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The Trouble with CBD Oil

Arno Hazekamp

Hazekamp Herbal Consulting, Leiden, The Netherlands

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Abstract
In just a few years, cannabidiol (CBD) has become immensely popular around the world. After initially being discovered as an effective self-medication for Dravet syndrome in children, CBD is now sold and used to treat a wide range of medical conditions and lifestyle diseases. The cannabinoid CBD, a non-psychoactive isomer of the more infamous tetrahydrocannabinol (THC), is available in a growing number of administration modes, but the most commonly known is CBD oil. There are currently dozens, if not hundreds, of producers and sellers of CBD oils active in the market, and their number is increasing rapidly. Those involved vary from individuals who prepare oils on a small scale for family and (Facebook) friends to compounding pharmacies, pharmaceutical companies, and licensed cannabis producers. Despite the growing availability of CBD, many uncertainties remain about the legality, quality, and safety of this new "miracle cure." As a result, CBD is under scrutiny on many levels, ranging from national health organizations and agricultural lobbyists to the WHO and FDA. The central question is whether CBD is simply a food supplement, an investigational new medicine, or even a narcotic. This overview paper looks into the known risks and issues related to the composition of CBD products, and makes recommendations for better regulatory control based on accurate labeling and more scientifically supported health claims. The intention of this paper is to create a better understanding of the benefits versus the risks of the current way CBD products are produced, used, and advertised.

What Is CBD Oil

Cannabidiol (CBD) oil is essentially a concentrated solvent extract made from cannabis flowers or leaves that is dissolved in an edible oil such as sunflower, hemp, or olive oil. Solvents used can vary from relatively innocuous organic solvents (ethanol, isopropyl alcohol) to more harmful ones (petroleum-ether, naphtha), or even supercritical fluids (butane, CO_2). The exact conditions and solvents applied have a great impact on, for example, the taste, color, and viscosity of the final product. Because many other plant components are co-extracted with the desired cannabinoids present in the herbal material, these are sometimes removed by a treatment known as "winterization." By placing the extract in a freezer (–20 to –80 °C) for 24–48 h, components with a higher melting point such as waxes and triglycerides, as well as chlorophyll will precipitate, so they can be removed by filtration or centrifugation [1]. This treatment can significantly improve the taste and color of the final product.

KARGER

E-Mail karger@karger.com
www.karger.com/mca

Arno Hazekamp
Hazekamp Herbal Consulting BV
Utrechtse Veer 12b
NL–2311 NC Leiden (The Netherlands)
E-Mail Hazekamp.hc@gmail.com

Cannabis oils may contain various concentrations of CBD, tetrahydrocannabinol (THC), and minor cannabinoids, mainly depending on the cannabis variety used for extraction. The most popular product currently is CBD oil, but for example cannabigerol (CBG)-rich oil has been spotted as well [2], and others will very likely follow soon. The THC-rich type of cannabis oil has already been known for some years, and is generally known under the name "Simpson oil" [3]. Terpenes may or may not be present in these products, depending on the preparation method used [4]. Because they are highly volatile, elevated temperatures (such as those applied during drying of plant materials, or during the evaporation of solvents) may result in a significant loss of terpene components [5]. However, it is possible to capture evaporated terpenes by condensation, and reintroduce them back into the final oil. Additional ingredients may be added to further adjust properties such as color, viscosity, taste, or shelf-life stability.

Oil has become a favorite mode of administration for many medical users of cannabis and cannabinoids for multiple reasons. First of all, concentrated extracts allow the consumption of a large dose of cannabinoids in an easily ingestible form. With CBD oil, there is no risk of intoxication (getting high) [6], so much larger doses can be consumed than would be possible for THC-rich products. Many users who prefer the holistic approach of using herbal cannabis worry about the stigma associated with the typical smell caused by smoking or vaporizing it. Cannabis oil has no smell that may identify a consumer as a cannabis user, and it can be used discretely even in a social setting, e.g., at work or around family. Moreover, it can be efficiently dosed simply by counting the number of drops consumed. These same benefits of using a concentrated extract were identified in a large survey among medicinal cannabis users published in 2013 [7], perhaps as an early indicator of the emergence of cannabis oils as a preferred method of ingestion. Currently, the market is developing further towards more sophisticated and patentable products, including oral capsules, liposomal products, skin creams, and chewing gums containing CBD.

Therapeutic Effects of CBD

Today, CBD is used for the treatment of a wide range of medical conditions. This started with the somewhat serendipitous discovery (by parents experimenting with self-medication for their children) that CBD had a therapeutic effect on a serious form of epilepsy in children, called Dravet syndrome [8]. This effect is now under clinical investigation with the pharmaceutical CBD product Epidiolex®, which is currently in phase 3 trials with encouraging results [9, 10]. The media attention generated by its effect on severely ill children gave CBD the push needed to become a much desired medicine almost overnight [11]. Other medical indications that may be treated with CBD, and are supported to some extent by clinical proof, include Parkinson's disease [12], schizophrenia [13], and anxiety disorder [14]. However, although research into the therapeutic effects of CBD is rapidly increasing, most current uses of CBD are not (yet) supported by clinical data. The popular use of these products means that physicians may be confronted with the effects of CBD oil even when they do not prescribe it themselves.

An excellent example is the use of CBD (and also THC) products for the self-medicating of cancer, with the intention of fully curing it [15]. This is based on an increasing body of preclinical evidence showing cannabinoids to be capable, under some conditions, of inhibiting the development of cancer cells in vitro or in vivo by various mechanisms of action, including induction of apoptosis, inhibition of angiogenesis, and arresting the cell cycle [16]. This is certainly exciting news, and research is ongoing around the world, but there is no solid clinical evidence yet to support that cannabinoids – whether natural or synthetic – can effectively and safely treat cancer in actual humans [17]. In fact, there are indications that certain types of cancer may even accelerate when exposed to cannabinoids [18]. This becomes problematic when patients choose to refuse chemotherapy treatment because they firmly believe in the rumored curative properties of cannabinoids. As a result, recommendation of cannabinoids for treating cancer should be done with great care, and with distinction as to the type of cancer being treated [19].

Increasingly, CBD oil is also being promoted as a prophylactic treatment in order to prevent certain diseases from developing at all. The argument used is that the human endocannabinoid system is involved in basic life functions such as appetite, immune response, reproduction, and pain management [20]. Because CBD functions as an indirect antagonist to human CB_1 and CB_2 receptors [21], it is reasoned that the presence of CBD prevents them from being overly activated, thereby protecting the nervous and immune systems from everyday stress. Furthermore, CBD is known to be a reasonably potent antioxidant, which further helps to protect against stressful

influences [22]. Although this clearly increases the market for CBD products, it also further erodes the scientific basis for the therapeutic use of CBD. After all, it is hard to prove scientifically that a disease was prevented by the use of a health-promoting product.

If CBD oil was used mainly by adult, well-informed, and reasonably healthy consumers, the impact of its widespread use would perhaps be quite acceptable and limited. However, this is not the case, as CBD is actively marketed for use by children (e.g., for Dravet syndrome, ADHD, autism), elderly people (Alzheimer's disease, dementia, Parkinson's disease), patients suffering from complex diseases (cancer, multiple sclerosis, chronic pain), and even pets (anxiety, appetite, sleep). Indiscriminate use of CBD may lead to various issues among these consumers. For example, CBD shows an exciting potential for treating epilepsy in children, but the long-term effects of high-dose CBD on these children's brain functions remain unclear, while there are strong clues that the endocannabinoid system is central in the proper neuronal development of the adolescent brain [23]. In order to halt the unchecked advertising of CBD products, health authorities in various countries have begun sending official warning letters to stop producers and sellers from making unfounded health claims [24, 25].

Legal Status of Hemp and CBD

The CBD present in oils and other products is usually derived from fiber-type varieties of cannabis (hemp), because these are naturally higher in CBD content than drug-type varieties (marijuana). Although cultivation of hemp is allowed in many countries around the world, this is usually governed by strict regulations. After being banned for decades, hemp cultivation in the USA has only recently been reintroduced, and is still gearing up for full industrial production [26].

In the European Union (EU), the cultivation of certain cannabis varieties is granted provided they are registered in the EU's *Common Catalogue of Varieties of Agricultural Plant Species* [27] and the THC content does not exceed 0.2% of the dried flowers of the plant [28]. In Canada, hemp is allowed to contain 0.3% THC [29], while Switzerland allows up to 1% THC [30]. In most countries, viable seeds for planting may be purchased from certified seed companies only, in order to make sure that the correct hemp variety is indeed being cultivated. Additionally, hemp may typically only be grown in agricultural fields outdoors, while indoor cultivation is usually forbidden. In some countries (e.g., The Netherlands), growing hemp is allowed only with the intent to produce fibers or seeds. As a result, the act of harvesting fiber cannabis for its CBD is a violation of narcotics laws [31]. New cannabis varieties (for example developed to yield a higher content of CBD) are not (yet) registered as approved hemp varieties, and therefore cannot be freely cultivated, while the official registration process takes several years to complete.

The legal status of CBD in the USA is extra complicated, because many individual states have introduced their own medicinal or even recreational cannabis laws, while the Federal Government does not accept any consumption of cannabis [32]. In the USA [33], but also in Germany and the UK [34], CBD has been technically classified as a new medicine, requiring manufacturers to meet much stricter safety, quality, and effectiveness standards. The statement that CBD is simply "legal in all 50 US states" is therefore misleading, if not untrue. It should be noted that even in places where CBD is technically illegal, products may still be easily available because the authorities are lax about enforcing the law, or discussions are still ongoing on how to deal with the influx of CBD. In short, whether CBD is legal depends of how it was made, what is in the final product, and where you are located.

An important issue in the discussion around cannabis-derived oils is: how much THC is a legal CBD product allowed to contain in order not to be considered a narcotic? Authorities sometimes choose to deal with these regulations in a pragmatic way, recognizing that laws once designed to control marijuana abuse may not be fully applicable to hemp. For example, in the Netherlands, a maximum level of 0.05% THC is allowed in CBD products, even though, formally, any detectable trace of THC is illegal according to Dutch narcotics laws. This approach is based on the fact that even hemp varieties of cannabis produce a small amount of THC, and therefore naturally derived CBD extracts will carry some THC in the final products.

The fact that the maximum CBD content in an oil is limited by the THC present in the herbal material used makes it attractive to add an additional amount of purified CBD to boost the percentage advertised on the label. Unfortunately, the Novel Food Catalogue of the EU states that "extracts of *Cannabis sativa* L. in which CBD levels are higher than the CBD levels in the plant source are novel in food" [35]. This means that enriching a natural hemp extract with pure (often synthetic) CBD makes it a Novel Food product, with the consequence that it must undergo significant safety assessment prior to being mar-

keted. However, it is still unclear in many EU countries if extracts with no added CBD also fall under this regime.

Given the many restrictions and conditions, it can be difficult to set up a fully legal and functional pipeline for the production and sale of CBD oil. Because different countries allow different activities with regards to cultivation, processing, extracting, etc., of hemp, entrepreneurs have often set up production pipelines that span multiple countries, where hemp is cultivated in one country, while extraction takes place in another, lab testing in a third, and sales take place in yet another country. This obviously makes it harder to determine exactly where a CBD product comes from, who is responsible for its final quality, and what standards were followed. For that reason, thorough analytical testing of final products by certified third-party labs is an essential tool to guarantee the safety and composition of CBD oils.

Identifying the Real Risks

The discussion on the legal status of CBD revolves mainly around the question: is it a medicine or a natural food supplement? The main difference is that medicinal drugs are considered unsafe until proven safe, whereas food supplements are considered safe until proven otherwise. As a result, the central question becomes whether or not CBD is safe for consumers (children, elderly, patients) in large and unregulated quantities. Although there is only limited knowledge about the long-term effects of chronic use, or about drug-drug interactions between CBD and other medications [36], human studies have indicated that CBD is very well tolerated even up to a daily dose of 1,500 mg [37]. Indeed, a recent World Health Organization (WHO) review concluded that "to date, there is no evidence of recreational use of CBD or any public health-related problems associated with the use of pure CBD" [38]. However, the risks to be assessed about CBD products may not have much to do with the pure compound CBD itself, but more with the unknown composition and quality of the products offered. In particular, we should be looking into the presence of contaminants in these concentrated extracts, and into incorrect or even misleading labels for the cannabinoid content of products.

It is well known that cannabis plants obtained from uncontrolled sources may be contaminated with various harmful substances [39], sometimes leading to severe health issues or hospitalization [40]. Contaminants include chemicals that were intentionally added in order to increase yield, weight, or potency (e.g., pesticides, metal particles [41], synthetic cannabinoids [42]) but also agents that entered the plant unintentionally (e.g., heavy metals, molds and bacteria [43], aflatoxins). For example, pesticides are frequently present in cannabis sold by Dutch coffee shops [44], but were also found in cannabis offered under state law in California [45] as well as medicinal cannabis from licensed producers in Canada [46]. If any of these contaminants were present in hemp used for CBD extraction, they would likely end up in a concentrated form in the final oil. One contaminant specifically relevant to cannabis (CBD or THC) oils is the residual presence of toxic solvents used during the extraction procedure [3].

Although contaminants come in various shapes and forms, most are relatively easy to detect, because many professional analytical labs exist that routinely screen for such contaminants in, for example, food crops, imported medicinal plants, or edible oils. The standard lab methods, as described in Pharmacopoeia monographs (e.g., USP, EP) or food regulations, could simply be applied to CBD oils, after some minor validation studies. For example, the detection of heavy metals or pesticides present in CBD oil does not significantly differ from the same analysis in, say, a shipment of olive oil. The only analysis that is not yet standard procedure in most analytical labs is the quantification of cannabinoids. Because cannabinoids are only found (with few exceptions [47]) in the cannabis plant, specific analytical methodology must be developed to properly determine the cannabinoid composition of the many CBD products available.

Although a range of analytical methods have been published in recent years [48], there is no general agreement on which analytical method is most suitable and accurate. Additionally, there are currently no generally accepted guidelines or certifications to determine the qualifications of cannabis labs. As a result, cannabinoid analysis can differ significantly between labs [49], even when the exact same sample is analyzed multiple times [50]. This not only poses a risk to consumers (who do not know how trust the label on their product) but may also lead to business-to-business conflicts about the quality or value of intermediate products. Additionally, inaccurate analytical results may lead to legal problems if the THC content of a CBD product unexpectedly turns out to be higher than the maximally allowed limit. It seems clear that a better agreement on the conditions for lab testing of cannabinoids is urgently needed.

Table 1. Analysis of Dutch cannabis oil samples obtained from actual patients, comparing the claimed cannabinoid content on the product label with lab results measured in the study [51]

Sample ID	CBD(A)			THC(A)		
	label, %	measured, %	deviation, rel. %	label, %	measured, %	deviation, rel. %
1	**27**	2.3	*–91.5*	**17**	0.1	*–99.4*
2	**25**	0	*–100*	**35**	4.6	*–86.9*
3	**12**	0.2	*–98.3*	–	0	*
4	**10.9**	2.8	*–74.3*	–	0.1	*
5	**10**	2.2	*–78*	**10**	4	*–60*
6	**8**	0.6	*–92.5*	**4**	0.2	*–95*
7	**8**	0.6	*–92.5*	**4**	0.1	*–97.5*
8	**6**	0.2	*–96.7*	**5**	0.1	*–98*
9	**5**	0	*–100*	**40**	3.4	*–91.5*
10	**4**	4.7	*+17.50*	–	0.2	*
11	**4**	5.4	*+35*	–	0.3	*
12	**4**	4	*0*	–	0	*
13	**4**	4.2	*+5*	–	0	*
14	**3**	3.1	*+3.3*	–	0.2	*
15	**2.75**	2.8	*+1.8*	–	0.1	*
16	**0.1**	0.1	*0*	**4**	6.3	*+57.5*
17	–	0.1	*	**7**	7.9	*+12.9*
18	–	0	*	**5**	0.7	*–86*
19	–	0	*	**5**	0.9	*–82*
20	–	0.1	*	**20**	15.8	*–21*
21	–	0	*	**7**	6.4	*–8.6*

CBD, cannabidiol; THC, tetrahydrocannabinol; CBD(A), total sum of CBD plus CBD-acid; THC(A), total sum of THC plus THC-acid. * Not applicable because no label claim was made.

What Studies Tell Us

Recently, an interesting study performed in the Netherlands highlighted multiple issues that may be extrapolated to CBD products elsewhere [51]. In this study, 46 different cannabis oil samples were collected directly from patients and analyzed for cannabinoid content. The obtained samples were home-made ($n = 29$) or purchased from a (web) store ($n = 17$). For 21 of the 46 products (46% of all samples), label information was available on CBD/THC content, so that the claimed content could be compared to the analyzed content as determined in the study. Results are shown in Table 1. In many cases the analyzed cannabinoid content strongly differed from the claimed content on the label, while in 7 samples no cannabinoids (CBD or THC) were found at all. Such deviations were found in home-made as well as commercially obtained products.

Additionally, as many as 26/46 samples (57%) had a THC content >1%, with one sample peaking at 57.5%. In 18/46 samples (39%) the oil contained virtually only THC (with CBD <0.1%). Although many of the samples analyzed were purposely made to contain a high THC content, it is unclear whether oil consumers are always aware they are consuming THC, and thereby exposing themselves to the adverse effects of this psychotropic compound, such as intoxication, panic attacks, or disorientation. It should be noted that although the exact legal status of CBD may be debatable, THC-rich extracts are strictly prohibited in virtually all countries.

Another interesting observation was the presence of high levels of non-decarboxylated cannabinoids in multiple samples. It is well known that CBD and THC are not produced as such by the metabolism of the cannabis plant. Instead, cannabinoids are excreted in the form of carboxylic acids such as CBD-acid and THC-acid [52]. The physiological effects of these "acidic" cannabinoids have been studied only to a very limited extent. Only after proper heating (e.g., during smoking, vaporizing, or baking with cannabis) are these natural precursors rapidly

converted into the more well-known CBD and THC, respectively. This process is called decarboxylation [52]. Although decarboxylation also takes place during the production of cannabis oils (e.g., during the evaporation of solvents, or during a separate decarboxylation step as part of the production process), 7/46 samples (15%) contained >25% of its cannabinoid content in the form of acidic cannabinoids, indicating poor control over the decarboxylation process. To address the issue, some producers simply add up the content of CBD and CBD-acid in order to boast a higher "total CBD" content on the label, while advertising this as "raw CBD."

Various studies done on CBD oils and other cannabis products around the world have come to similar conclusions about incorrect label information [24, 53, 54] and the presence of contaminants [54–57]. In the absence of a clear legal status for CBD, or agreement on common safety and quality standards, it may not be surprising that current CBD products leave something to be desired. The time has come for regulators to give CBD the attention it deserves in order to ensure that affordable, safe, and reliable CBD products are available to those who depend on them.

Conclusion

Almost overnight, CBD oils have become an interesting combination of popular holistic medicine, miracle cure, and a natural answer to the synthetic drugs dominating modern medicine. With CBD, patients receive the promise of being in control of their own ailments, and no longer feeling at the mercy of their treating physicians. This has turned out to be a particularly powerful message. Many patients use CBD oils freely for ailments both confirmed and self-diagnosed, and the rapid innovations with CBD products have actually been quite impressive. But while new CBD products keep entering the market virtually unchecked, effective regulatory control of these products has stayed far behind. As a result, unknown risks about long-term effects remain unaddressed, especially in vulnerable groups such as children, the elderly, and the chronically or terminally ill. It should be noted that this discussion goes well beyond CBD only, as new products containing additional cannabinoids like CBG, THCV, and acidic cannabinoids are following closely behind. We know even less about these compounds than about CBD, and very limited human safety data are available.

Although CBD seems destined to play an important role as a therapeutic agent for a growing number of medical indications, we should seriously ask ourselves if the current unregulated production and sale of CBD oils is done responsibly. Despite the fact that CBD is mainly sold as "just" a food supplement, it is often used by severely ill people with the intention of improving their body functions in a way that their standard medication could not. This obviously puts CBD uncomfortably close to the realm of medicines. Interestingly, the WHO, based on a review of available scientific data and input from international experts, recently concluded that CBD does not immediately require rescheduling as a drug [38], although a fuller review on the risks and benefits of CBD is still being planned. Nevertheless, perhaps the use of CBD products should be assessed in a broader perspective, to cover all ingredients used in the preparation, as well as any contaminants that are already known to be common in recreational cannabis.

Determining risks and benefits through proper clinical trials remains highly desired, but these will take considerable time and funds. As a result, clinical data will not appear any time soon, while patients will not simply stop using the many CBD products to which they have become accustomed. Taking back regulatory control over CBD could therefore start with a more short-term and achievable approach, i.e., demanding accurate and proper labeling, reflecting in detail what each product does and does not contain, and how it was manufactured. For a clearer judgment of the potential therapeutic effects, the risks, but also the legality of a cannabis extract, it is important to know its exact composition. After all, published data from around the world has taught us that misleading labels as well as harmful contaminants are real and actual problems for CBD products. The analytical methodology and the third-party labs needed for this approach largely already exist, and could easily be optimized to quickly get a better grip on the unrestrained cannabinoid market. This approach would hold each producer strictly accountable for the quality and safety of their own products, as long as there are real legal consequences for those businesses that break the rules. Add to this a system for regular professional audits and inspections, and a crackdown on unsubstantiated health claims, and we have a reasonable system to ensure that CBD can be used responsibly by those who need it, until much needed clinical data become available.

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