BioBloom. Hemp

Cannabidiolic Acid (CBDA) - Properties and Effects

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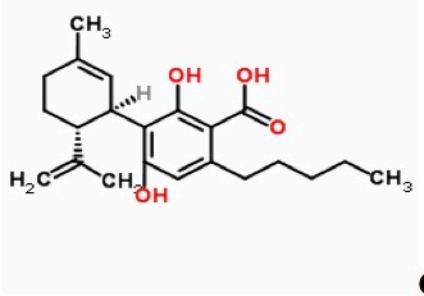
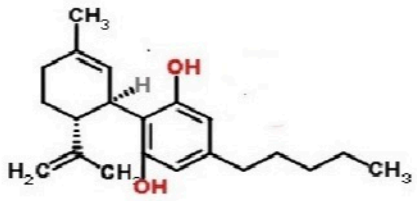
Zusammenfassung
Cannabidiolsäure (kurz CBDA) ist das Hauptcannabinoid in Industriehanf. Unter Temperatur- und Lichteinfluß wandelt sich CBDA in Cannabidiol (CBD) um. Diese Umwandlung ist in Extrakten jedoch keineswegs vollständig; abhängig von den Bedingungen finden sich stets mehr oder weniger hohe Anteile an CBDA neben CBD. Der CBDA-Gehalt im Produkt ist höher, wenn früh geerntet wird und wenn sämtliche Prozesse möglichst wenig Licht- und Temperatureinflüssen ausgesetzt sind.
CBDA ist zwar in seinen Eigenschaften dem CBD ähnlich, hat aber unterschiedliche Wirkungen. Im Gegensatz zu CBD ist CBDA ein Hemmer der Cyclooxygenase 2 (COX-2), also einem Enzym, das für die Bildung von pro-inflammatorischen Metaboliten wie Prostaglandine verantwortlich ist. Auch betreffend einer Interaktion mit dem „Serotonin-Rezeptor" 5-HT1A lässt CBDA eine wenigstens 10x höhere Wirksamkeit bei Übelkeit, Erbrechen und Angstzuständen erwarten. Schließlich wird vermutet, dass CBDA die eigentlich antimikrobiell-wirksame Substanz in Cannabinoidgemischen ist. Gegen Tumorzellen ist CBDA ebenfalls wirksam, wenn auch, in vitro, schwächer als CBD.
Besonders erwähnenswert ist, dass CBDA die Bioverfügbarkeit von CBD etwa um einen Faktor zwei erhöht. Anders ausgedrückt, ein Extrakt mit einem etwa 1:1 Anteil von CBDA:CBD hat nicht nur die volle Wirkung eines „reinen" CBD-Extrakts, sondern zusätzlich die Vorteile von CBDA. Tierversuche lassen vermuten, dass CBDA besser bioverfügbar sein dürfte, doch fehlen derzeit Daten am Menschen.

Introduction

Cannabidiolic acid (CBDA) was the earliest discovered cannabinoid acid. It was first isolated in 1955 (Izzo et al., 2009; Brenneisen 2007). In fresh plant material, particularly in unripe samples, 95% of CBD exists as its acid (Turner et al., 1980). In industrial hemp extracts and products that have been prepared by keeping exposure to light and heat to a minimum, CBDA is the main cannabinoid, depassing concentrations of cannabidiol (CBD) by a factor of 10 and more. But even if heated, the decarboxylation process is not complete.



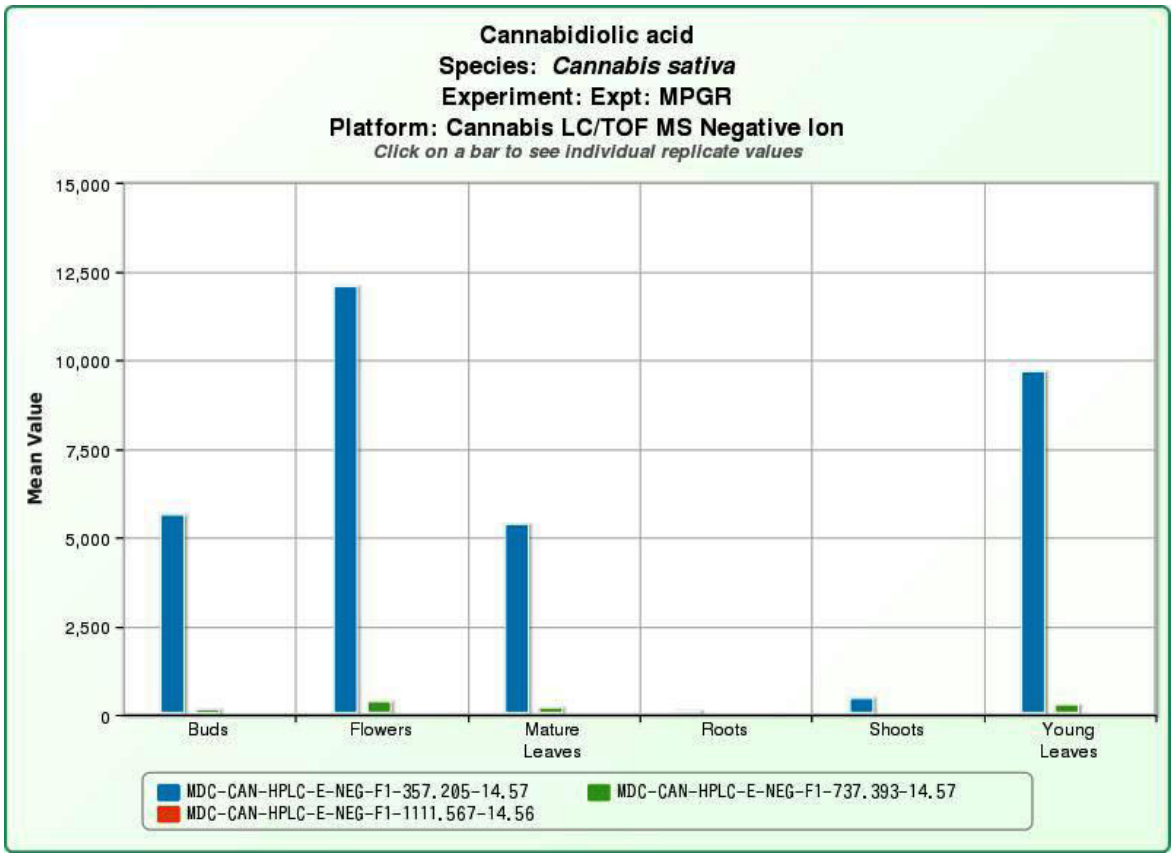
CBDA



CBD

Solubility CBDA [water, 25°C (est)]: 3.158 ng/ml (http://www.thegoodscentscompany.com/data/rw1399421.html)
Solubility CBD [water, 25°C (est)]: 5.509 ng/ml (http://www.thegoodscentscompany.com/data/rw1399301.html)

CBDA content is highest in flowers and young leaves:



From: Medicinal Plant Metabolomics Resource, http://metnetweb.gdcb.iastate.edu/mpmr_public/metabolites/?id=88913;

Conversion of CBDA to CBD

The decarboxylation of CBDA to CBD is non-enzymatically; CBD increases slowly after harvesting, during storage or through heating and exposure to light which are the two most important factors. In unheated extracts, concentrations of cannabinoid acids (mcg/ml) can be about 100 times that of the decarboxylated forms:

	CBD	CBDA	CBDA/CBD	THC	THCa	THCa/THC
Extract High in CBD - Unheated	26	3,500	135	48	3,300	69
Heated	*1,900*	*0.9*	*0.0005*	*1,100*	*9.3*	*0.008*
Extract A, High in THC - Unheated	3.9	28	7	90	14,500	161
Heated	*29*	*17*	*0.586*	*10,060*	*150*	*0.015*

Heated for 7 minutes at 200°C; From: **Verhoeckx** et al., 2006; concentrations (mcg/ml);

To note, D-9-tetrahydrocannabinolic acid exists in two forms, THCA-A and THCA-B, but only THCA-A is relevant; (here abbreviated as THCa in order to avoid confusion with the metabolite of THC, 11-nor-delta9-tetrahydrocannabinol-9-carboxylic acid (delta9-THC-COOH) that is sometimes also abbreviated as THCA).

As can be seen from the table above, decarboxylation is only partial, even when heated at 200°C for 7 minutes (Verhoeckx et al., 2006). Therefore, small amounts of CBDA but also of D-9-tertahydrocannabinolic acid (THCa) can still be found, even when extracts are heated. The fact that the presence of THCa (THCA-A) can be detected in blood and urine after smoking marijuana has been proposed as a (forensic) possibility to demonstrate exposure to cannabis (Kyriazou et al., 2014).

Very little is known about the speed of this transformation of CBDA to CBD; it seems to be about half the speed of transformation of THCa. Therefore, it is estimated to be in the order of 6 months (dark, room temperature) to several years (dark, +4°C; Wang et al., 2016). Light has the greatest influence. After heating at 60°C for two hours (pH = 7) no inactivation of CBDA has been observed whereas heating at 100°C reduced the activity by 50% (Gal et al., 1969).

Pharmacokinetics

CBDA shows a good bioavailability as determined in male Wistar rats. Following to single administration, absolute bioavailability of i.p. injected pure CBDA was 80% with 10 mg/kg, 62% with 1 mg/kg and 36% with 0.1 mg/kg; oral bioavailability was 19% after 10 mg/kg. After repeated oral administration, bioavailability of CBDA increased to 39% after 10mg/kg, and was 7% after i.p. administration of 0.1mg/kg (Jones et al., 2014). Oral bioavailability of CBDA-botanical drug substance (extract) was slightly higher than of pure CBDA which points toward enhancement of absorption by natural byproducts.

At present, no human data with pure CBDA are available. Intriguingly, the bioavailability of CBD was roughly twice as high when about 42% of the total amount of CBD (decarboxylated CBD + CBDA) of an extract administered orally, was in form of CBDA (Eichler et al., 2012). Therefore, not only the bioavailable amount of CBD of such a partially decarboxylated extract is equivalent to a fully decarboxylated extract, but offers the additional advantages of functional CBDA. At present, it is not clear whether CBDA enhances the absorption of CBD or reduces its first pass effect in the liver.

Targets and effects of CBDA

CBDA exerts pharmacological properties by its own and interacts with a number of targets of the endocannabinoid system. CBDA has weak activity on CB1 and CB2 receptors, is a partial agonist of the Transient Receptor Potential type TRPA1, of TRPV1, an antagonist of TRPM8 and a cyclooxygenase (COX-2) inhibitor (IC50: 2.2 mM; Izzo et al., 2009). CBDA binds strongly to Hydroxy-Tryptamin receptor 5-HT1A and weakly to 5-HT5A; the corresponding botanical drug substance (BDS) does not interact (Jones et al., 2014). In contrast to THC and CBD, CBDA inhibits cyclooxygenases (COX-2 about 10-times stronger than COX-1; Takeda et al., 2008; Ruhaak et al., 2011). Cyclooxygenases are enzymes that produce powerful inflammatory mediators such as prostaglandins. The effect on COX-2 is about 10-times weaker than diclofenac ("Voltaren™"), but the amount that can be taken safely is more than 10-times higher. From that, anti-inflammatory effects and a possible use for pain control might be delineated. More details are given below:

Target	Concentration	Role of CBDA	Reference
COX-1	IC50: 20-470 mcM	Weak Inhibitor; Cyclooxygenase has a pro-inflammatory role	Ruhaak et al., 2011; Takeda et al., 2008;
COX-2	IC50: 2.2mcM	Inhibitor; COX-2 has a pro-inflammatory role	Takeda et al., 2008;
DAGL	IC50: 19.4mcM	Weak Inhibitor;	De Petrocellis 2011;
GPR55	1-10 mcM	Involved in inflammation and tumour development; (CBDA slightly better antagonist than CBD, EC50 between 1 and 3 mcM)	Anavi-Göffer et al., 2012; Izzo 2009
5-HT1A ("serotonine receptor")	< 1mcM	Involved in anxiolysis, attenuation of nausea, vomiting, cerebral infarction; CBDA is at least 10-times more potent than CBD; (CBD ≈80% displacement at 16 mcM)	Bolognini et al., 2013; Cascio et al., 2014 ; Izzo 2009
5-HT5A	15mcM	Weak inhibitor (IC50 15mcM; Ki 750 nM);	Bolognini et al., 2013
TRPA1	1-10 mcM; EC50: 12 mcM	Agonist, attenuates nociception, (CBD, EC50, 0.096 mcM; more effective),	De Petrocellis et al., 2011, 2008; Izzo 2009
TRPM8	1-10 mcM	Antagonist (EC50: 0.9-1.9 mcM); (CBD, IC50: 0.08-0.14-0.503 mcM; more effective)	De Petrocellis et al., 2008, 2011; Izzo 2009
TRPV1 ("Capsaicin receptor")	> 10mcM; EC50: 10 mcM	Agonist, marginally weaker than CBD; activation induces apoptosis in cancer cells and evokes vasodilation; (CBD, EC50: 1-3 mcM)	De Petrocellis et al., 2011; Ligresti et al., 2006; Izzo 2009
TRPV4	1-10 mcM	mainly involved in sensory (nociceptive) functions; similar effective as CBD;	De Petrocellis et al., 2012

DAGL - diacylglycerol lipase (DAGLα & DAGLβ; produce 2-AG from the hydrolysis of diacyl-glycerols);
GPR55 – G-Protein coupled Receptor 55;
5-HT - Hydroxy-Tryptamin receptor
TRP – Transient Receptor Potential, A-ankrin type, M-melastatin type, V-vanilloid type;

Properties and potential uses of CBDA

Condition	Reference
Anxiolytic, in vivo, 0.05-5 mg/kg; *p.o.*	Brierley et al.2016;
Anti-inflammatory (Inhibition of COX-2); analgesic	Ruhaak et al., 2011; Takeda et al., 2008
inhibits gastrointestinal contractions & transit *in vivo*,	Cluny et al., 2011
reduced nausea and vomiting *in vivo* (Lithium-, cisplatin-induced) in dosages around 0.1 – 0.5mg/kg	Bolognini et al., 2011; Rock et al., 2016
Antitumor effects, *in vitro* & *in vivo* (breast-, gastric-, glioma-, liver-, pancreatic-, renal-, thyroid cancer cell lines);	Ligresti et al., 2006; Takeda et al., 2016, 2015, 2012; Hill et al., 2014
Antimicrobial activity *in vitro* (Gram-positive bacteria including methicillin-, tetracycline-, macrolide-resistant Staphylococcus aureus strains *)	Grlic 1962; Farkas, Andrassy 1976;

*) From: https://pubchem.ncbi.nlm.nih.gov/compound/Cannabidiolic_acid#section=Top

In various animal models, already low doses of CBDA prevented vomiting (shrews, 0.1 or 0.5 mg/kg i.p.) and nausea (rats, 0.01 or 0.1 mg/kg i.p.) with greater potency than CBD (Bolignini

et al., 2013), enhanced suppression of Lithium (Li-)-induced nausea in comedication with ineffective doses of metoclopramide (0.1 µg CBDA/kg; Rock, Parker 2013) and suppressed anticipatory nausea (Rock et al., 2014). Combination with THC or odansetron has synergistic effects (Rock, Parker 2015; Rock et al., 2015).

CBDA and CBD have inhibitory actions on the intestines of Suncus murinus that are not neuronally mediated or mediated via CB(1) or CB(2) receptors (Cluny et al., 2011).
CBDA exhibits antitumor effects on various cancer cell types and can inhibit the migration of highly aggressive breast cancer (Takeda et al., 2017; Takeda et al., 2016; Takeda et al., 2012). It was however less potent (in vitro) than CBD (Ligresti et al., 2006; Hill et al., 2014).

CBDA was found to inhibit Gram-positive bacteria and to have a high inhibiting effect on the spores of Bacillus cereus. It seems to represent the main antibiotic agent in cannabis resin. Its sporostatic effect is roughly equivalent to that of the antibiotics nisin and tylosin (Grlic 1962; Farkas, Andrassy 1976) and has been proposed as food preservative (Gal et al., 1969.

Toxicity of CBDA

Genotoxicity of pure CBDA and its corresponding botanical drug substance (BDS) were tested in vitro (bacterial reverse mutation assay, Ames test) and in vivo (rat micronucleus test, RMT) up to the maximum doses. There was no evidence of genotoxicity neither of pure CBDA nor for its corresponding BDS. The only observations were transient salivation (pure CBDA) or ataxia and decreased activity (CBDA-BDS) at the highest dose. Signs returned to normal by the 3rd day (Ayerkawa et al., 2014).
No other data are currently available.

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