



REFERENCE SUBSTANCES FOR HERBAL PRODUCTS

A leading global manufacturer, **PhytoLab offers over 1,500 extensively documented herbal reference substances** of all classes of natural compounds. Our portfolio includes a range of cannabinoids that can be applied in qualitative and quantitative analysis and quality control of hemp and medical cannabis, their extracts, isolates and finished products derived thereof.

Hemp

Cannabinoids are produced exclusively by *Cannabis sativa* L. (hemp), a member of the plant family *Cannabaceae*. This family comprises ca. 170 species grouped in about 11 genera, including *Cannabis*, *Humulus* (hops) and *Celtis* (hackberries). The origin of hemp is thought to be Central Asia, where it can be found in the wild from Iran to southern Siberia. Cannabis plants have been used and cultivated for thousands of years for a multitude of purposes. Cannabis is also one of the most widely used recreational drugs around the world.

Cannabinoids

Cannabis plants produce a group of natural compounds called cannabinoids, which induce mental and physical effects when consumed. The most prevalent cannabinoids are the psychotropic Δ^9 -tetrahydrocannabinol (Δ^9 -THC), and the pharmacologically active cannabidiol (CBD). Δ^8 -THC, a double bond isomer of Δ^9 -THC, occurs naturally only at very low to insignificant levels as a degradation by-product of Δ^9 -tetrahydrocannabinolic acid.

From a chemical point of view **cannabinoids are diterpenes**. Biosynthesis starts by enzymatic coupling of geranyl pyrophosphate and olivetolic acid (or divarinic acid in case of the propyl instead of the of pentyl homologues). Cannabigerolic acid (CBGA) is the central intermediate, from which tetrahydrocannabinolic acid (THCA), cannabidiolic

acid (CBDA) and cannabichromenic acid (CBCA) are formed by further enzymatic action. Depending on their basic chemical skeleton various types of cannabinoids are distinguished and used to classify the more than 100 known structures. **The acidic forms of the cannabinoids dominate in the plant.** Decarboxylation mostly takes place during storage, upon exposure to light, heating, or under alkaline conditions. Cannabinolic acid (CBNA) and cannabinol (CBN) are oxidative degradation products of THCA, THC, CBDA and CBD. Numerous isomers (double bond isomers as well as stereoisomers) of the cannabinoids exist.

Legal status

The legal status of both, cannabis as a plant and products thereof, including isolated phytocannabinoids, varies and is globally subject to many different regulations which very often seem to be similar but may differ in nuances.

Currently available phyproof® cannabinoids

Reference Substance	Product #
Cannabidiol	85705
Cannabidiolic acid	85839
Cannabidivarin	85955
Cannabigerol	85956
Cannabigerolic acid	85958
Cannabinol	86068



Monographs

The **United States Pharmacopoeia (USP)** currently has monographs on Dronabinol and Dronabinol Capsules. USP defines maximum impurity limits in dronabinol, i.e. 1.5 % CBN, 0.5 % Δ^9 -THC, 2.0 % Δ^8 -THC and 1.0 % for any other impurity. Furthermore, in January 2022 USP published a draft monograph on cannabidiol in Pharmacopoeial Forum. The proposed monograph aims to provide specifications for highly purified CBD from *Cannabis sativa*. In order to differentiate the naturally derived CBD from synthetically derived CBD potential synthetic substances (e.g., olivetol, 4-monobromo-CBD) are included in the tests for organic impurities besides the common natural impurities (i.e. cannabidiol hydroxyquinone, cannabidiol-C4, CBDA, cannabidivarin, CBN, Δ^8 -THC, Δ^9 -THC, THCA).

In **Europe** there are currently only (non-harmonized) national pharmacopoeial monographs available for Cannabis Flowers (e.g. German Pharmacopoeia (DAB), Swiss Pharmacopoeia (Ph. Helv.), Danish Pharmacopoeia) and Cannabis Extracts (DAB). The **European Pharmacopoeia currently has three cannabis monographs under development**, i.e. *Cannabis flos*, *Cannabis extractum siccum*, and *Cannabis extractum spissum*.

The **DAB contains monographs on Cannabis Flowers and Standardized Cannabis Extract**. In the DAB, cannabis flowers are identified by microscopy and TLC using CBD and Δ^9 -THCA as reference substances. Δ^9 -THC and CBD content are not specified, but they are determined by HPLC, taking into account also the content of the respective cannabinoid acids. A maximum limit of 1.0 % cannabinol is set. The DAB monograph on Standardized Cannabis Extract limits the Δ^9 -THC content to 1-25 %, while no limit is set for CBD. CBN content must not exceed 2.5 %.

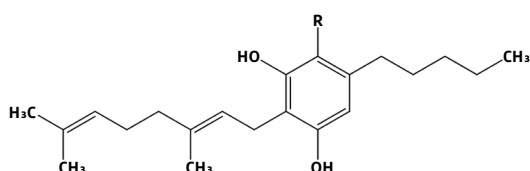
A monograph on pure cannabidiol can be found in the German Drug Codex (Deutscher Arzneimittel-Codex, DAC). Identification is performed by IR and TLC, while HPLC is used in the test for related substances and the assay. Limits of 0.10 % each are set for CBN, Δ^8 -THC, Δ^9 -THC and each non-specified impurities (maximum total impurities: 0.5 %).

Reference Substances

Our **phyproof® Cannabinoid Reference Substances** are not subject to German Narcotics Law. All substances are tested for their content of potentially regulated impurities such as Δ^8 -THC, Δ^9 -THC and Δ^9 -THCA and results are given on the COA. Acceptable maximum limits were set to 0.10 % each, and to 0.20 % for the sum of Δ^9 -THC and Δ^9 -THCA (in analogy to the cannabidiol monograph in DAC).

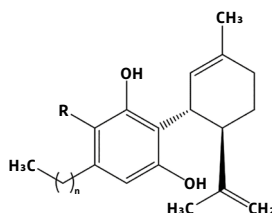
For a reliable analysis and quality control of cannabis products well characterized reference substances are essential. PhytoLab offers a wide range of cannabinoids, all of them are characterized as primary reference substances and supplied together with a comprehensive certificate of analysis. For a full listing and up-to-date information on prices and specifications please contact us or visit our webshop at phyproof.phytolab.com.

Structure of common cannabinoids



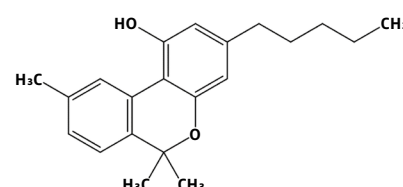
Cannabigerol-type (CBG)

Cannabigerol R = H
Cannabigerolic acid R = COOH



Cannabidiol-type (CBD)

Cannabidiol R = H; n = 4
Cannabidivarin R = H; n = 2
Cannabidiolic acid R = COOH; n = 4



Cannabinol (CBN)

