Quantification of Cannabichromene among Nineteen Cannabinoids in Key Lime Pie Hemp Flowers by Liquid Chromatography Ultraviolet Detection

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By Jillian Mulholland

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This honors thesis was prepared under the direction of the candidate's honors thesis advisor, Dr. Song, Department of Chemistry at Western Illinois University, and it has been approved by the members of the candidate's thesis committee.

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Dr. Liguo Song
Thesis Advisor

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Dr. Keith Boeckelman
Department Chair

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Date

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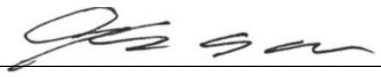

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December 9, 2024
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Abstract

The recent increase in popularity of *Cannabis indica* and *sativa* for its recreational and medicinal purposes produced the demand for analytical methods that are reliable and accurate for the identification and quantification of cannabinoids. A liquid chromatography ultraviolet detection (LC-UV) method was developed for the quantification of cannabichromene (CBC) in key lime pie hemp flowers among nineteen cannabinoids. The quantification was achieved using external standard calibration between 0.02 and 25 μg/mL. The limit of quantitation (LOQ) was determined to be 0.04% CBC in hemp flowers. To recover CBC, the sample was combined with methanol to prepare a 25 mg/mL mixture. After ultrasonication, centrifugation and filtration, the extract was serially diluted to 50 μg/mL and analyzed by LC-UV. The CBC content in key lime pie hemp flowers was measured to be 0.59% with relative standard deviation (RSD) of 1.6% in triplicate. The method was not interfered with by other cannabinoids present in hemp flowers.

Introduction

The two primary species of *Cannabis* are *Cannabis sativa* and *Cannabis indica*. *Cannabis sativa* is what is known as "hemp" while *Cannabis indica* is more commonly known as marijuana. Both species of *Cannabis* produce a unique class of compounds known as cannabinoids (**Figure 1**).

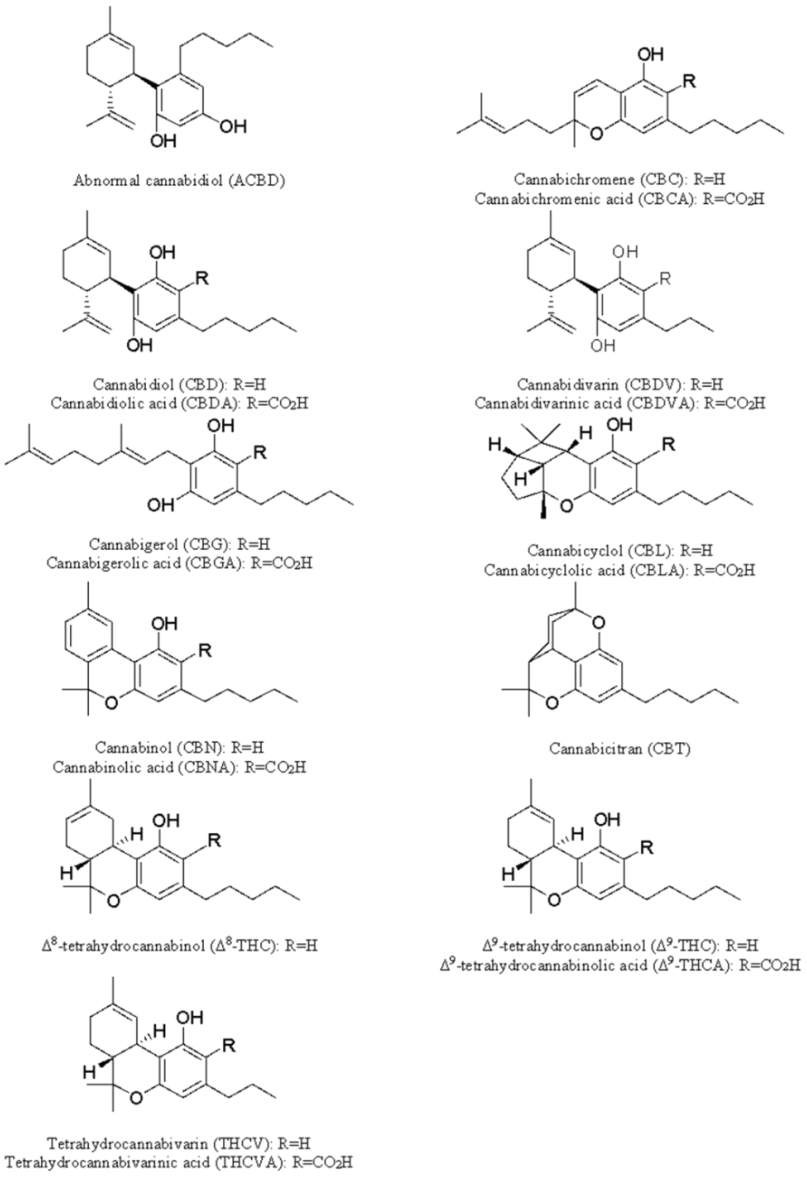


Figure 1. Chemical structure of nineteen cannabinoids

Cannabis plants, typically *Cannabis indica*, is known for its psychotropic effects, which occurs when the Δ^9-THC content is approximately 1%. Δ^8-THC also has psychotropic effects; however, the effects are milder. *Cannabis sativa*, on the other hand, does not exhibit these psychotropic effects due to its low levels of Δ^9-THC and prominent levels of cannabidiol (CBD). CBD has found uses in the treatment for various diseases and disorders, some of which include anxiety, insomnia, pain, PTSD, and depression.

The 2018 Farm Bill was passed by Congress in December 2018, which established a clear distinction on the classification of hemp from marijuana. The 2018 Farm Bill also provided clarification on how to make cultivating, processing, and selling hemp and hemp-derived products easier. The distinction that was made established the Δ^9-THC concentration for hemp to be no more than 0.3% on a dry weight basis. This allowed for the separation of *Cannabis sativa* from *Cannabis indica*. Once the 2018 Farm Bill was enacted, there was a rapid increase in commercial products that contained hemp and hemp-infused products, such as hemp-infused edibles, hemp-infused topicals, and hemp concentrates.

Before the passing of the 2018 Farm Bill, Americans have used marijuana for medical purposes. For instance, in 1996, California passed the first Medical Marijuana Law.[1] This exempted patients and their primary caregivers from criminal liability under state law for possession and cultivation of marijuana for medical use. However, the Federal Controlled Substance Act (CAS) of 1970 defined *Cannabis* as a Schedule I substance, making medical and recreational use and growing hemp illegal. There have also been more states since California passed the first Medical Marijuana Law with laws enacted that conflict with the government's efforts to regulate marijuana.

In recent years, some states in the United States have begun legalizing *Cannabis* on a state level, but it remains on the CAS list as a Schedule I substance. Being a Schedule I substance prevents any accepted medical use and shows a high potential for abuse. As of December 2024, 23 states have fully legalized *Cannabis*, 5 states have decriminalized and allowed medical use, 8 states allow medical use, 2 states have decriminalized *Cannabis*, and 4 states remain fully illegal for *Cannabis* use. Decriminalization of *Cannabis* means that it is still illegal, however, it prohibits people from being prosecuted for personal use.

Hemp products have seen an increase in medicinal purposes in the past couple of years.[2-7] Several cannabinoids have been studied to be pharmaceutical targets for treatments of various diseases and illnesses, such as to treat anorexia, pain, inflammation, multiple sclerosis (MS), epilepsy, cancer, cardiovascular disorders, and more.[2-7] CBD is one of the major cannabinoids produced by hemp and has been used in a variety of medical uses. Specifically, Epidiolex (CBD) oral solution was approved by the Food and Drug Administration (FDA) in June 2018 for treating seizures that are related to two severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, for patients two years or older. Another cannabinoid that has medicinal use is cannabigerol (CBG), which has been seen to potentially contain analgesic and anti-inflammatory properties. Cannabinol (CBN) may contain immunosuppressive properties. Cannabichromene (CBC), may have great potential to treat inflammation and for promoting growth of new brain cells.

Along with cannabinoids used for medicinal purposes, cannabinoids are also commonly seen in wellness and skincare products. For instance, CBD-infused lotions are one of the most popular products sold. CBD-infused lotions provide several benefits, such as pain relief, skin hydration, and soothes dry and irritated skin. However, cosmetic products that contain

cannabinoids, such as CBD-infused lotions, are not currently regulated at the federal level. With no prohibition, therefore no regulations, of cannabis derived ingredients by the U.S. Food and Drug Administration (FDA), the FDA does not have an obligation to approve cosmetic products containing cannabis before being sold to customers.[8] There have been several studies on the quantity of CBD in these types of products, most finding quantities of the cannabinoids being either greater or less than the amount that was advertised on the label. A validated method for liquid chromatography tandem mass spectrometry (LC/MS/MS) has been used for the analysis of samples for cannabinoids. One of these studies, which used LC/MS/MS to quantify CBD and THC in 40 hemp products in a variety of matrices, such as creams and cosmetics.[8] This study discovered that some products contained higher CBD levels than what was advertised, which again introduces the argument for testing of commercial hemp products.

CBC is one of four major cannabinoids in *Cannabis sativa* L. and the second most abundant cannabinoid in drug-type cannabis. The other major cannabinoids include Δ^9-THC, cannabinol, and cannabidiol. Δ^9-THC has been observed to decompose during storage to less psychoactive compounds, such as CBN (**Figure 2**). In the scheme, hydroxylated cannabinoids, such as 9,10-dihydroxy-$\Delta^{6a(10a)}$-THC (VI), 10-ethoxy-9-hydroxy-$\Delta^{6a(10a)}$-THC (VII), and 8,9-dihydroxy-$\Delta^{6a(10a)}$-THC (VIII), have also been noted to also participate in the conversion of Δ9-THC to CBN.[9]

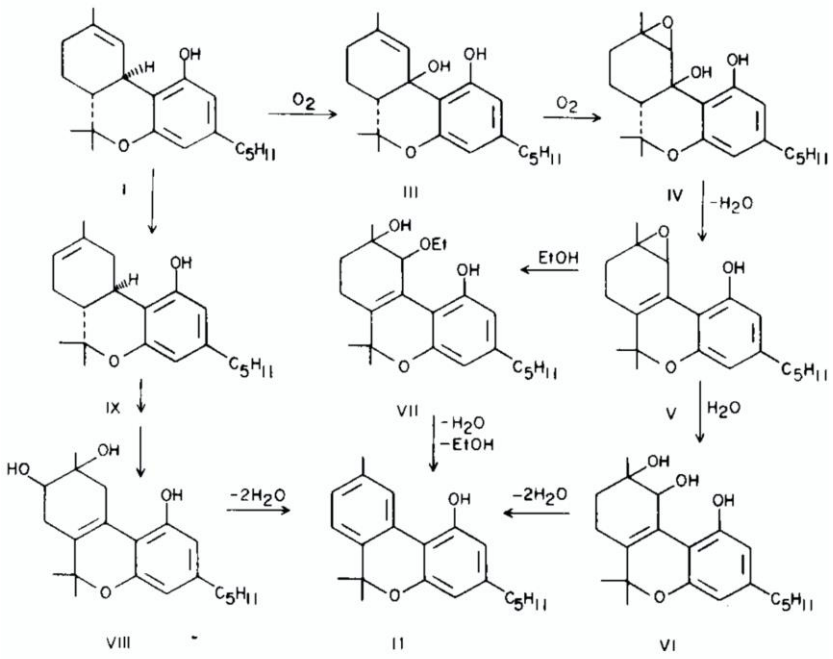


Figure 2. Pathway for decomposition of Δ^9-THC (I) to CBN (II). Image credit: *J. Heterocyclic Chem*.

CBN is one of the non-psychotropic cannabinoids present in *Cannabis sativa*. As stated earlier, CBN exhibits immunosuppressive properties, as well as anticancer, antimicrobial, analgesic, and anti-inflammatory properties. CBN has 10% of the psychotropic properties of THC, which makes its medical uses unique.[10] For instance, CBN can induce apoptosis in cancer cells which leads to a decrease in cellular proliferation and in tumor volume. CBN can also perform similar to non-steroidal anti-inflammatory drugs (NSAIDs), which perform by reducing pain, fever, and other types of inflammation at the pain-inducing event. CBD and aspirin were compared through several tests, one of which was the acetic-induced writhing test. Compared to aspirin, CBN was efficient in decreasing the frequency of the writhing and increasing the pain threshold of the non-injected paw.[10]

With *Cannabis* products becoming widely used in the medical field for a variety of treatments, although usage of cannabinoids such as CBD can cause side effects which must be considered before becoming available for prescription. CBD can cause diarrhea, nausea, irritability, and more. In the body, CBD will interact with common biological targets that are implicated in drug metabolism and excretion, making drug-drug interactions (DDIs) more likely to occur between over-the-counter medications, such as NSAIDs, antimicrobials, and antiepileptics.[11] This can result in reduced effectiveness, unexpected side effects, or create dangerous combinations of drugs. For instance, DDIs can occur between CBD and NSAIDs, which can lead to possibly severe outcomes, such as aseptic meningitis.[11]

CBC, along with some of its homologs, analogs, and isomers were studied for its anti-inflammatory activity.[12] Its anti-inflammatory properties were studied through both the carrageenan-induced rat paw edema assay and the erythrocyte membrane stabilization method. Through the study completed by Turner, et. Al, the inhibition of heat-induced erythrocyte hemolysis by CBC and its homologs and isomers was studied (**Table 1**).[12] Here, it is observed that CBC exhibited the highest percentage of inhibition at 98%. Other concentrations of CBC were tested, with the percentage of inhibition starting at 55%, then increasing to 67%, and 79%.[12] Compared to aspirin (**Table** 1), CBC and most of its isomers, homologs, and analogs performed better at inhibition. Aspirin performed with an inhibition percentage of 21%, while phenylbutazone at both concentrations performed below that (10% and 16%). Isocannabichromene, however, performed at the second highest inhibition percentage behind CBC (75%). The dose response curve for the inhibition of CBC concentrations from **Table 1** can also be observed below (**Figure 3**).

Compound	Concentration of test solution (*M*)	Inhibition (%)
Cannabichromene (IV)	1×10^{-4}	98
	5×10^{-5}	79
	2.5×10^{-5}	67
	1.25×10^{-5}	55
Isocannabichromene (VII)	1×10^{-4}	75
Cannabichromene-C_1 (V)	1×10^{-4}	86
Cannabichromene-C_0 (VI)	1×10^{-4}	69
Isocannabichromene-C_0 (VIII)	1×10^{-4}	43
Phenylbutazone	1×10^{-4}	16
	2×10^{-5}	10
Aspirin	2.5×10^{-4}	21

Table 1. Inhibition of heat-induced erythrocyte hemolysis by cannabichromene and its homologs and isomers. Credit: *J Clin Pharmacol.*

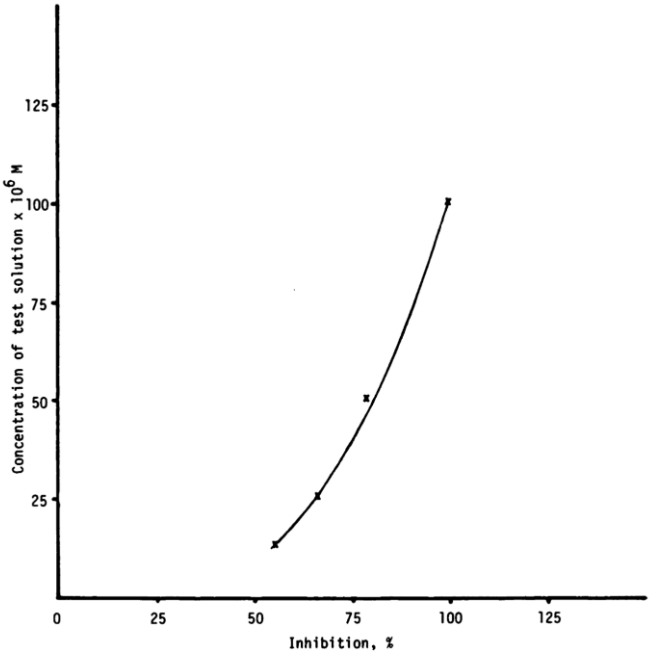


Figure 3. Dose-response curve for the inhibition of heat-induced erythrocyte hemolysis with different concentrations of cannabichromene. Image credit: *J Clin Pharmacol*.

Cannabinoids have been shown to play a crucial role in regulating platelet function in thrombosis, which is a condition that occurs when a blood clot forms within a blood vessel or

heart chamber. However, there have been many clinical reports that have associated cannabis use with thrombogenic development which culminates into acute coronary artery disease.[13] These studies have discrepancies about the influence of cannabinoids on the formation of thrombus, or blood clots, and platelet aggregation. With additional research, it has been shown that cannabinoids efficiently inhibit platelet aggregation.[13] This can be an issue due to platelets being less likely to form clots, which could lead to potential excess bleeding. This can be dangerous in situations such as surgery or with trauma due to a greater risk for complications to arise. There are medications available to purposefully inhibit platelet aggregation, however, those are typically prescribed to patients that are at a high risk of blood clots.

While *Cannabis* products have been proven to have medicinal uses, there are also long-term effects that come with using the drug. For instance, it has been reported that there are deficits in the performance of complex cognitive tasks in long-term *Cannabis* users, however, there is little evidence to suggest that these deficits are qualitatively or quantitatively more severe than those seen after acute drug use.[14] One method to assess cognitive function is to measure IQ. It was observed that compared to a person's IQ before *Cannabis* use, current use resulted in a decline in scores with significantly correlated in a dose-dependent manner. With former heavy cannabis users, however, there was no decline observed.[14] Due to *Cannabis* use becoming more of an issue in recent years, there are little to no studies performed on significant long-term effects. This could pose an issue for young people using *Cannabis* today while not fully understanding the consequences.

There are several ways that *Cannabis* can be consumed. These include inhalation through either smoking or vaping, edibles, tinctures, and topicals. For about the last decade, vaping has become of concern to healthcare officials for e-cigarette or vaping product use-associated lung

injury (EVALI). Those that are diagnosed with EVALI might exhibit some, or many, of the following symptoms: shortness of breath, cough, chest pain, fever and chills, nausea, vomiting, abdominal pain, and more. EVALI can exhibit as being acute or subacute, with even severe cases being fatal. It is a relatively new condition, which also raises issues due to healthcare providers and medical researchers not sure of the long-term effects or outlook. Many people associate *Cannabis* with being a harmless drug, however, that is not the case. Up until February 2020, the Centers for Disease Control (CDC) recorded 68 deaths and 2807 hospitalizations. EVALI is associated significantly with the use of e-cigarettes containing Δ^9-THC according to 82% of patients, 33% of patients reported using only Δ^9-THC e-cigarettes, and 14% reported using electronic nicotine delivery systems.[15]

Cannabis e-cigarettes, can also be known as dab pens, are devices that vaporize cannabis concentrates as well as other additives, such as thinning and preservative agents. These e-cigarettes can be contaminated with vitamin E acetate (**Figure 5**), which has been associated with EVALI. Through vaping, it can form ketene, which is a dangerous gas ketene. When ketene is inhaled, it can cause irritation of the eyes, nose, and throat as well as possibly causing pulmonary edema. Ketene inhalation could also lead to EVALI due to its irritative effects. The substructure of vitamin E acetate exhibits similarities to Δ^8-THC acetate, which can pose an issue for consumers due to the possible production of ketene gas during vaping. While Δ^9-THC exhibits the most psychotropic effects, Δ^8-THC also exhibits similar effects but much milder. The cannabinoid acetates contain a phenyl acetate substructure, which again can be observed in **Figures 4 and 5**. Under thermolytic conditions, phenyl acetate is able to convert to ketene and phenol.[16] Since Δ^8-THC acetate and vitamin E acetate contain the phenyl acetate substructure,

the vaping of Δ^8-THC acetate, or cannabinoid acetates in general, can lead to unhealthy amounts of ketene exposure.

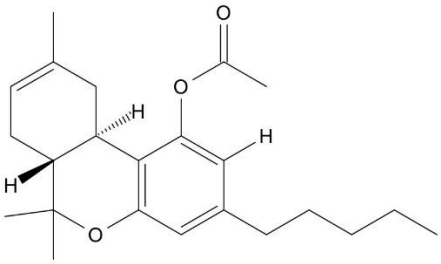


Figure 4. Chemical structure of Δ^8-THC acetate

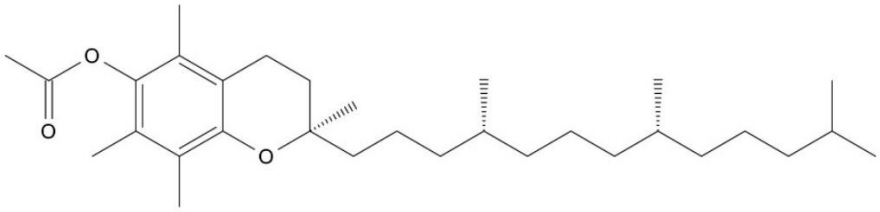


Figure 5. Chemical structure of vitamin E acetate (α-Tocopheryl acetate)

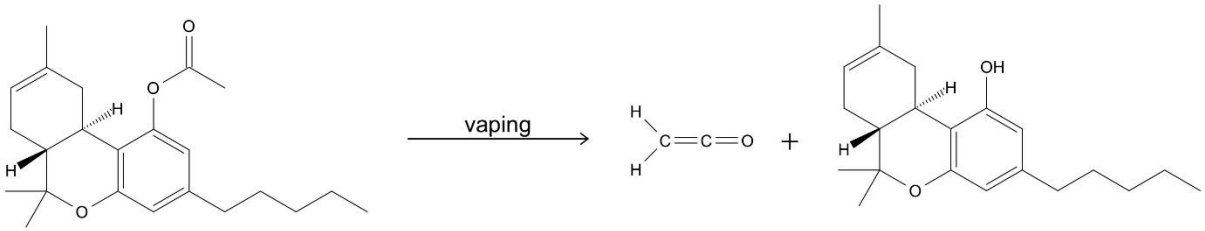


Figure 6. Formation of ketene from Δ^8-THC acetate

The National Institute for Occupational Safety and Health (NIOSH) is a research agency that focuses on the study of worker safety and health. They had established an immediately dangerous to life or health (IDLH) value for ketene, which is 5 ppm.[16] However, exposure to a

smaller concentration of ketene for extended periods can also prove to be harmful. The concentration of ketene that a person could be exposed to also depends on the volume of the hit since dabbing will require a larger inhalation volume compared to vaping using an e-cigarette. Because of this difference in inhalation volume, the ketene will be more diluted for a person using an e-cigarette. Another issue that is raised with ketene inhalation is that it could interact with water that is present in the respiratory tract and could form acetic acid prior to reaching the lungs.[16] This can cause further irritation to the nose, throat, and lungs, coughing, chest tightness, as well as in severe cases pulmonary edema.

Results and Discussion

The figure below (**Figure 7**) is a liquid chromatography with ultraviolet detection (LC-UV) chromatogram of the nineteen cannabinoids observed in **Figure 1**. The main purpose of this chromatogram is to establish that all the cannabinoids can be separated with baseline separation. Achieving baseline separation ensures that no two cannabinoids will co-elute, therefore preventing from isolation and quantification of cannabinoids.

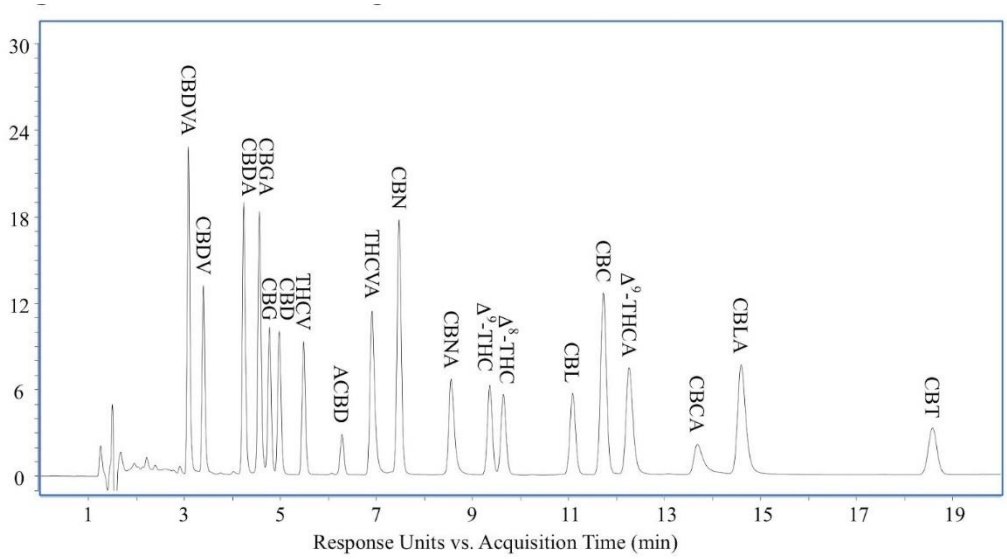


Figure 7. LC-UV chromatogram of nineteen cannabinoids

CBC has a retention time of approximately 11.4 minutes. The CBC peak (**Figure 7**) can be observed to elute at this time, which means that future testing to isolate this cannabinoid will result in a peak being observed at an acquisition time, or retention time, of approximately 11.4 minutes.

Serial dilution with the CBC standard was performed with methanol to achieve the following standard sample concentrations: 1.0, 2.5, 12.5, 25.0 and 50 µg/mL samples of CBC. The figures below (**Figures 8-12**) provide the LC-UV chromatograms from the least concentrated sample (1.0 µg/mL) to the most concentrated sample (25.0 µg/mL).

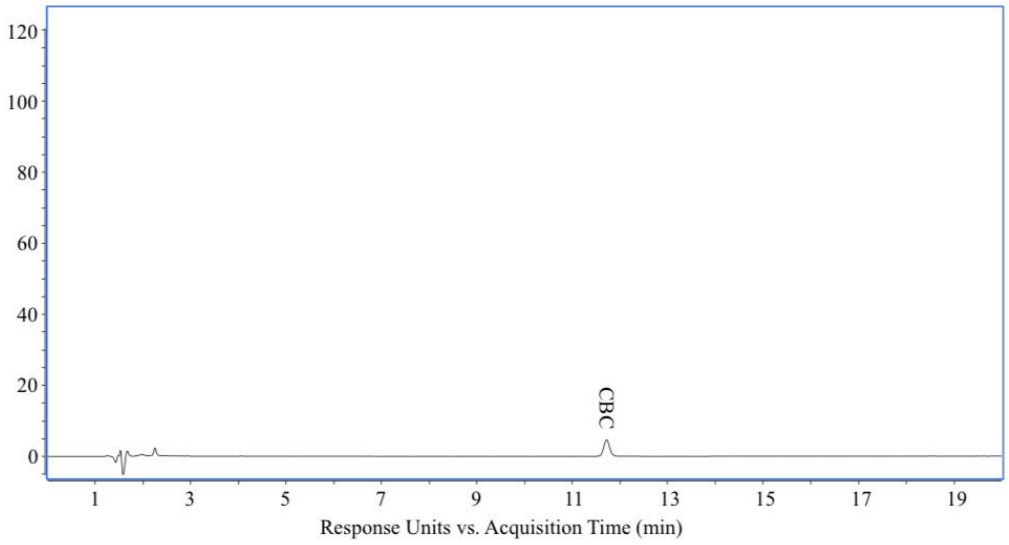


Figure 8. LC-UV chromatogram of 1.0 µg/mL CBC

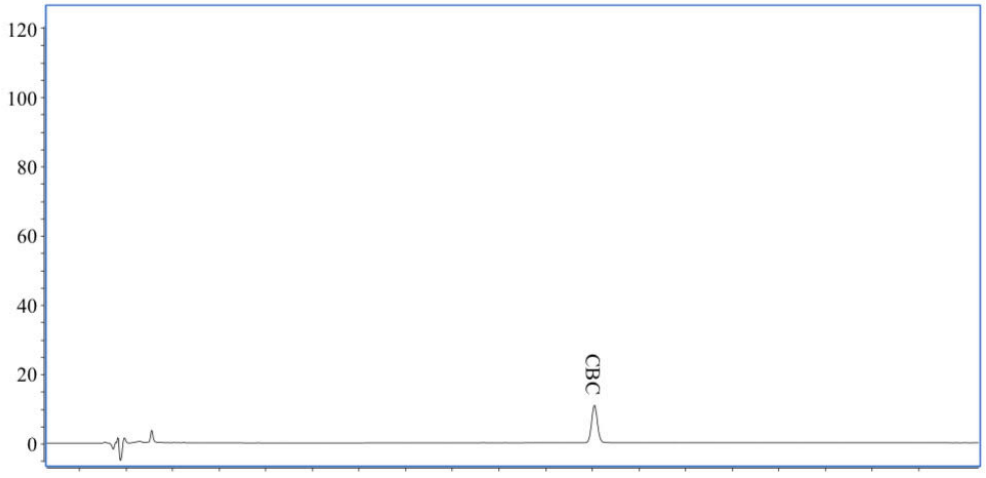


Figure 9. LC-UV chromatogram of 2.5 µg/mL CBC

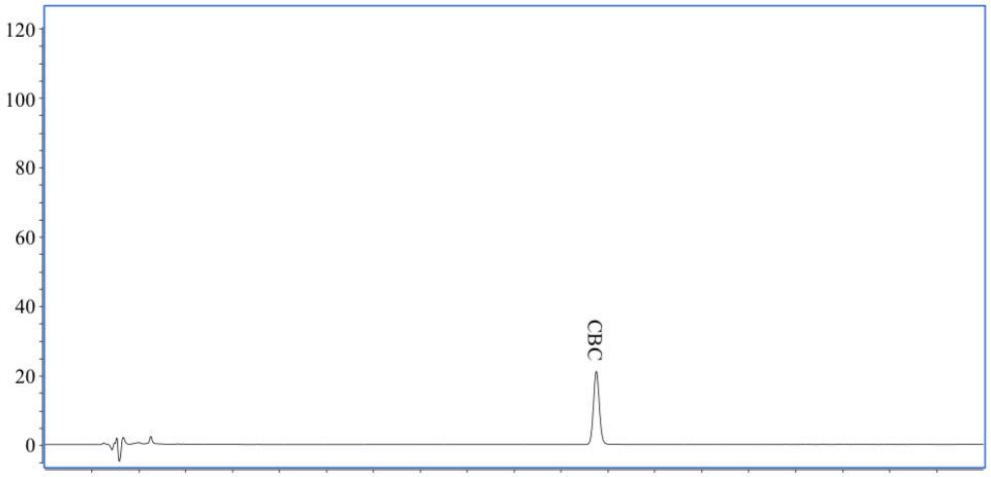


Figure 10. LC-UV chromatogram of 5.0 µg/mL CBC

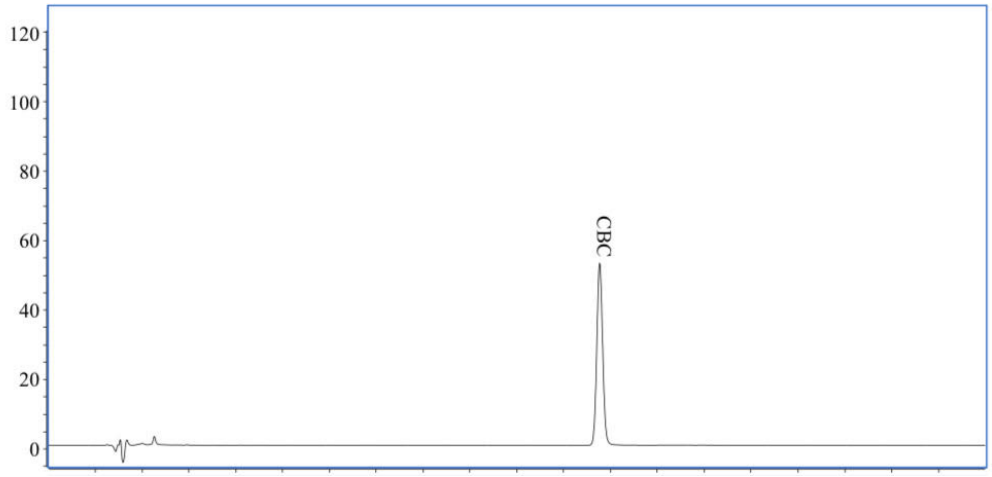


Figure 11. LC-UV chromatogram of 12.5 µg/mL CBC

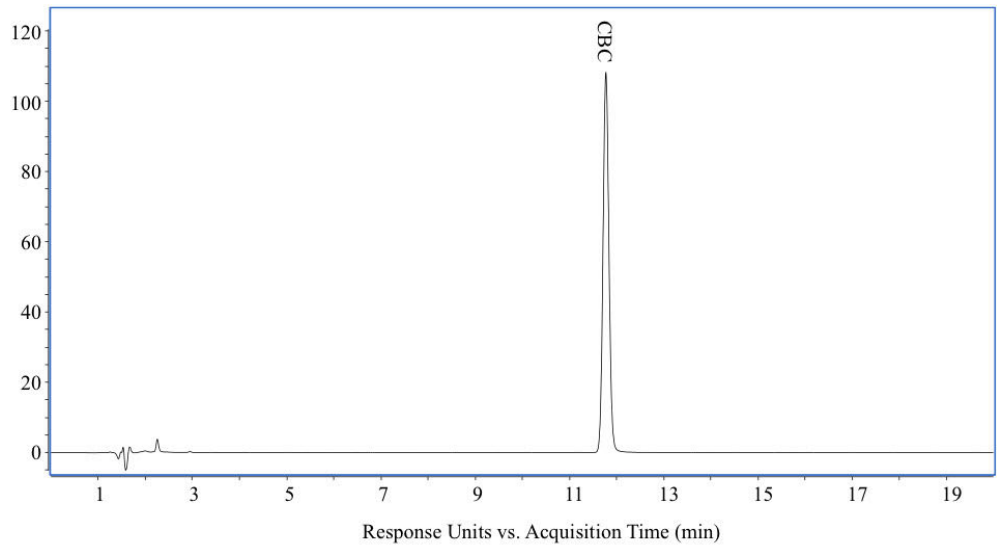


Figure 12. LC-UV chromatogram of 25.0 µg/mL CBC

Comparing **Figure 7** to **Figures 8-12**, the CBC peak is eluted at approximately 11.4 minutes. The CBC standard that was used for the chromatograms (**Figures 8-12**) increases in concentration, which also shows an increase in the response units. There are also some noise appearing around 1.5 minutes, which is most likely caused by the methanol used to make the solutions.

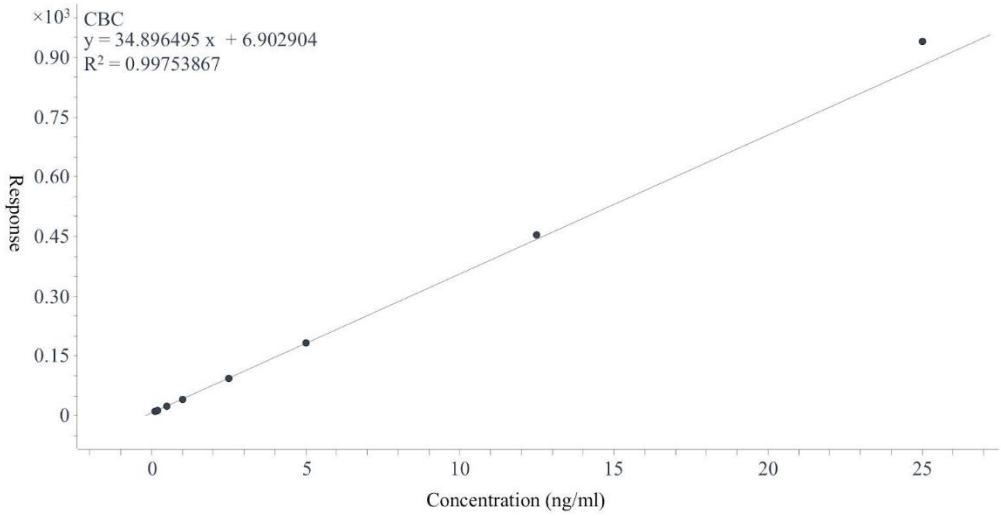
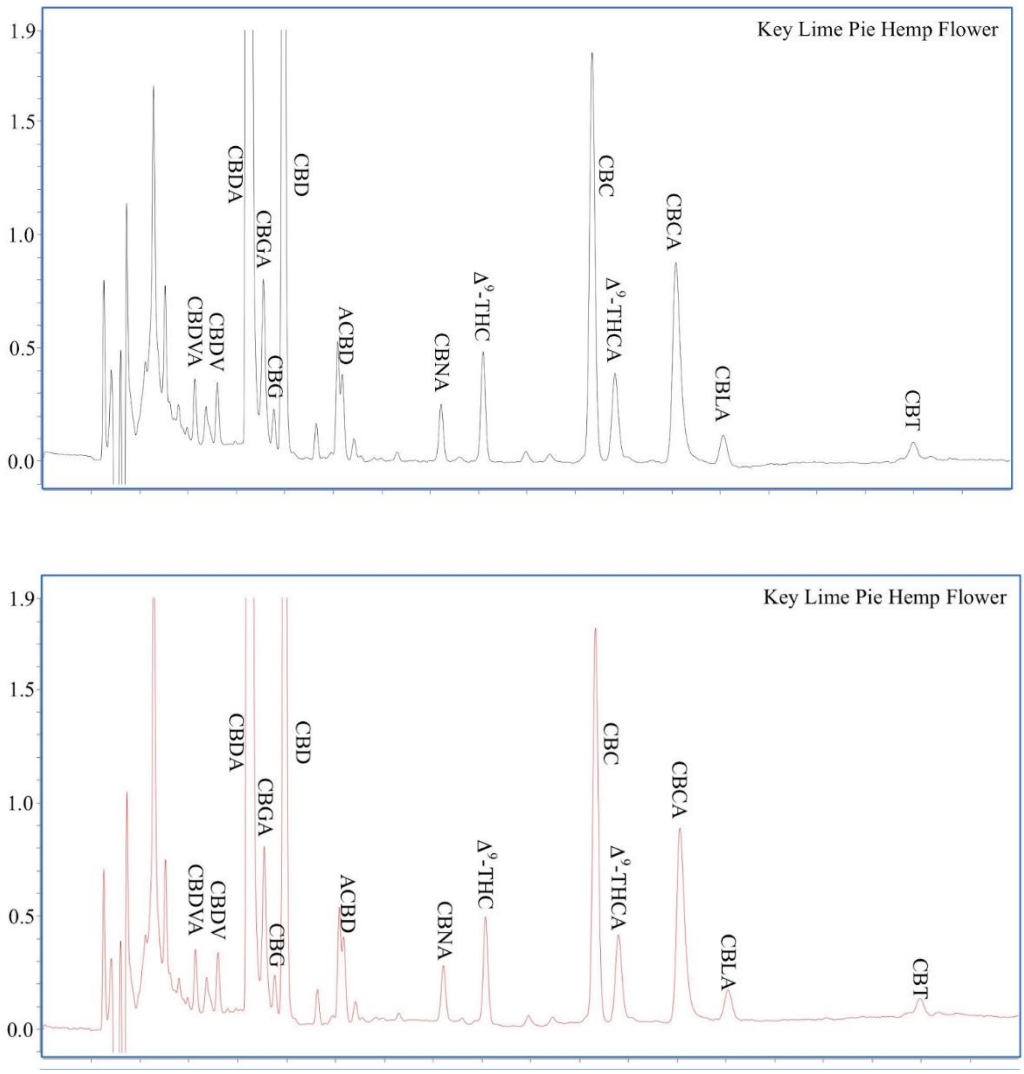


Figure 13. External standard calibration curve

The data from **Figures 8-12** were compiled into an external standard calibration curve (**Figure 13**). As stated above, there is a positive correlation between the concentration of the solutions and the response units. This is proven further by the R^2 value that was calculated from the external standard calibration curve, which was 0.99753867.



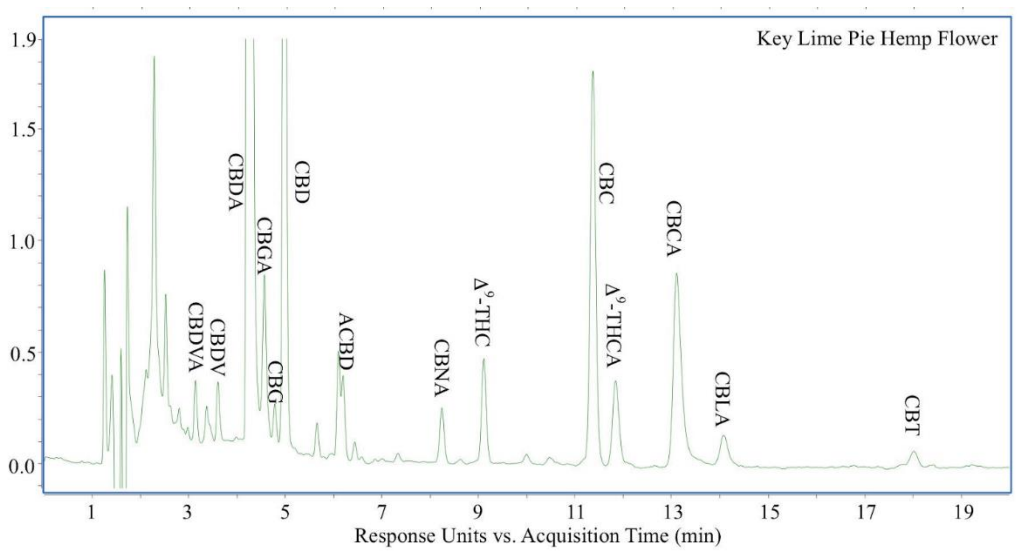


Figure 14. LC-UV chromatograms of 50 µg/mL extract in methanol in triplicate

The 50 µg/mL extract in methanol sample preparation was performed in triplicate (**Figure 9**) to ensure that the sample used would provide the same result when repeated. CBC eluted at approximately 11.2 minutes, which is close to the approximate 11.4-minute acquisition time of the CBC standard solutions (**Figures 3-**7). In the triplicate LC-UV chromatograms, baseline separation was achieved for CBC in all. This further supports the idea that CBC was eluted in a way that quantification can be achieved in the sample. The equation produced from the external standard calibration curve (**Figure 8**) was used to calculate the CBC concentration in the key lime pie hemp flower sample. The CBC content in the key lime pie hemp flowers was calculated to be 0.59%. The triplicate tests were also used to determine the relative standard deviation (RSD), which measured to be 1.6% in triplicate.

Methodology

A. Reagents

LC grade water, acetonitrile, ammonium formate, and formic acid were purchased from Fisher Scientific (Pittsburgh, PA, USA). All cannabinoid standards were purchased as certified reference materials (CRMs) in DEA exempt preparations. The Key Lime Pie hemp flowers were purchased from Industrial Hemp Farms (Denver, CO, USA).

B. Preparation of samples

A sample was first ground using a Waring lab blender (Torrington, CT, USA). The sample was further powdered using a Spex Genolyte 1200 (Metuchen, NJ, USA). Approximately 100 mg of the powdered sample was weighed into a 15 mL centrifuge tube and suspended with methanol to make a 25 mg/mL mixture. The centrifuge tube was ultrasonicated for 20 minutes. Two 1 mL extracts were centrifuged at 13,000 rpm for 10 minutes, then approximately 1 mL of the extract (0.5 mL from each centrifuge tube) was filtered with a 0.2 µm syringe filter. Afterwards, the extract was serially diluted with methanol to 50 µg/mL.

C. LC-UV

The instrument was an Agilent 1260 Infinity II LC system (Santa Clara, CA, USA) equipped with a solvent degasser, binary pump, temperature controlled autosampler, and column oven. Two Restek Raptor ARC-18 2.7 µm 150 mm x 2.1 mm (Bellefonte, PA, USA) columns were used for the separation. The column oven was set to a temperature of 30°C. The mobile phase composition was most optimized at 75% acetonitrile and 25% 0.5 mM ammonium formate + 0.02% formic acid in water. The flow rate was set to 0.4 mL/min with an injection volume set to 4 µL. The UV detection used was set to 230 nm.

Conclusions

The LC-UV method that was used has been proven to be useful in the quantification of CBC among nineteen cannabinoids in hemp flowers. The limit of quantification (LOQ) was calculated by taking the lowest concentration used (0.02 μg/mL) and the concentration of the sample used (50 μg/mL) and multiplying it by 100 to get 0.04% CBC in hemp flowers or 0.02 μg/mL in methanol. The CBC content in key lime pie hemp flowers was determined to be 0.59% with a relative standard solution (RSD) of 1.6% in triplicate. The RSD with the R^2 value from the external standard calibration curve (**Figure 8**) exhibits good precision. The main objective of this study was to determine analytical methods that were reliable and accurate for the identification and quantification of cannabinoids. This was accomplished through baseline separation that was achieved during the LC-UV separation of nineteen cannabinoids as well as the triplicate key lime pie hemp flower samples.

This LC-UV method can further be used to assist the U.S. Department of Agriculture (USDA) to regulate hemp-derived products.[7] Currently, there are few regulations on hemp-derived products. With continued testing on quantification of cannabinoids, this data can be utilized to establish a requirement for the concentration of hemp in hemp-derived products. A hope for this method is to result in a law similar to the 2018 Farm Bill being introduced.

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