# Getting High to Get Well: Scientific Evidence of Therapeutic Uses of Cannabinoids and Terpenoids

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# Getting High to Get Well: Scientific Evidence of Therapeutic Uses of Cannabinoids and Terpenoids

*The therapeutic potential of the active compounds in Cannabis—cannabinoids and terpenoids—is under investigation by many researchers around the world. This report serves as a guide to these compounds. It describes them in relation to their therapeutic potential as antiemetics and analgesics, as well as their potential application in the treatment of epilepsy, glaucoma, pain, neurodegenerative disorders, diabetes, cancer, and other health conditions and diseases. It also discusses the human body's cannabinoid receptors, describes the most abundant cannabinoid and terpenoid compounds, explores the synergic effect between cannabinoids and terpenoids, and provides a bibliography of related scientific research articles.*

## Is *Cannabis* a panacea?

*Cannabis* is sometimes hailed as a panacea. And while it may not be a remedy or cure for every health condition or disease, the plant is indeed highly medicinal—and medically undervalued.

We know *Cannabis* works, but why it works is a subject of heightened interest today as legislation changes to open more opportunities for scientific research and therapeutic applications. Scientists in Israel, Canada, and other countries are finding that specific cannabinoids and terpenoids—the pharmacologically active chemical compounds within this plant species—have specific characteristics that combat particular diseases, relieve certain ailments, or alleviate pain[1]. These findings have implications for *Cannabis* strains, since the content of cannabinoids and terpenoids varies among strains.

Advanced Nutrients is about to embark on scientific research of its own, testing our hydroponic nutrient products on different strains of *Cannabis* to determine how to maximize not only the genetic potential, but also the therapeutic potency, of this miraculous plant. In preparation for this new initiative, our scientists have delved into the literature and reviewed what the scientific community knows today about the most abundant and effective cannabinoids and terpenoids. We wanted to share this preliminary research with you as soon as possible in order to arm you with knowledge that could improve your health or enable you to better understand the broad therapeutic potential of *Cannabis*.

This Advanced Nutrients report serves as a reference guide to the most active compounds in *Cannabis*. It discusses the body's cannabinoid receptors and details the mechanisms and effects of 16 principle cannabinoids, whose properties are still under investigation. It presents the known biomedical effects of the five most abundant cannabinoids in both bulleted and tabular form. It explores known synergic interactions between terpenoids and cannabinoids. Finally, it provides a bibliography of scientific journal articles about the usefulness of *Cannabis* in 18 common diseases and health conditions.

## Cannabinoid receptors $CB_1$ and $CB_2$

Why are cannabinoids active in the human body? The body's endocannabinoid system mediates the effects of cannabinoids. The endocannabinoid system is a group of neuromodulatory lipids and their receptors, including

1 **Disclaimer:** Although this report discusses the medical and scientific literature surrounding *Cannabis*, it is not a substitute for a prescription from a doctor. Advanced Nutrients cannot be held responsible for the actions of readers. We recommend you consult your doctor before deciding to medicate with *Cannabis*, any of its derivatives, or any other medicine.

the cannabinoid receptors $CB_1$ and $CB_2$, which are activated by cannabinoids and some terpenoids (Figure 1):

- **$CB_1$ receptors** are concentrated in the brain and central nervous system, and they also appear sparsely in other areas of the human body. They are largely responsible for mediating the effects of cannabinoid binding in the brain.
- **$CB_2$ receptors** are found mainly in the cells of peripheral tissues, especially those cells associated with the immune system and cell formation. $CB_2$ receptors are also present in limited amounts and distinct locations in the brain.

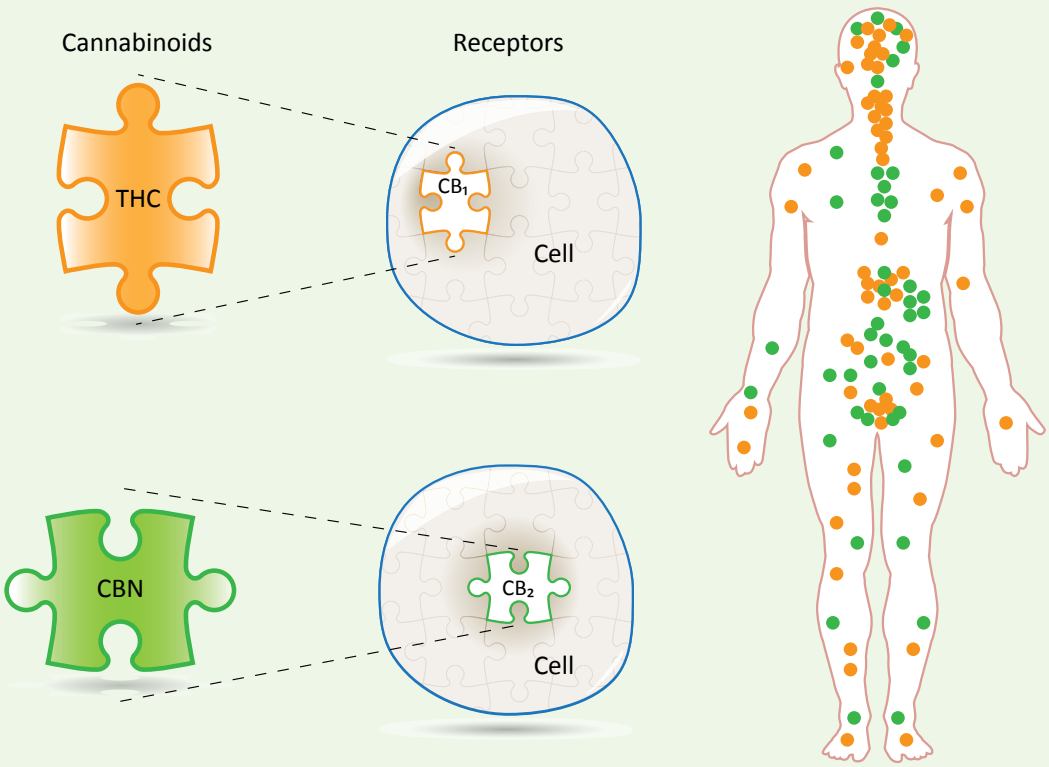



**Figure 1.** Two types of cannabinoid receptors, $CB_1$ and $CB_2$, are situated on the surfaces of cells throughout the human body. Not unlike the empty spaces in a jigsaw puzzle, these receptors "fit" only certain cannabinoids. Having bound with a receptor, the cannabinoid "piece" transmits a chemical signal through the receptor into the cell. This accounts not only for the psychotropic effects of certain cannabinoids, but also for many, if not all, of their pharmacological effects as well.

**Cannabinoids**

The plant *Cannabis* produces over 421 chemical compounds, including about 80 compounds called "phytocannabinoids" that have not been detected in any other plant (Izzo et al., 2009).

Much research has focused on the most psychotropic component of *Cannabis*, $\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC), which binds to specific cannabinoid ($CB_1$ and $CB_2$) receptors.

Other cannabinoids present in *Cannabis* include cannabinol (CBN), cannabidiol (CBD), cannabichromene (CBC), and cannabigerol (CBG). Compared to THC, these cannabinoids have no significant psychotropic effects, but they do have an impact on the overall effects of *Cannabis* by binding to cannabinoid receptors (Ben Amar, 2006).

Many other cannabinoids are presented in very small quantities; their biomedical effects and toxicity are under investigation.

***List of cannabinoids discussed in this report***

$\Delta^8$-tetrahydrocannabinol ($\Delta^8$-THC)

$\Delta^8$-tetrahydrocannabinolic acid ($\Delta^8$-THCA)

$\Delta^9$-tetrahydrocannabinol ($\Delta^9$-THC)

$\Delta^9$-tetrahydrocannabinolic acid ($\Delta^9$-THCA)

Cannabichromene (CBC)

Cannabichromenic acid (CBCA)

Cannabicyclol (CBL)

Cannabidiol (CBD)

Cannabidiolic acid (CBDA)

Cannabielsoin (CBE)

Cannabigerol (CBG)

Cannabigerolic acid (CBGA)

Cannabinol (CBN)

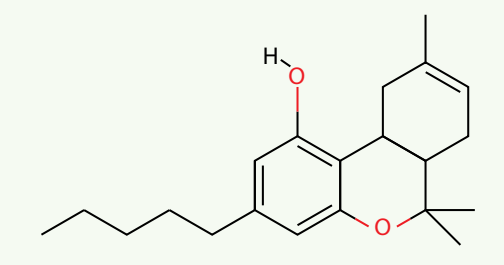
Cannabinolic acid (CBNA)

Cannabitriol (CBT)

Cannabivarin (CBV)

**Description of individual cannabinoids**

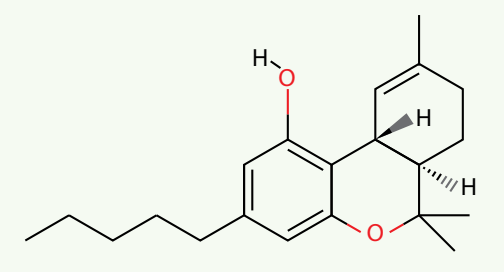
***Δ⁸-tetrahydrocannabinol (Δ⁸-THC), Δ⁸-tetrahydrocannabinolic acid (Δ⁸-THCA)***



In general, $\Delta^8$-THC is regarded as an artifact because it results from the isomerization of $\Delta^9$-THC. The concentration of $\Delta^8$-THC in *Cannabis* is usually minimal, and it does not contribute significantly to the activity of the plant. The pharmacology of $\Delta^8$-THC is similar to that of $\Delta^9$-THC, although it may be less potent. Its antiemetic properties are as effective as those of $\Delta^9$-THC.

$\Delta^8$-THCA is a precursor of Δ8-THC biosynthesis.

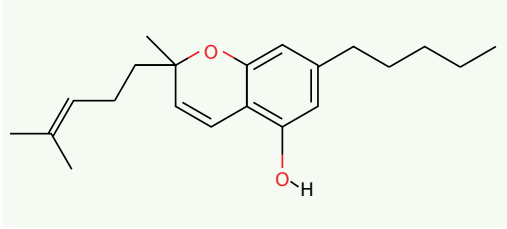
***Δ⁹-tetrahydrocannabinol (Δ⁹-THC), Δ⁹-tetrahydrocannabinolic acid (Δ⁹-THCA)***



Isolated in its pure form in 1964 by Gaoni and Mechoulam at the Weizmann Institute of Science in Rehovot, Israel, $\Delta^9$-THC is the primary psychotropic compound in *Cannabis*. Nevertheless, THC has its use in medicine. It has been observed that very low doses can be neuroprotective. $\Delta^9$-THC may help against pain and Parkinson's disease (Carroll et al., 2012; van Vliet et al., 2008), and it is used as an adjunctive analgesic treatment for adult patients with advanced cancer. It is therapeutically used as an antiemetic and to boost the appetite of people with AIDS. Furthermore, the cannabinoid CBD may inhibit some of the negative psychotropic properties of $\Delta^9$-THC (i.e., "take the edge off"). Even so, THC is not recommended for people under the age of 20 because their brains are still developing, and it can significantly impair driving.

$\Delta^9$-THCA is a precursor of $\Delta^9$-THC biosynthesis.

***Cannabichromene (CBC), cannabichromenic acid (CBCA)***

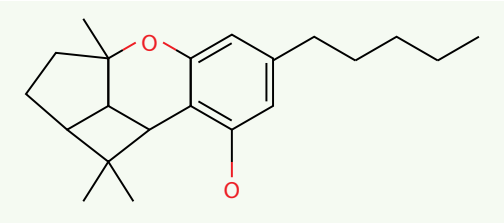


The discovery of CBC, a non-psychotropic cannabinoid (De Petrocellis et al., 2011), was independently reported by Claussen and colleagues and by Gaoni and Mechoulam in 1966. CBC has anti-inflammatory, antiviral, antibacterial,

and antifungal properties. CBC is considered one of the four major cannabinoids in *Cannabis* (along with CBD, THC, and CBN) and the second most abundant cannabinoid quantitatively (behind THC) in some strains of *Cannabis* growing in the United States. The observation that high doses of CBC are correlated with increased brain levels of THC suggests the potential pharmacokinetic effects of the two cannabinoids when applied in combination. The combination of CBC and THC has a synergistic effect that leads to enhanced anti-inflammatory actions (De Long et al., 2010; De Long et al., 2011). This observation has attracted considerable attention because it shows that CBC may be a useful therapeutic agent with multiple mechanisms of action. CBC has also demonstrated a significant antidepressant effect.

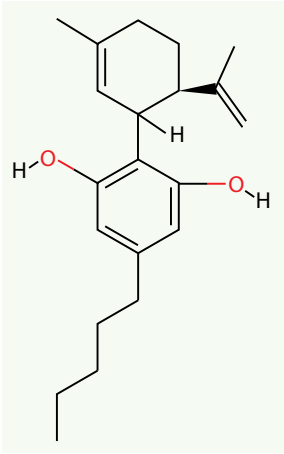
CBCA is a precursor of CBC biosynthesis.

***Cannabicyclol (CBL)***




A non-psychoactive cannabinoid, CBL may have influence prostaglandins, which are lipid compounds that regulate the contraction and relaxation of smooth muscle tissue, among other actions. CBL may also have stimulatory effects on arachidonate metabolism, which mediates many physiological processes, such as reproduction and endocrinology.

***Cannabidiol (CBD), cannabidiolic acid (CBDA)***

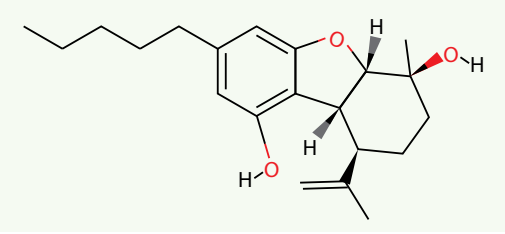



CBD, a major non-psychotropic cannabinoid, was first isolated in 1940 by Adams and colleagues. It represents up to 40% of the cannabinoid compounds present in *Cannabis* plant extracts. CBD exerts numerous pharmacological effects that are mediated by multiple mechanisms (Granjeiro et al., 2011; Walsh et al., 2010). It has been clinically evaluated in anxiety (Almeida et al., 2013), psychosis (Fernández Ruiz et al., 2013; Iuvone et al., 2004), and movement disorders, and it has been found to relieve neuropathic pain in patients with multiple sclerosis (Booz, 2011). CBD has acted in some experimental models as an anti-inflammatory, anticonvulsant, antioxidant, antiemetic, anxiolytic, and antipsychotic agent, and is therefore a potential medicine for the treatment of neuroinflammation, epilepsy, oxidative injury, vomiting and nausea, anxiety, and schizophrenia, respectively. The neuroprotective potential of CBD, based on the combination of

its anti-inflammatory and antioxidant properties, is of particular interest and is presently under preclinical evaluation for treatment of numerous neurodegenerative disorders. CBD, combined with Δ9-THC, is under clinical evaluation in patients with Huntington's disease (Hill et al., 2012).

CBDA is a precursor of CBD biosynthesis.

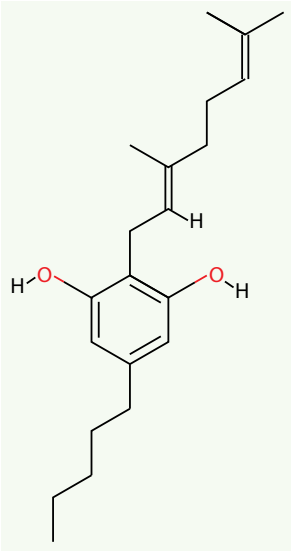
***Cannabielsoin (CBE)***



CBE is a novel metabolite of cannabidiol (CBD). The biosynthesis of CBE from CBD has been studied in guinea pigs, mice, rats, and rabbits in vitro. The effects of CBE on pentobarbital-induced sleep (a treatment for insomnia) and body temperature were assessed in mice. CBE possessed little activity.

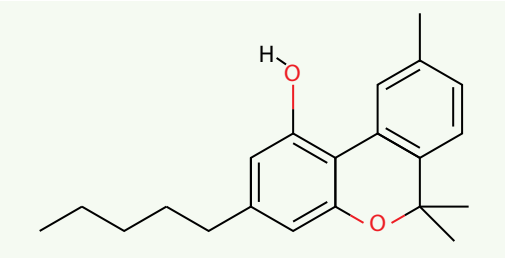
***Cannabigerol (CBG), cannabigerolic acid (CBGA)***

CBG is a non-psychotropic cannabinoid that was isolated in 1964 by Gaoni and Mechoulam. CBG has been studied in fewer pharmaceutical investigations than the cannabinoids described earlier in this report. It exerts antitumor activity and antibacterial activity, which makes it a potential candidate for the treatment of antibiotic-resistant bacteria (Almeida et al., 2013). CBG may block the antiemetic and antinauseant effects of CBD. These findings suggest that it may be more effective to treat nausea with specific cannabinoids, such as CBD, rather than with the entire complex of cannabinoids, which may interact with each other. Some studies have shown that CBG may lower blood pressure. CBG has a beneficial effect on inflammatory bowel disease, as well as therapeutic potential as an antidepressant and for the treatment of psoriasis.



CBGA is a precursor of CBG biosynthesis.

***Cannabinol (CBN), cannabinolic acid (CBNA)***

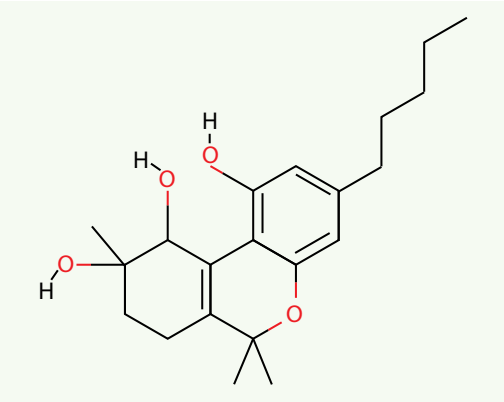


Isolated in 1896 by Wood and colleagues in Cambridge, CBN is also a psychoactive

compound, but with a greatly reduced effect on the central nervous system compared to THC. CBN is formed through the spontaneous degradation of THC. It has been observed to inhibit inflammation and hypermotility of the digestive tract. CBN causes immune suppression (e.g., used in medicine to reduce the risk of rejection of skin grafts or organ transplants or to control autoimmune diseases): A variety of experiments have demonstrated that CBN inhibits T-cell immune responses (Herring et al., 2001; Jan et al., 2002). CBN is of potential therapeutic use during cancer treatment (De Petrocellis et al., 2013; Guindon and Hohmann, 2013). Research is currently being conducted on CBN as a therapeutic option for amyotrophic lateral sclerosis (ALS) (Pertwee, 2002).

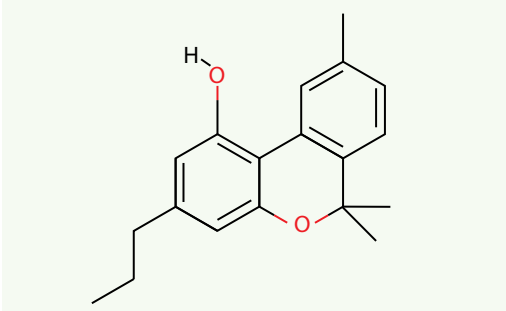
CBNA is a precursor of CBN biosynthesis.

***Cannabitriol (CBT)***




Nine CBT-type cannabinoids have been identified that are characterized by additional OH- substitution. CBT itself exists in the form of many isomers. Its biological function remains unknown.

***Cannabivarin (CBV)***




A non-psychoactive cannabinoid, CBV is an analog of cannabinol (CBN) that is shortened by two methylene bridges (-CH2-). CBV has been shown to have an anticonvulsant effect (used in the treatment of bipolar disorder and neuropathic pain) in mice and rats.

**Health benefits of the five most abundant cannabinoids**

**THC:**

- Exhibits a neuroprotective effect; useful in the treatment of Parkinson's disease and Huntington's disease
- Reduces pain, including cancer-related pain
- Suppresses the appetite, reducing obesity
- Protects the heart, reducing the risk of artery blockage
- Reduces vomiting and nausea
- Acts as an antiepileptic
- Modulates the memory of strong emotions
- Reduces intraocular pressure (IOP)
- Is antiproliferative, inhibiting the growth of cancer cells
- Has an antidepressant effect
- Promotes bone formation and the healing of fractures
- Inhibits bacterial growth

**CBC:**

- Relieves pain
- Reduces inflammation
- Has an antidepressant-like effect
- Inhibits fungal and bacterial growth
- Is antiproliferative, inhibiting the growth of cancer cells
- Aids sleep

**CBD:**

- Relieves anxiety
- Relieves pain
- Is used in the treatment of diabetes and its complications
- Is antihypertensive, used in the treatment of high blood pressure
- Protects the heart, reducing the risk of artery blockage
- Has an antidepressant-like effect
- Exhibits a neuroprotective effect; useful in the treatment of Parkinson's disease, Alzheimer's disease, Huntington's disease, and multiple sclerosis
- Reduces vomiting and nausea
- Stimulates the appetite
- Reduces inflammation
- Acts as an antipsychotic; useful in the treatment of schizophrenia
- Inhibits growth of cancer cells; is antiproliferative
- Acts as an antiepileptic
- Treats psoriasis
- Promotes bone formation and the healing of fractures
- Inhibits bacterial growth

**CBG:**

- Is antiproliferative, inhibiting the growth of cancer cells
- Relieves pain
- Inhibits bacterial growth
- Promotes bone formation and the healing of fractures
- Acts as an anti-inflammatory
- Has an antidepressant-like effect

- Treats psoriasis
- Has a neuroprotective effect in multiple sclerosis
- Reduces intraocular pressure (IOP)

**CBN:**

- Is antiproliferative, inhibiting the growth of cancer cells
- Relieves pain
- Promotes bone formation and the healing of fractures
- Is immunosuppressant, reducing the risk of rejection of skin grafts or organ transplants and helping to control autoimmune diseases
- Suppresses muscle spasms
- Inhibits bacterial growth

**Therapeutic potential of the five most abundant cannabinoids in *Cannabis***

| Action | Δ9-THC | CBC | CBD | CBG | CBN | Description |
|---|---|---|---|---|---|---|
| Relieves pain | ✓ | ✓ | ✓ | ✓ | ✓ | Analgesic |
| Suppresses appetite | ✓ | | | | | Anorectic/appetite suppressant |
| Inhibits bacterial growth | ✓ | ✓ | ✓ | ✓ | ✓ | Antibacterial |
| Has an antide-pressant-like effect | ✓ | ✓ | ✓ | ✓ | | Antidepressant |
| Reduces blood sugar levels | | | ✓ | | | Antidiabetic |
| Reduces vomiting and nausea | ✓ | | ✓ | | | Antiemetic |
| Reduces seizures and convulsion | ✓ | | ✓ | | | Antiepileptic |
| Treats fungal infection | | ✓ | | | | Antifungal |
| Reduces intraocular pressure (IOP) | ✓ | | | ✓ | | Antiglaucomal |
| Reduces inflammation | | ✓ | ✓ | ✓ | | Anti-inflammatory |
| Aids sleep | ✓ | ✓ | ✓ | | | Anti-insomnia |
| Reduces risk of artery blockage | ✓ | | ✓ | | | Anti-ischemic/cardioprotective |
| Inhibits cell growth in tumors/cancer cells | ✓ | ✓ | ✓ | ✓ | ✓ | Antiproliferative |
| Treats psoriasis | | | ✓ | ✓ | | Antipsioratic |
| Used to manage psychosis/ schizophrenia | | | ✓ | | | Antipsychotic |

| Action | Δ9-THC | CBC | CBD | CBG | CBN | Description |
|---|---|---|---|---|---|---|
| Suppresses muscle spasms | ✓ | | ✓ | | ✓ | Antispasmodic |
| Relieves anxiety | | | ✓ | | | Anxiolytic |
| Stimulates appetite | | | ✓ | | | Appetite stimulant |
| Promotes bone growth | ✓ | | ✓ | ✓ | ✓ | Bone stimulant |
| Reduces transplant rejection, controls autoimmune | | | | | ✓ | Immunosuppressive |
| Prevents nervous system degeneration | ✓ | | ✓ | ✓ | | Neuroprotective |
| Modulates emotional memory | ✓ | | | | | Neuropsychological |

**By treated health condition or disease:**

| Disease/Health Condition | Active Compounds |
|---|---|
| Alzheimer's disease [1, 2, 3, 4, 5, 6, 7, 8, 9] | CBD |
| Anxiety [1, 2, 3, 4, 5] | CBD |
| Bacterial diseases [1, 2, 3, 4, 5] | $\Delta^9$-THC, CBC, CBD, CBG, CBN |
| Cancer treatment [1, 2, 3, 4, 5, 6, 7, 8, 9] | $\Delta^9$-THC, CBC, CBD, CBG, CBN |
| Depression [1, 2, 3, 4, 5, 6, 7] | $\Delta^9$-THC, CBC, CBD, CBG |
| Diabetes [1, 2, 3, 4, 5, 6, 7] | CBD |
| Emesis (vomiting and nausea) [1, 2, 3, 4, 5] | $\Delta^9$-THC, CBD |
| Epilepsy [1, 2, 3, 4, 5] | $\Delta^9$-THC, CBD |
| Glaucoma [1, 2, 3, 4, 5] | $\Delta^9$-THC, CBG |
| Huntington's disease [1, 2, 3, 4, 5, 6, 7, 8, 9] | $\Delta^9$-THC, CBD |
| Hypertension (high blood pressure) [1, 2, 3, 4, 5] | CBD |
| Inflammation [1, 2, 3, 4, 5, 6] | CBC, CBD, CBG |
| Ischemia [1, 2, 3, 4, 5, 6, 7] | $\Delta^9$-THC, CBD |
| Multiple sclerosis [1, 2, 3, 4, 5, 6] | CBD, CBG |
| Pain [1, 2, 3, 4, 5, 6, 7] | $\Delta^9$-THC, CBC, CBD, CBG, CBN |
| Parkinson's disease [1, 2, 3, 4, 5, 6, 7] | $\Delta^9$-THC, CBD |
| Psoriasis [1, 2, 3, 4, 5] | CBD, CBG |
| Schizophrenia [1, 2, 3, 4, 5] | CBD |

**Terpenoids**

Terpenoids are a large and diverse class of naturally occurring organic chemicals. They share a precursor with cannabinoids, geranyl pyrophosphate, which is formed via the deoxylulose pathway in *Cannabis* and is a parent compound to both cannabinoids and terpenoids.

The aroma and flavors of *Cannabis* do not originate from cannabinoids, but from the more volatile terpenoids, which are primarily responsible for differences in fragrance among *Cannabis* strains. They are part of the essential oil of *Cannabis*, a complex mixture composed primarily of monoterpenoids, sesquiterpenoids, and cannabinoids.

Terpenoids present in the essential oil of *Cannabis* are pharmacologically active and may modify or enhance the physiological effects of cannabinoids, resulting in greater medicinal benefit than the pure cannabinoid compounds.

According to Turner et al. (1980), 58 monoterpenoids and 38 sesquiterpenoids have been identified in hemp. The concentration of monoterpenoids is generally higher than that of sesquiterpenoids, varying from 47% to 93% of total terpene content (Mediavilla and Steinemann, 1997). Monoterpenoids are more volatile compared to sesquiterpenoids and therefore primarily responsible for differences in fragrance. Some sesquiterpenoids occur in the essential oil of other medicinal plants, including *Michelia champaca L.* and *Bulnesia sarmienti*.

Cannabinoid-terpenoid synergy may increase the likelihood of new therapeutic applications. Interactions between cannabinoids and terpenoids can produce synergy with respect to treatment of pain, inflammation, depression, anxiety, addiction, epilepsy, cancer, and fungal or bacterial infections. For example, the sesquiterpene β-caryophyllene has been shown to selectively target $CB_2$ receptors and to act as a functional $CB_2$ ligand. β-caryophyllene has the potential to become an attractive candidate for clinical trials due to its targeting of $CB_2$ receptors and its anti-inflammatory effects.

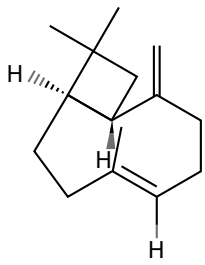
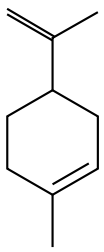
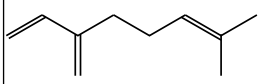
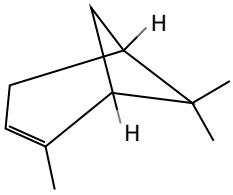
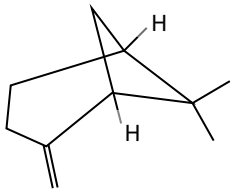
**The main monoterpenoids:**

***Limonene***
***β-myrcene***
***α-pinene***
***β-pinene***

**The main sesquiterpenoids:**

***β-caryophyllene***
***α-guaiene***
***α-humulene***

**Synergy between *Cannabis* terpenoids and cannabinoids and their therapeutic potential**

| Terpenoid | Structure | Pharmacological activity | Synergistic cannabinoid |
|---|---|---|---|
| β-caryophyllene |  | • Gastric cytoprotection<br>• Anti-inflammatory | • THC<br>• CBD |
| Limonene |  | • Anxiolytic<br>• Antiproliferative<br>• Against dermatophytes<br>• Against *Propionibacterium acne*<br>• Antigastroesophageal reflux | • CBD<br>• CBD, CBG<br>• CBG<br>• CBD<br>• THC |
| β-myrcene |  | • Anti-inflammatory<br>• Analgesic<br>• Antispasmodic<br>• Anticarcinogenic | • CBD<br>• CBD, THC<br>• THC<br>• CBD, CBG |
| α-pinene |  | • Anti-inflammatory<br>• Neuroprotective<br>• Antiasthmatic | • CBD<br>• CBD<br>• THC |
| β-pinene |  | • Antiproliferative<br>• Neuroprotective | • CBD<br>• CBD |

* * *

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## References

### Cannabinoids

***$\Delta^8$-THC and $\Delta$-THCA:***

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