



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 and related substances that can be applied in forensics, 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 approx. 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. Hemp fiber is used for producing e.g. paper, textiles, and ropes. Hemp seeds and hemp seed oil are consumed as a food. Nowadays, the plant is grown globally due to its versatility. 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. Terpenoids form a second important group of constituents. The number and also the content of cannabinoids varies in different parts of the plant. 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 divarinolic 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.

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 % exo-THC, 2.0 % Δ^8 -THC and 1.0 % for any other impurity. Furthermore, in January 2022 USP published a draft monograph in Pharmacopeial 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*. These future monographs will be very helpful in terms of equal EU quality requirements. The draft monograph on *Cannabis flower* has been pre-published in October 2023 on the EDQM website. In the draft cannabis flowers are identified by microscopy, TLC and HPLC using CBD, Δ^9 -THC and cannabidiolic acid as reference substances. Total CBN content is determined by liquid chromatography as well.

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 was also used as the basis for the *Ph. Helv.* monograph on Cannabis flowers. The monographs are very similar, but limits and methods for determination of loss on drying differs, and also the assay conditions show slight differences. 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 cannot exceed 2.5 %. As the cannabinoid acids are said to be decarboxylated during drying or preparation of the extract their content is not relevant in the extract monograph.

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).

Reference Substances

For a reliable analysis and quality control of cannabis products well characterized reference substances are essential. PhytoLab offers a wide range of cannabinoids and related substances, all of them are characterized as primary reference substances and supplied together with a comprehensive certificate of analysis. In addition, our portfolio includes many additional natural products such as terpenes and flavonoids that are relevant to cannabis quality. For a full listing and up-to-date information on prices and specifications please contact us or visit our webshop at phyproof.phytoLab.com.

Currently available phyproof® cannabinoids and related reference substances

Reference Substance	Product #
Cannabidiol	85705
Cannabidivarin	85955
Cannabigerol	85956
Cannabinol	86068
Cannabidiol hydroxyquinone	10016
Cannflavin A	85954
Cannabicitran	22093
Hexahydrocannabinol	22700
Naturally occurring acids	
Cannabichromevarinic acid	10047
Cannabichromenic acid	10017
Cannabidiolic acid	85839
Cannabigerovarinic acid	10018
Cannabigerolic acid	85958
Markers for synthetic CBD	
Olivetol	10024
4-Monobromocannabidiol	10048
Other related reference substances	
Cannabisin A	86661
Cannabisin B	86662
N-Caffeoyltyramine	10153

phyproof® Reference Substances

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