

Forum

Cannabidiol Claims and Misconceptions

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Once a widely ignored phytocannabinoid, cannabidiol now attracts great therapeutic interest, especially in epilepsy and cancer. As with many rising trends, various myths and misconceptions have accompanied this heightened public interest and intrigue. This forum article examines and attempts to clarify some areas of contention.

Cannabidiol

Cannabidiol (CBD) is a 21-carbon terpenophenolic compound exclusive to cannabis after its decarboxylation from a cannabidiolic acid precursor (Figure 1). It is a pharmacological agent of wondrous diversity, an absolute archetypal 'dirty drug', encompassing analgesic, anti-inflammatory, antioxidant, antiemetic, anti-anxiety, antipsychotic, anticonvulsant, and cytotoxic effects (confined to malignant cell lines), which are mediated by a wide variety of signaling mechanisms including activity on cannabinoid receptors, 5-HT_{1A}, GPR55, GPR18, TRPV1, and other transient receptor potential channels (see [1,2] for more comprehensive reviews).

The newfound interest in CBD has been accompanied by an alarming number of mischaracterizations that will be the focus of this forum article. These include apparent confusion as to the correct assignation of CBD's psychopharmacological activity, particularly alleged sedative effects, its mechanism of action as an antagonist at the CB₁ receptor, its legal status in commerce, and its metabolic fate in human administration. Better understanding of these issues will be of great importance for patients,

recreational consumers, physicians, and legislators as they further consider the role and disposition of this versatile phytocannabinoid.

Misconception: Cannabidiol Is Non-psychoactive and Non-psychoactive and Non-psychoactive

CBD is frequently mischaracterized in lay, electronic, and scientific sources as 'non-psychoactive' or 'non-psychoactive' in comparison to tetrahydrocannabinol (THC), but these terms are inaccurate, given its prominent pharmacological benefits on anxiety, schizophrenia, addiction, and possibly even depression. More accurately, CBD should be preferably labeled as 'non-intoxicating', and lacking associated reinforcement, craving, compulsive use, etc., that would indicate a significant drug abuse liability [1].

Misconception: CBD Is Sedating

Some early anecdotal literature cited a low incidence of sedation after CBD administration, and contemporaneously, this side effect is frequently attributed to CBD. However, low to moderate doses are distinctly alerting, as proven in its ability to counteract sedative effects of THC, delay sleep time as documented via electroencephalography, and reduce THC-associated 'hangover' [3]. Numerous modern studies, even those with single doses of 600 mg of oral CBD, in normal subjects have been free of sedative effects [4]. By contrast, CBD as Epidiolex (an investigational cannabis extract with traces of THC, other cannabinoids, and terpenoids) employed in very high doses of 25 mg/kg/day or more to treat intractable epilepsy has produced sedation under conditions of polypharmacy, especially linked to elevated levels of *N*-desmethyloclobazam when co-administered with clobazam, which resolves well after reduction of the dose of the latter [5].

Whereas pure CBD is not sedating, many CBD-containing drug and hemp chemovars do display this liability. This is not attributable to CBD concentration *per*

se, but rather to the predominance of myrcene in high titer in many commercial varieties. Myrcene, a monoterpene, displays a prominent narcotic-like profile that is seemingly responsible for the 'couch-lock' phenomenon frequently associated with modern cannabis phenomenology [1]. Selective breeding of low myrcene chemovars reduces or eliminates this liability, yielding cannabis plants or extracts that are more suitable to the patient who must also work or study (Figure 2).

Misconception: CBD Is a CB₁ Antagonist Like Rimonabant

Rimonabant, also called SR141617 or Acomplia, is a synthetic CB₁ inverse agonist that was marketed briefly in Europe to treat obesity and metabolic syndrome. It was removed from the market due to numerous serious associated adverse events, including anxiety, suicidal ideation, nausea, and even *de novo* cases of multiple sclerosis [2]. This situation produced a chilling effect on development programs for other CB₁ inverse agonists and even extended to harsh scrutiny of the natural compounds, CBD and tetrahydrocannabivarin, which, in contradistinction, act as neutral antagonists at CB₁. The mechanism of action of CBD seems, rather, to stem from negative allosteric modulation of CB₁ [6], particularly in the presence of THC, and it produces none of the rimonabant-type adverse events [2].

Misconception: CBD Is Legal in All 50 States

In keeping with its versatile pharmacology without associated drug abuse liability or serious side effects, CBD is an un-scheduled drug in most nations. This is not the case in the USA, where, pharmacology notwithstanding, CBD has been a forbidden Schedule I agent with its own Drug Enforcement Administration (DEA) number, and designation as a THC analog. In spite of this continuing prohibition, domestic commerce in CBD in one form or another is rampant in storefronts and

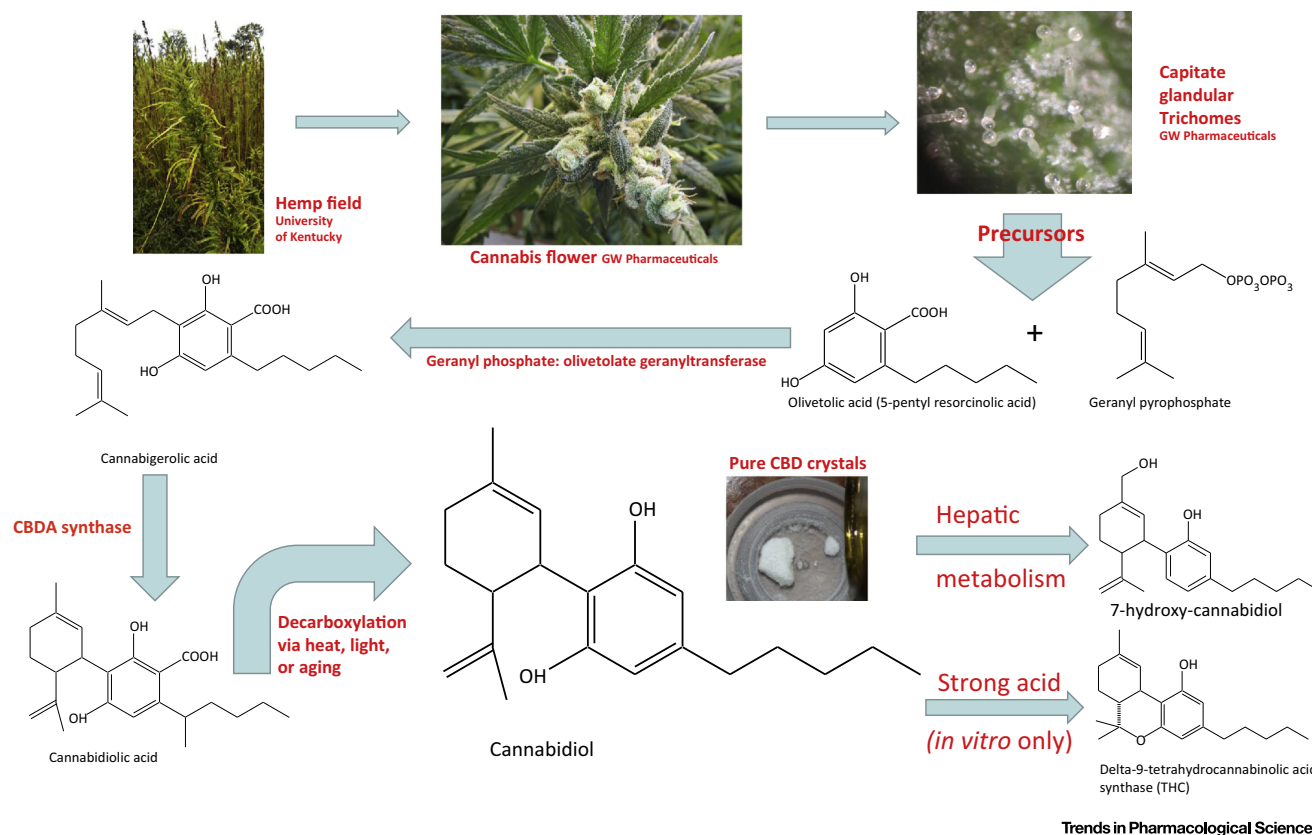


Figure 1. Cannabidiol (CBD) Production, Biosynthesis, and Metabolism. CBD is biosynthesized in hemp or drug chemovars of *Cannabis sativa*, and is produced in greatest concentration in capitate glandular trichomes in the unfertilized female flowering tops of the plant. Its main precursors are olivetolic acid and geranyl pyrophosphate, which produce cannabigerolic acid and then cannabidiolic acid (CBDA) via catalysis by CBDA synthase, an enzyme co-dominant with Δ^9 -tetrahydrocannabinolic acid synthase. Subsequently, decarboxylation via light exposure, heating, or aging results in CBD. *In vivo*, first-pass hepatic metabolism produces 7-hydroxy-cannabidiol, whose specific pharmacology has yet to be ascertained. While exposure to strong acids can produce an isomerization of CBD to tetrahydrocannabinol (THC), this reaction does not occur *in vivo* in humans (all images by E.B.R.).

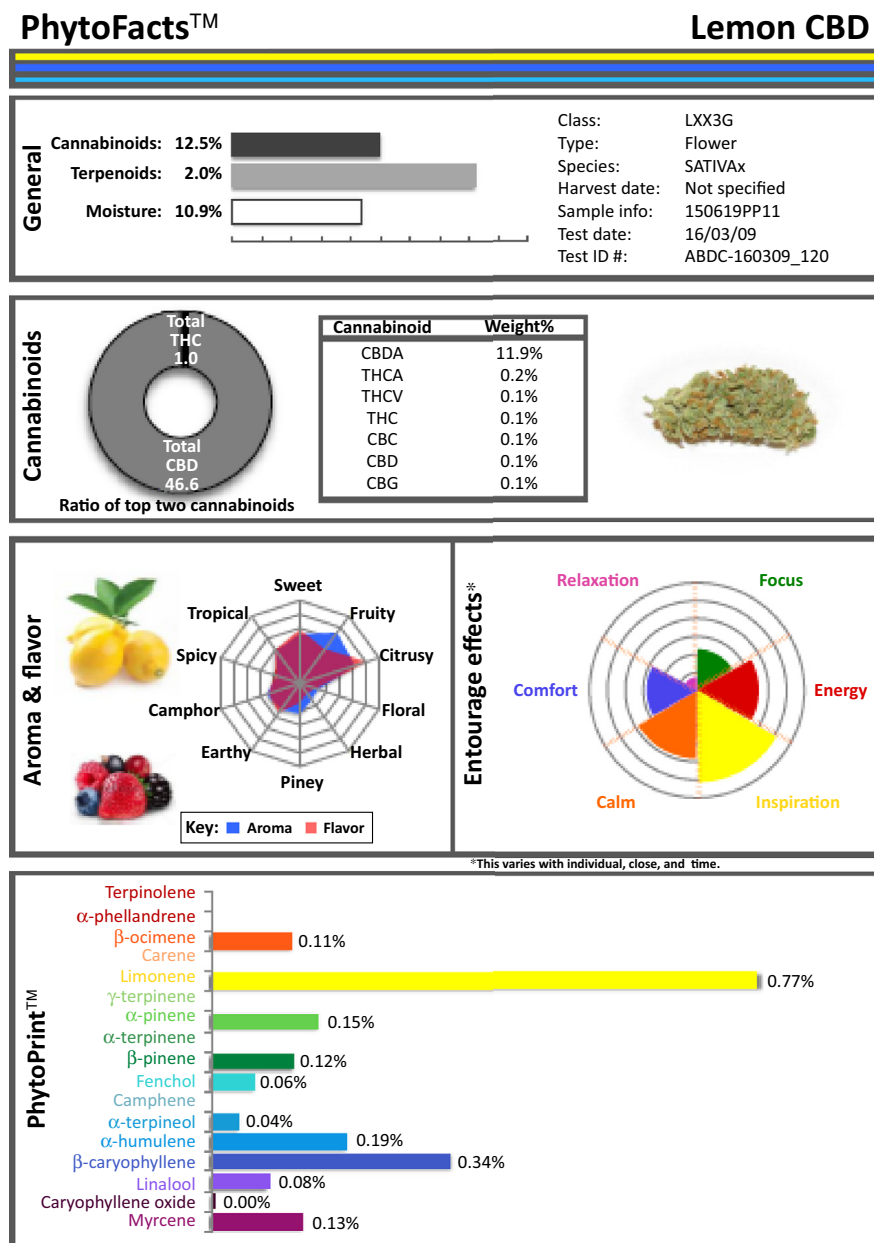
on the Internet, frequently accompanied by claims that its extraction from hemp refuse is a legal process. While currently tolerated without federal prosecution as of this writing, such practices may concentrate pesticides and other agricultural toxins [7], and are explicitly illegal under the Controlled Substances Act of 1970 [8], wherein, although possession of hemp stalks and certain other plant parts are not expressly forbidden, chemical extraction of those parts clearly is. This 'exception to the exception' is clear in text of the Act. An additional confound of American law is that, at a time when Epidiolex becomes an approved pharmaceutical agent and is necessarily assigned to a less restricted schedule,

this same status will not extend to CBD from other sources, which must remain in Schedule I until meeting similar standards of efficacy, safety, and consistency. Only reclassification of CBD by the Food and Drug Administration and DEA, or an act of Congress, would alter this scheduling discrepancy and continuing anomaly.

Misconception: CBD Turns into THC in the Body

This false claim has been frequently invoked online, and has gained currency, and perhaps even credibility, after publication of a recent article [9], in which it was demonstrated that CBD could be converted into THC after prolonged exposure to 'simulated' gastric acid. While this

isomerization reaction has been known for decades, first reported with putative end products by Roger Adams in 1940, and with definitive structures by Yehiel Gaoni and Raphael Mechoulam in the 1960s, there is no evidence whatsoever that the reaction occurs *in vivo* in humans [10]. First, no known enzyme exists that can catalyze such a bioconversion. In addition, pharmacokinetic and metabolism studies in human clinical trials refute such a reaction. In a double-blind placebo-controlled study of CBD in Huntington disease, 14 patients were administered oral doses of 10 mg/kg/day (approximately 700 mg) over 6 weeks [11]. Mean plasma levels of CBD were 5.9–11.2 ng/mL, but no plasma levels



psychotic symptomatology, sedation, and intoxication, CBD was well tolerated without such THC manifestations. More germane to this debate, neither THC nor its primary hepatic metabolite, 11-hydroxy-THC, was noted after CBD administration. Effectively, there seems to be no compelling evidence that CBD undergoes cyclization or bioconversion to THC in humans.

Concluding Remarks

CBD is an intriguing agent of unparalleled pharmacological diversity that is nevertheless surprisingly benign in all its observed effects. Its use has become widespread in certain geographical areas, particularly in 'legal' states in the USA, and it is on the threshold of becoming an approved pharmaceutical agent in intractable epilepsies. Given this current *nouvelle richesse* following its long history of obscurity, it is incumbent upon the scientific and medical communities to understand better the mechanisms of action of CBD, its limitations, and particularly the myths and misconceptions that its meteoric rise in popularity have engendered.

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Figure 2. PhytoFacts of Type III Cannabidiol (CBD)-Predominant Non-sedating Chemovar 'Lemon CBD'. The PhytoFacts analysis of the chemovar reveals it to be a Type III, CBD-predominant plant, with THC-to-CBD ratio of 46.6:1, with high titers of limonene, caryophyllene, humulene, and alpha-pinene, but relatively low myrcene content. Such a chemovar would be expected to be non-sedating, with good efficacy as an anti-inflammatory analgesic, also applicable to depression, anxiety, and treatment of addiction [1]. (Report courtesy of NaPro Research, <https://phytofacts.info/>). THC, tetrahydrocannabinol.

of THC (down to picogram sensitivity) were found in any assays. Similarly, a more recent randomized controlled study examined single oral doses of 600 mg of CBD or 10 mg of THC in 16 healthy males [12]. Whereas THC was highly statistically significant productive of adverse events such as anxiety, dysphoria, positive

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