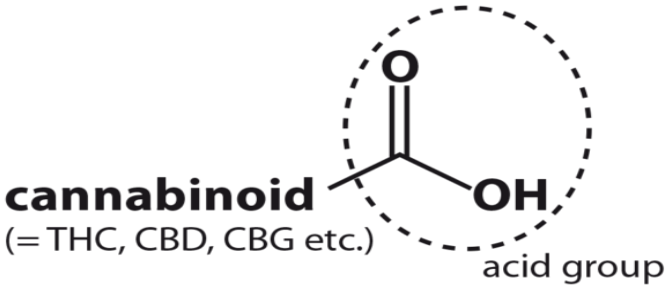
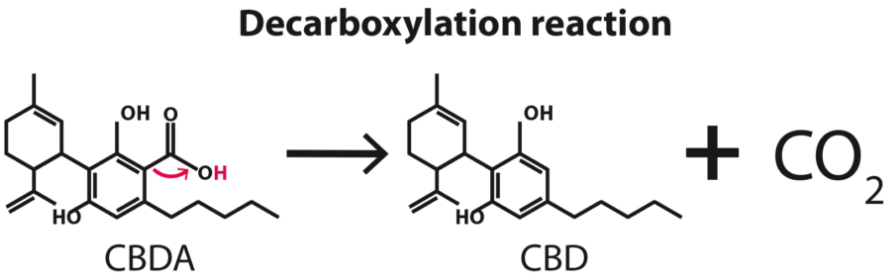
Cannabinoids: Acidic and non-acidic (decarboxylated) form



In the hemp plant, the cannabinoids are mainly found in the acidic form. This means that each cannabinoid molecule has an acidic group attached to it. They are naturally formed by the plant in this way. In the living plant and in well-preserved dry matter, typically more than 90% of the cannabinoids are in the acidic form.



Decarboxylation of CBDA to CBD

CBDA		**CBD**		**CO_2**	
Molar mass	358.478 g·mol−1	Molar mass	314.469 g·mol−1	Molar mass	44.009 g·mol−1
Chemical formula	$C_{22}H_{30}O_4$	Chemical formula	$C_{21}H_{30}O_2$	Chemical formula	CO_2

- The cannabinoid acids (CBDA, CBNA, etc.) ALWAYS have 22 carbon atoms (C) and ALWAYS 4 oxygen atoms (O), as well as the same number of hydrogen atoms (H), which varies from cannabinoid to cannabinoid.
- The non-acidic (decarboxylated) cannabinoids (CBD, CBN etc.) ALWAYS have 21 carbon atoms (C) and ALWAYS 2 oxygen atoms (O), as well as the same number of hydrogen atoms, which varies from cannabinoid to cannabinoid (H).

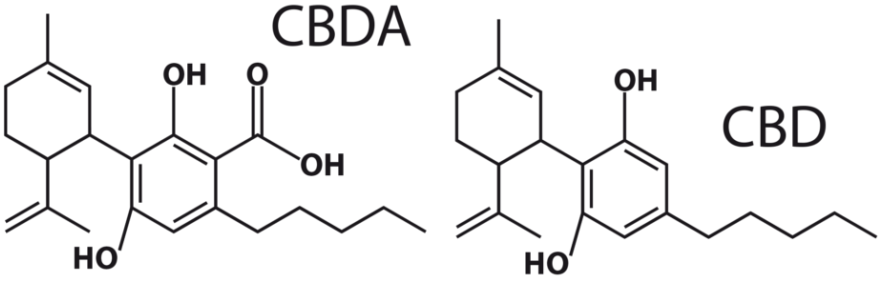
Cannabinoids can undergo a reaction called decarboxylation. This means that they lose this acid group. This chemical reaction is a longer process that can be greatly accelerated by heating. The duration is directly related to the level of the temperature. This happens e.g. E.g. if a cannabis product is smoked (combustion, immediate decarboxylation) or heated long enough (e.g. at 115°C or 192°F/1h).

De-carb-oxylation = **1** carbon atom (C) and **2** oxygen atoms (O) are removed from the cannabinoid acid (CBDA, CBNA etc.), which combine to form CO2.
The molecular mass of the cannabinoid acid (CBDA, CBNA etc.) is thus = the sum of the molecular masses of the non-acidic (decarboxylated) cannabinoids + CO2 (44.009 g·mol−1)

In addition to THC, hemp contains more than 130 cannabinoids. For the sake of clarity, reference is always made below to the decarboxylated (non-acidic) form of cannabinoids.

Cannabinoids

CBD: Cannabidiol

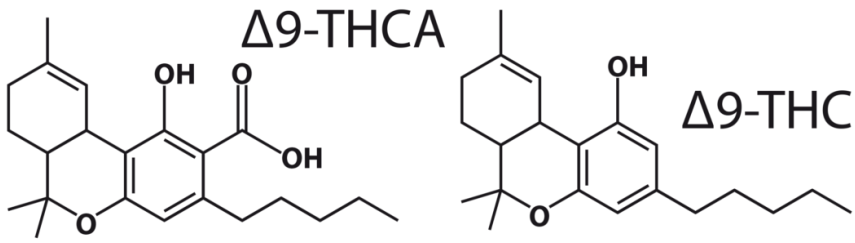


CBDA		**CBD**	
Molar mass	358.478 g·mol−1	Molar mass	314.469 g·mol−1
Chemical formula	$C_{22}H_{30}O_4$	Chemical formula	$C_{21}H_{30}O_2$

Along with Δ9-THC, CBD is one of the two main cannabinoids in the hemp plant and was first isolated and identified in 1940 by the American chemist Roger Adam and his collaborators (Adams et al., 1940).

Unlike Δ9-THC, CBD has no psychoactive effects (Pisanti et al., 2017). If present in sufficient amounts, CBD can also mitigate or even suppress the psychotropic effects of Δ9-THC (Niesink and van Laar, 2013; Schubart et al., 2011).

Δ9-THC: delta-9-Tetrahydrocannabinol

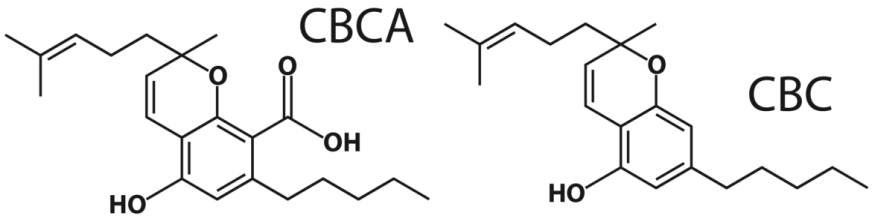


Δ9-THCA		**Δ9-THC**	
Molar mass	358.478 g·mol−1	Molar mass	314.469 g·mol−1
Chemical formula	$C_{22}H_{30}O_4$	Chemical formula	$C_{21}H_{30}O_2$

Δ9-THC belongs together with CBD to the two main cannabinoids of the hemp plant. It was first discovered in 1964 by Israeli researchers Dr. Yechiel Gaoni and Prof. Raphel Mechoulam isolated and identified (Gaoni und Mechoulam, 1964).
Δ9-THC has a strong psychotropic effect and has therefore been classified as a controlled substance by numerous national and international regulations. In Switzerland, the legal limit of Δ9-THC is mainly regulated by two ordinances of the Federal Office of Public Health (FOPH) and depends on the type and designation of the product:

- 1% in non-edible hemp products (e.g. tobacco substitutes) according to the regulation 812.121.11
- 0.00002 bis 0.003% in edibles (depending on the type of product) according to regulation 817.022.15.

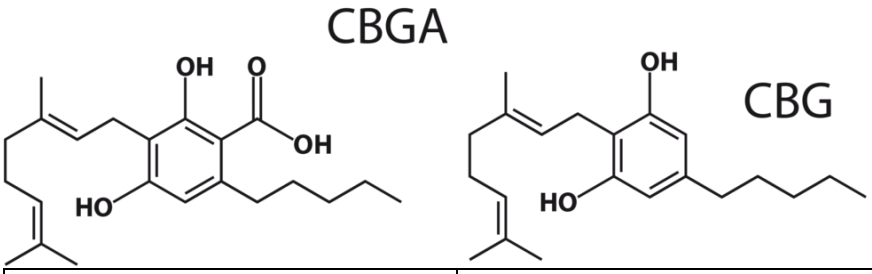
CBC: Cannabichromen



CBCA		**CBC**	
Molar mass	358.478 g·mol−1	Molar mass	314.469 g·mol−1
Chemical formula	$C_{22}H_{30}O_4$	Chemical formula	$C_{21}H_{30}O_2$

CBC is a cannabinoid commonly found in hemp and is widely considered non-psychotropic (Russo, 2011; Turner et al., 1980).
In indoor grown hemp, CBC is usually present in the same amounts as THC, but can reach concentrations up to 5x higher than THC in outdoor grown hemp.

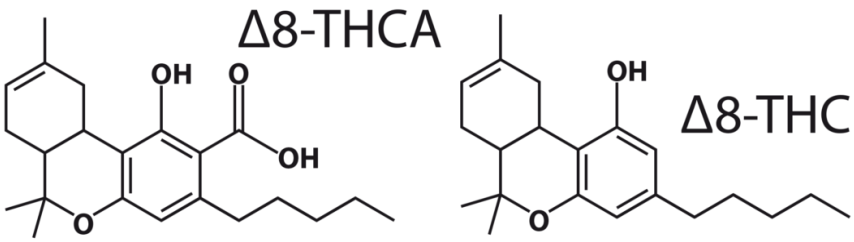
CBG: Cannabigerol



CBGA		CGC	
Molar mass	360.494 g·mol−1	Molar mass	316.485 g·mol^{-1}
Chemical formula	$C_{22}H_{32}O_4$	Chemical formula	$C_{21}H_{32}O_2$

CBG, which is considered a "precursor" or "primordial" cannabinoid, is first produced by the hemp plant and later converts to other cannabinoids such as CBD and Δ9-THC.

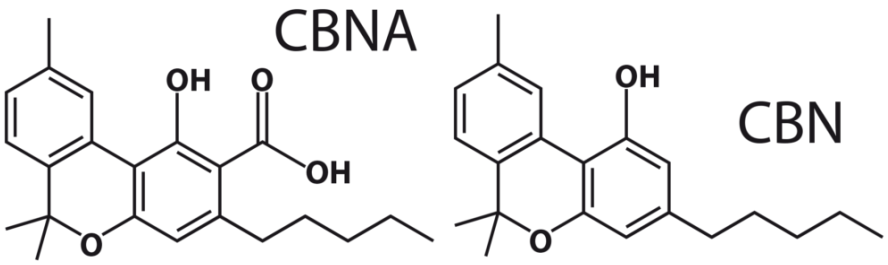
Δ8-THC: delta-8-Tetrahydrocannabinol



Δ8-THCA		Δ8-THC	
Molar mass	358.478 g·mol−1	Molar mass	314.469 g·mol^{-1}
Chemical formula	$C_{22}H_{30}O_4$	Chemical formula	$C_{21}H_{30}O_2$

Δ8-THC is the (−)-trans-Δ8-tetrahydrocannabinol isomer ($C_{21}H_{30}O_2$, M_r) and has a similar molecular structure to Δ9-THC, but is reported to have significantly lower psychotropic effects (according to the American National Health Institute).
In CBD-rich hemp, it occurs as a breakdown product of CBD, typically at a concentration of 1-2% of total CBD.
Often Δ8-THC is converted from the non-psychotropic CBD in a first step and in a second step into HHC (hexahydrocannabinol/$C_{21}H_{32}O_2$) or more precisely into its (-)-trans-hexahydrocannabino isomer ($C_{21}H_{32}O_2$,M_r).

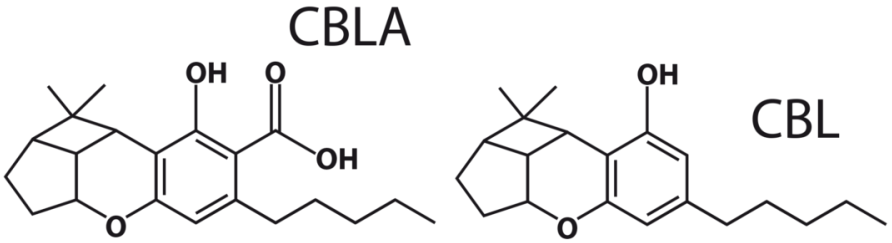
CBN: Cannabinol



CBNA		CBN	
Molar mass	354.446 g·mol−1	Molar mass	310.437 g·mol^{-1}
Chemical formula	$C_{22}H_{26}O_4$	Chemical formula	$C_{21}H_{26}O_2$

CBN is a breakdown product of Δ9-THC.
The degradation of Δ9-THC to CBN can be accelerated by artificial "aging" (UV light, heat).
Not classified as psychotropic.
Has a calming to slightly sedating effect.

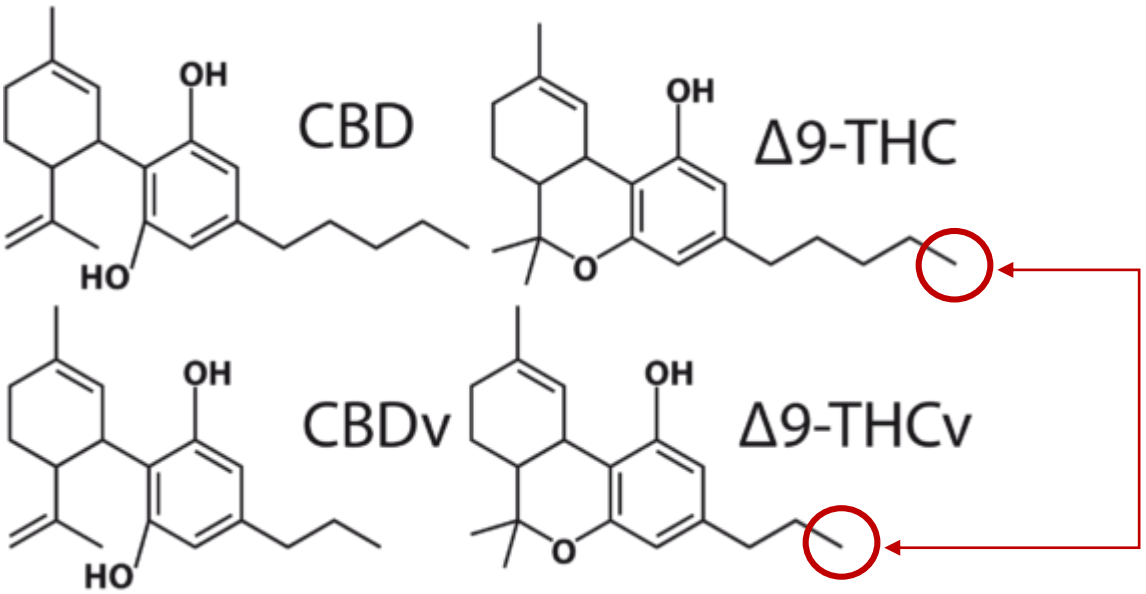
CBL: Cannabicyclol



CBLA		CBL	
Molar mass	358.478 g·mol−1	Molar mass	314.469 g·mol^{-1}
Chemical formula	$C_{22}H_{30}O_4$	Chemical formula	$C_{21}H_{30}O_2$

CBL is a breakdown product of CBC.
The degradation of CBC to CBL can be accelerated artificially (radiation, acidic environment).
Not classified as psychotropic.

CBDv, THCv, CBCv asf.: the group of the Cannabinoid-Varines

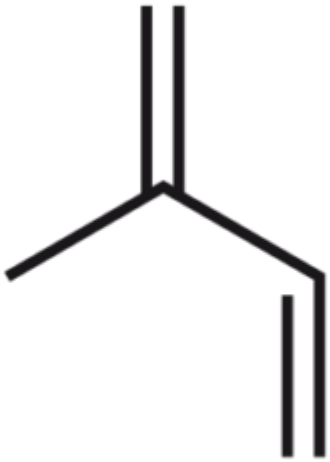


CBD	CBDv	THC	THCv
Molar mass	Molar mass	Molar mass	Molar mass
314.469 g·mol−1	286.415 g·mol−1	314.469 g·mol−1	286.415 g·mol−1
Chemical formula	Chemical formula	Chemical formula	Chemical formula
$C_{21}H_{30}O_2$	$C_{19}H_{26}O_2$	$C_{21}H_{30}O_2$	$C_{19}H_{26}O_2$

The varin group of cannabinoids includes a number of cannabinoids with a very similar structure to the molecules listed above (CBD, THC, CBN, etc.), but with a shorter alkyl chain (see figure above).
They therefore have 2 less carbon atoms (C) and 4 less hydrogen atoms (H) than the corresponding cannabinoid.
They are usually found in hemp in lower amounts than the other cannabinoids.

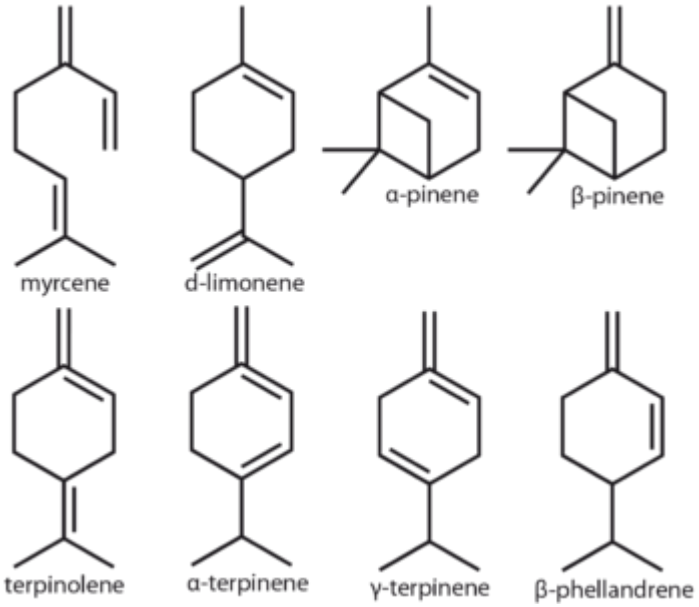
Terpens und Terpenoids

Terpenes are an important family of chemicals produced by hemp plants, as well as many other plants and animals.
These are aromatic molecules that give the different varieties of hemp their characteristic smell and taste.
So far, more than 200 different terpenes have been identified in the hemp plant.

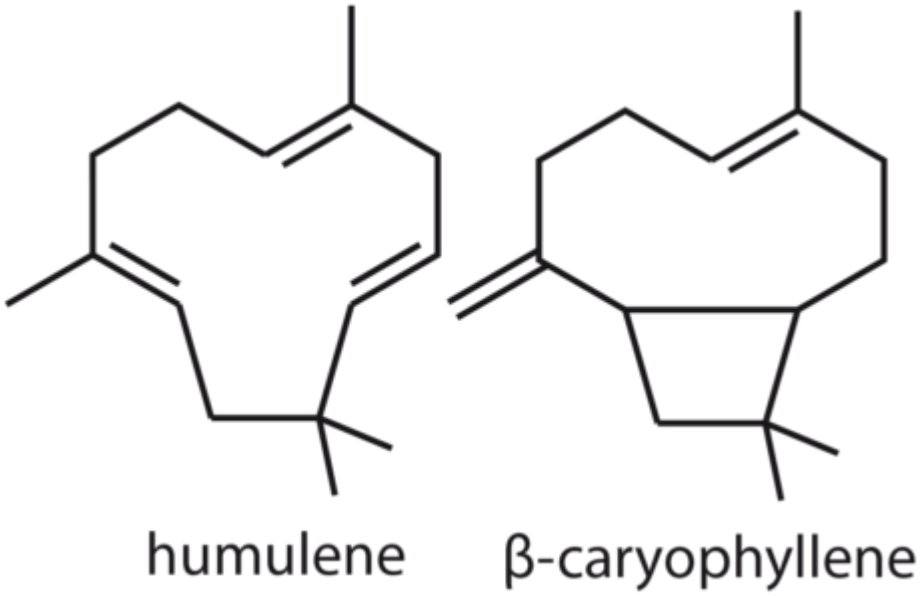


isoprene

These molecules are unsaturated, pure hydrocarbons, all of which are made up of the same basic unit: isoprene.
The biological functions of terpenes have received only limited research. A well-known application is e.g. B. the effect of the subgroup of pheromones as attractants for insect traps. Many terpenes also have antimicrobial effects.
The effect of treating viruses is still the subject of ongoing research.
Essential oils, which are obtained from plants, consist mainly of terpenes or terpenoids
According to the number of isoprene units from which they are composed, terpenes are divided into different subgroups:
Monoterpens (2 Units),
Sesquiterpens (3 Units),
Diterpens (4 Units) usw.

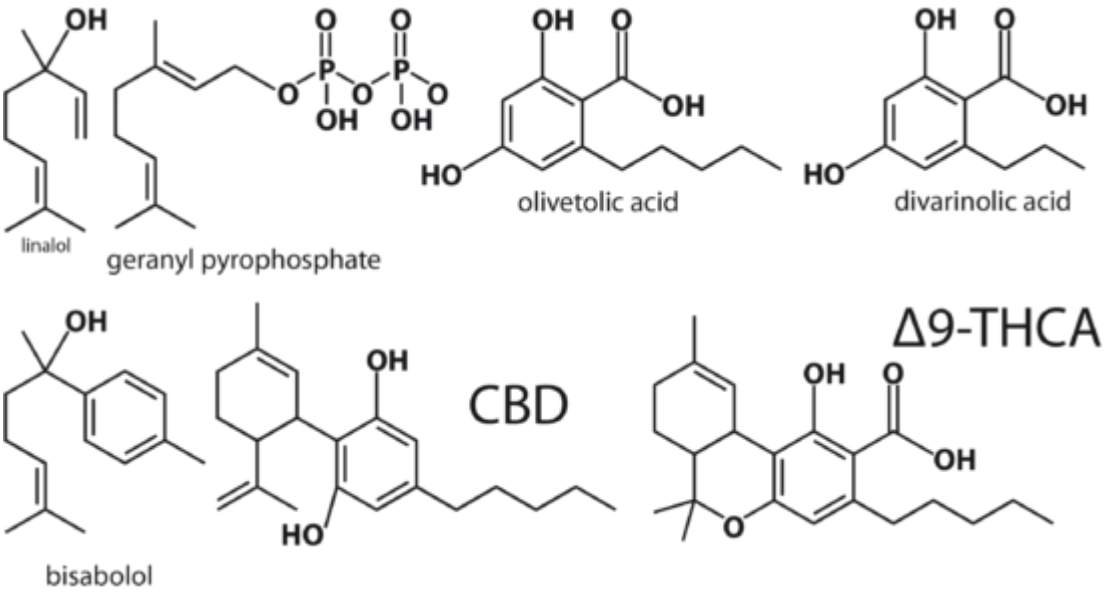


Example of Monoterpens



Example of Sesquiterpens

The hemp plant also produces a large number of substances called terpenoids. These are the same hydrocarbons as terpenes, but with functional groups that usually contain oxygen (e.g. alcohol, acids, ketones, esters...). They are also often referred to as "oxygenated terpenes".
Strictly speaking, cannabinoids are diterpenoids (meaning they are made up of 4 isoprenes with additional functional groups). The similarity in the molecular structure is clearly visible.



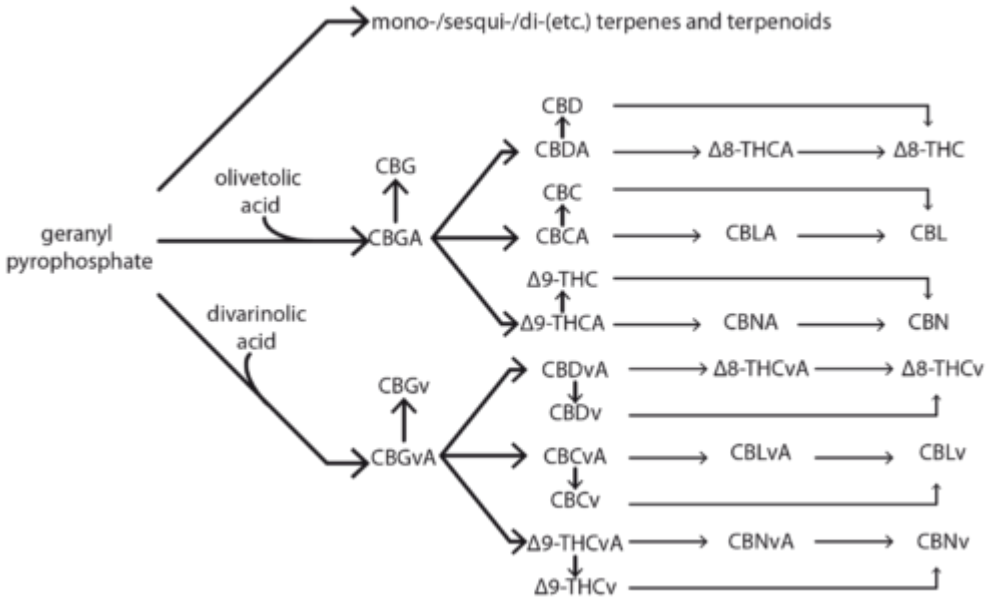
Example of Terpenoids

Some of the various terpenoids are considered important precursors to all other terpenes, terpenoids and, accordingly, cannabinoids. This means that the hemp plant first forms these precursors and then changes them further through biosynthesis to form the compounds described above (see next section).

Synthesis of the Cannabinoids

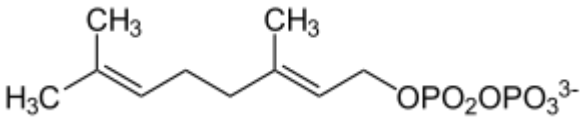
The precursor **Geranyl Pyrophosphate (GP)** is considered the precursor to all other terpenes. The hemp plant also contains two other precursors, **olivetolic acid (OA)** and **divarinolic acid (DA)**, which then react with GP in a biosynthesis to form CBG and CBGv, respectively.

All other cannabinoids found in hemp are then formed from these two "cannabinoid precursors".



Bio-Synthesis of Terpens und Cannabinoids in Hemp.

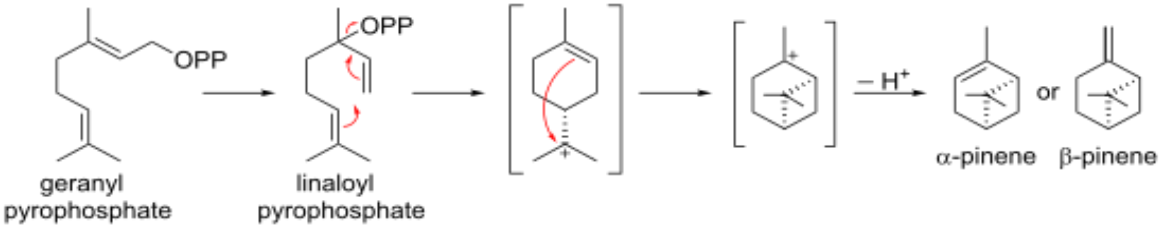
Geranylpyrophosphate



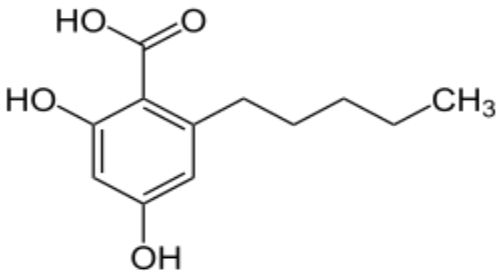
Geranylpyrophosphat	
Geranyldiphosphat	
Molar mass	314.21 g·mol−1
Chemical formula	$C_{10}H_{20}O_7P_2$

Geranyl pyrophosphate is a biomolecule found as a building block in terpene biosynthesis. Chemically it is an ester of geraniol (an alcohol with two additional C=C double bonds) and diphosphoric acid.
Geranyl pyrophosphate is the parent compound of several thousand plant monoterpenes.
For example, α-pinene and β-pinene are synthesized from geranyl pyrophosphate.

In humans, geranyl pyrophosphate serves to synthesize squalene, an important precursor for cholesterol synthesis.



Olivetolic acid



Olivetol	
4-Hydroxy-6-*n*-pentylsalicylsäure	
Molar mass	224.25 g·mol−1
Chemical formula	**$C_{12}H_{16}O_4$**

Olivetolic acid is the carboxylic acid derivative of Olivetol.

It is a meroterpenoid that serves as a biogenetic precursor to various derivatives of dibenzopyran - the so-called cannabinoids.

Cannabigerolic acid is formed by enzymatic condensation of the two precursors geranyl pyrophosphate and olivetolic acid, which is then enzymatically converted into the various cannabinoid acids such as e.g. B. tetrahydrocannabinolic acid is rearranged.

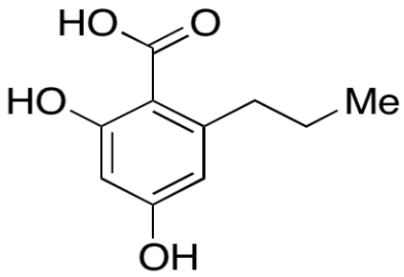
Olivetolic acid occurs naturally in the fungus Cetrelia sanguinea and has a monoclinic crystal structure.

Olivetolic acid can also be produced artificially. In a recent publication, special amoebas (Dictyostelium) are used to synthesize olivetolic acid (patent pending: Leibniz Institute for Natural Product Research and Infection Biology - Hans Knöll Institute in Jena -Leibniz-HKI-).

The research team finally succeeded in producing a functional hybrid enzyme that produces olivetolic acid without any further additives.

“Through our research, we have shown that the amoeba Dictyostelium can be used as a biotechnological production platform for polyketide-based natural products. Our next goal now is to add the two missing enzymes to be able to produce the end product THC in the amoebas»https://www.leibniz-hki.de/de/pressemitteilung/cannabinoide-aus-amoeben.html
https://www.nature.com/articles/s41587-021-01143-8

Divarinic acid



Divarinsäure	
6-Propyl-b-resorcylic Acid	
Molar mass	196.074 g·mol−1
Chemical formula	$C_{10}H_{12}O_4$

Divarinic Acid is an antibacterial compound that strongly inhibits bacterial growth of Bacillus subtilis, Staphylococcus aureus, Escherichia coli and Pseudomonas aeruginosa.
As a precursor to varine, divarinic acid reacts in a biosynthetic process with geranyl pyrophosphate and rearranges to form cannabigerovarin and cannabigerovaric acid.

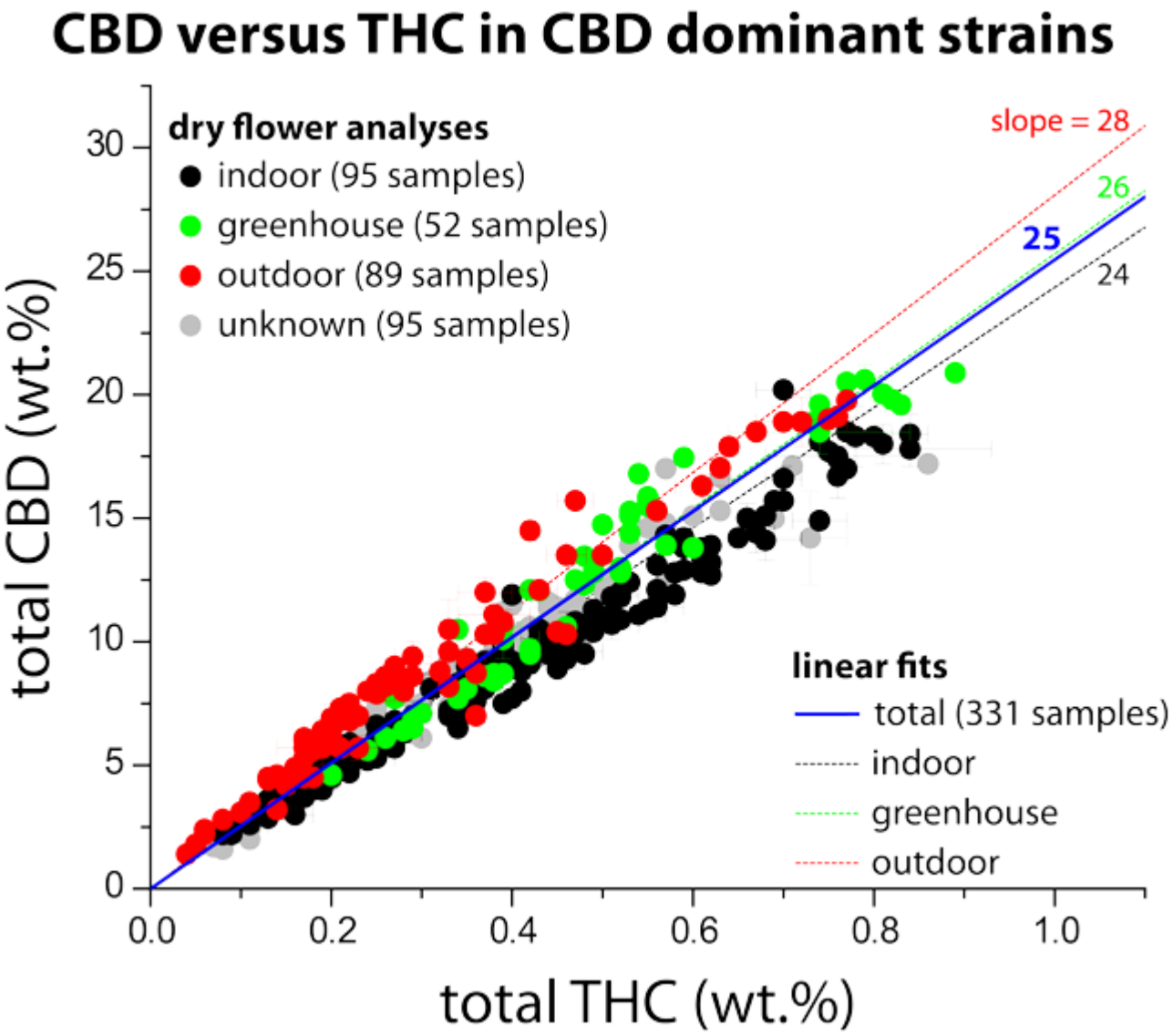
Ratio of Cannabinoids

The ratio of levels of the different cannabinoids depends primarily on genetics and environmental factors. This particularly affects the CBD:Δ9-THCu ratio, which falls within a very narrow range of values.

Three main groups of hemp can be identified:
– The CBD dominant strains with a CBD:THC ratio generally between 20:1 and 32:1. Some strains can have a ratio as low as 15:1 but are rarely encountered.
– the balanced strains with a CBD:THC ratio between 1:1 and 4:1.
– the THC dominant strains with a CBD:THC ratio well below 1:50 to 1:200.

Since CBD:THC of the CBD dominant strains is genetically determined and distinctly different from the other two types, it can be predicted by analyzing young plants.

The deviations fall within a fairly narrow range, as can be seen in the graph below:



Sources

Adams, R., Hunt, M. & Clark, J.H. (1940). Structure of Cannabidiol, a Product Isolated from the Marihuana Extract of Minnesota Wild Hemp. I. Journal of the American Chemical Society 62, 196-200.
Gaoni, Y. & Mechoulam, R. (1964). Isolation, Structure, and Partial Synthesis of an Active Constituent of Hashish. Journal of the American Chemical Society 86, 1646-1647.
Pisanti, S., Malfitano, A.M., Ciaglia, E., Lamberti, A., Ranieri, R., Cuomo, G., Abate, M., Faggiana, G., Proto, M.C., Fiore, D., Laezza, C. & Bifulco, M. (2017). Cannabidiol: State of the art and new challenges for therapeutic applications. Pharmacology & Therapeutics 175, 133-150.
Russo, E.B. (2011). Taming THC: potential cannabis synergy and phytocannabinoid-terpenoid entourage effects. British Journal of Pharmacology 163, 1344-1364.
Schubart, C.D., Sommer, I.E.C., van Gastel, W.A., Goetgebuer, R.L., Kahn, R.S. & Boks, M.P.M. (2011). Cannabis with high cannabidiol content is associated with fewer psychotic experiences. Schizophrenia Research 130, 216-221.
Turner, C.E., Elsohly, M.A. & Boeren, E.G. (1980). Constituents of Cannabis sativa L. XVII. A review of the natural constituents. Journal of Natural Products 43, 169-234.

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