hepatic pre-systemic metabolism

CBD passes through the liver via the portal vein when administered orally. It then enters the systemic circulation where it travels to the site of action. Although most drugs undergo some extent of first pass metabolism in the liver – whereby the concentration of the drug is reduced by enzymatic metabolism – it is estimated that up to 75% of orally absorbed CBD is removed by hepatic metabolism.⁷²

Variable oral bioavailability

Additional factors that impact the bioavailability of CBD include delivery format, dosage, food intake and individual patient response. For example, studies show that plasma concentrations of CBD are increased faster following intravenous administration, smoking or inhalation of the drug because these routes by-pass initial metabolism – hence bringing higher bioavailability.^{73,74,75}

Regarding the impact of food intake, the solubility and absorption of CBD generally increases when co-administered with a high-fat meal, because lipophilic molecules can dissolve in the fat content of food.^{76,77,78} As individuals have different diets and mealtimes, this leads to considerable variability in the oral bioavailability of CBD and increases the potential for sub-optimal CBD efficacy or adverse effects.



up to
75%

of orally absorbed CBD is removed by hepatic metabolism⁷²

Optimizing CBD formulations

The use of CBD in the treatment of medical conditions is predicted to be game-changing, but the molecule can bring some significant formulation challenges – specifically related to oral bioavailability. This is creating new opportunities to optimize CBD-based formulations and enable the ingredient to fulfill its full potential as a therapeutic agent. Furthermore, boosting the bioavailability of CBD might mean that a smaller quantity of the drug is needed to be effective; reducing dosage for the patient, limiting the risk of side effects associated with drug-drug interactions and lowering costs.

Expert view



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1. How does CBD bioavailability influence patient compliance?

Because the oral bioavailability of CBD is so low, the active ingredient is needed in a large quantity to have the necessary therapeutic effect. Increasing the dose might help overcome these issues, but even though CBD has a favorable toxicity profile, this approach could potentially result in increased risk of drug-drug interactions and undesirable side effects; affecting patient compliance as a consequence.

2. What alternative routes to oral administration are being explored in CBD innovation?

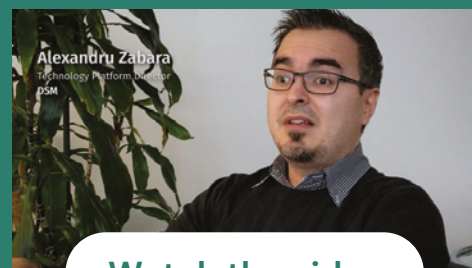
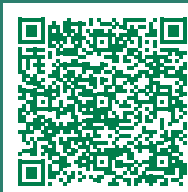
Aside from oral administration, alternative applications, like inhalation, vaporization, sublingual and intravenous routes are being investigated. But these present their own challenges. For example, the inhalation of drugs can require complex equipment and there are sometimes difficulties associated with patient self-administration. Whereas sublingual drops can bring issues related to taste and amount of API that can be effectively dosed using this approach. As such, oral administration remains a preference, for formulators and patients alike.

3. How can formulators optimize the bioavailability of CBD?

An optimal formulation strategy will address CBD bioavailability in multiple ways – improve the dissolution of CBD in the gut, increase absorption across the gut wall and reduce the extent of first-pass metabolism.

Lipid-based drug delivery systems offer a natural approach to improving the bioavailability of molecules with low water solubility, like CBD. This well-established technology works by transporting active ingredients through the gastrointestinal tract, into the lymphatic or blood circulation and to the target area(s) in the body without the drug degrading; thus increasing bioavailability of CBD.

Learn more about the benefits of lipid-based formulations for enhanced oral bioavailability of CBD.



Watch the video

Key considerations for prescription

The most important factor when prescribing CBD is whether or not there is sufficient scientific data to evidence that the molecule is efficacious in treating a disease or condition. The field is changing rapidly, but proof of efficacy is limited to CBD as an anti-epileptic API only. A second critical factor is dose, route (vaporized, transdermal, oral) and frequency of administration – which can all contribute to adverse drug reactions if not considered with caution.⁵² The two most common adverse effects related to CBD are drowsiness and sedation.^{79,80,81,82}

Drug–drug interactions

Drug–drug interactions are also an important issue when prescribing any drug product. CBD is often added to a regimen of other medications, especially other anti-epileptics. However, like any active ingredient, CBD exhibits complex pharmacodynamic and pharmacokinetic properties, meaning it has the potential to interact with other medications and medical conditions – which could lead to serious health consequences.

For example, studies testing CBD in epilepsy have reported CBD–induced drug–drug interactions with medications commonly used to treat mood disorders – like benzodiazepines, valproate and other anticonvulsants.^{83,84} Thus, while it has been concluded that CBD has a low risk of clinically significant drug–drug interactions and is well-tolerated when combined with other drugs, the potential for drug–drug interactions necessitates careful monitoring.⁸⁵

To protect patient health, healthcare providers should be aware of the risk of drug–drug interactions and adverse effects and strategically prescribe CBD and manage patient regimens. This is particularly important when considering any off-label CBD drug product use.



Glossary

Pharmaceutical cannabis-based products	Formulated, processed or synthetic cannabis sold as a finished product after undergoing full clinical trials and holding a medical marketing authorization (e.g. Cesamet®, Sativex® and Epidiolex®).
Medical cannabis	A cannabinoid-based non-registered medicine (unlicensed) – and sold as an unlicensed medicine.
Cannabinoid	A group of bioactive compounds found in the Cannabis sativa plant or synthetic compounds that can interact with the endocannabinoid system. The cannabis plant produces approximately 80-100 cannabinoid molecules.
CBD	Cannabidiol (CBD) is one of the main cannabinoids which can be either synthesized or derived naturally from Cannabis sativa plants. CBD is non-psychoactive and exhibits wide-ranging properties that may benefit health and wellness. It is found in large quantities in hemp.
THC	Tetrahydrocannabinol (THC) is the other major cannabinoid present in cannabis. THC produces the “high” associated with ingesting cannabis. It is mainly found in the marijuana plant.
Rare cannabinoid	Also known as novel or minor cannabinoids, rare cannabinoids (CBx) are every other cannabinoid found in cannabis besides CBD and THC. As their name indicates, CBx are found in lower concentrations in the Cannabis sativa plant than the major cannabinoids.
Natural vs synthetic CBD	Natural CBD is derived from the Cannabis sativa (mainly hemp) plant. Synthesized CBD has been developed artificially but is considered to be chemically identical to naturally-occurring CBD.

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