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Chemical composition of aerosols from the e-cigarette vaping of natural and synthetic cannabinoids

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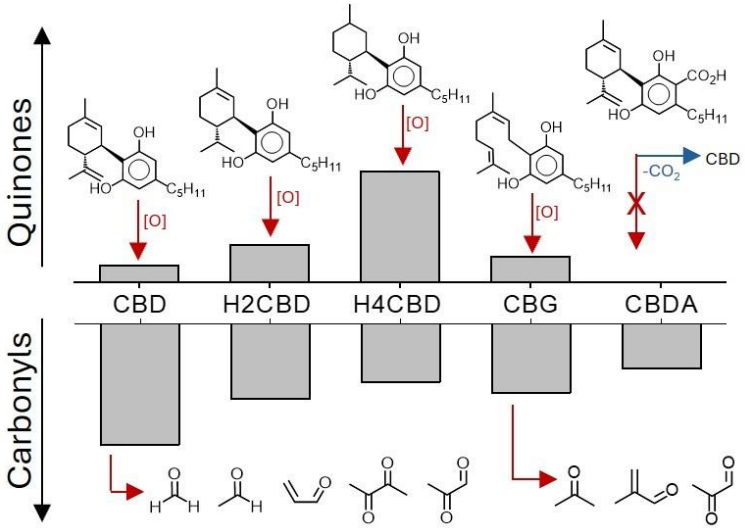


Abstract Vaping cannabinoids in electronic (e-) cigarette devices is rapidly increasing in popularity, particularly among adolescents, although the chemistry affecting the composition of the vape aerosol is not well understood. This work investigates the formation of aerosol mass, bioactive hydroxyquinones, and harmful or potentially harmful carbonyls from the e-cigarette vaping of natural and synthetic cannabinoids in propylene glycol and vegetable glycerin (PG/VG) solvent at 50 mg/mL concentration in a commercial fourth-generation vaping device. The following cannabinoids were studied: cannabidiol (CBD), 8,9-dihydrocannabidiol (H2CBD), 1,2,8,9-tetrahydrocannabidiol (H4CBD), cannabigerol (CBG), and cannabidiolic acid (CBDA). Quantification of analytes was performed using liquid chromatography coupled to accurate mass spectrometry. The addition of cannabinoids significantly increased aerosol and carbonyl formation compared to the PG/VG solvent alone. All cannabinoids in the study formed hydroxyquinones during vaping (up to ~1% mass conversion) except for CBDA, which primarily decarboxylated to CBD. Hydroxyquinone formation increased, and carbonyl formation decreased, with a decreasing number of double bonds among CBD and its synthetic analogues (H2CBD and H4CBD). During the vaping process, ~ 3 – 6 % of the cannabinoid mass can be observed as carbonyls under the study conditions. Oxidation of the terpene moiety on the cannabinoids is proposed as a major contributor to carbonyl formation. CBD produced significantly higher concentrations of formaldehyde, acetaldehyde, acrolein, diacetyl, and methylglyoxal compared to the other cannabinoid samples. CBG produced significantly higher acetone, methacrolein, and methylglyoxal. Conversion of CBD to tetrahydrocannabinol (THC) was not observed under the study conditions. The chemical mechanism basis for these observations are discussed.

Keywords: cannabis vaping, carbonyls, cannabinoid analogues, quinones

1. Introduction

The 2018 Farm Bill nationally legalized hemp, a strain of *Cannabis sativa* characterized by a delta-9 tetrahydrocannabinol (Δ9-THC) content of less than 0.3%.[1] The major cannabinoid component in hemp is cannabidiol (CBD). Consequently, CBD production from *C. sativa* has increased nationwide due to its therapeutic potential and its usage in treating opioid addiction, anxiety, depression, and epilepsy.[2] Synthetic cannabinoids that are structurally similar to natural cannabinoids have also emerged on the market, including synthetic analogues of CBD. These cannabinoid analogues have been used in products such as chocolates, gummies, candies, and e-liquid vape mixtures and oils.[3] Although CBD and other cannabinoids can be consumed in many different forms, vaping is an increasingly important use scenario. CBD vaping represents approximately 19% of product use in adult CBD users in the United States as of 2022.[4] Moreover, 21% of adolescent (11-18 year old) e-cigarette users also vape CBD,[5] and the prevalence of CBD vaping is rising globally, with the market size of CBD e-liquids projected to reach $74 billion by 2030.[6] The increasing popularity of CBD and cannabinoid vaping among adolescents may be due to several key drivers:[7, 8] the convenience and perceived discreteness of vaping, under-recognition of risks, the high volume of CBD vape products in commerce, youth-targeted marketing, perception of health benefits due to its lower-temperature vaporization process, and regulatory reforms that have simplified access to an array of vaporizer products.

Vaping cannabinoids by means of cannabis e-cigarettes may involve various types of formulations.[9] This work focuses on mixtures of solvents such as vegetable glycerin (VG) and propylene glycol (PG) with the addition of CBD or other natural or synthetic cannabinoids. Even though claims on safety have been stated by manufacturers, there is limited research on the chemical properties of inhalable aerosols produced from vape products containing CBD and its analogues.[10] The aerosolization process in vaping involves the use of a heated metal coil,

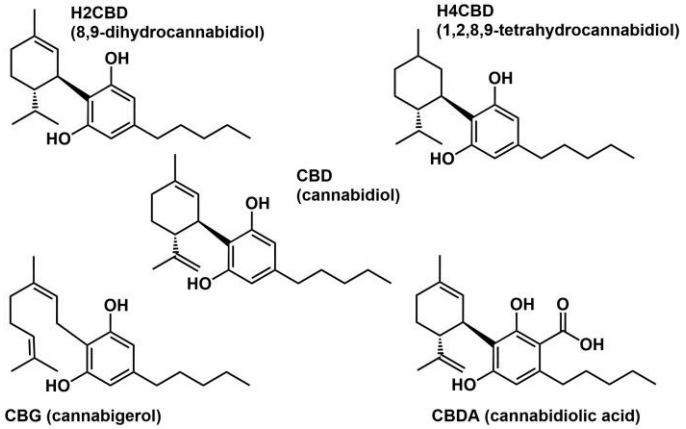


Figure 1. Chemical structures, common names, and abbreviations for the cannabinoids studied in this work.

in which PG and VG alone were found to produce harmful carbonyl compounds such as formaldehyde and acrolein that can have adverse effects on the respiratory system.[11, 12] Cannabinoids in vapes have been found to oxidize and thermally degrade.[13] It has further been suggested that the heated, oxidative, and acidic microenvironment in vape e-liquids has the potential to transform CBD to the psychoactive Δ^9-THC,[14, 15] although this reaction has not been shown in e-cigarettes. Research on the pyrolysis and e-cigarette aerosolization of CBD has also reported its transformation into a hydroxyquinone form upon exposure to air,[16] which may also have health implications.[17]

The e-cigarette or vaping product use-associated lung injury (EVALI) health crisis highlights a critical gap in our understanding of the safety and composition of vape products, particularly cannabis vapes, for which regulation in the United States is still in its infancy.[18] A recent *in vivo* mice and *in vitro* human cells study showed that inhalation of CBD vape aerosol resulted in more severe lung damage and higher oxidative stress compared with nicotine vaping.[19] Yet, the chemical compositions of aerosols emitted from the vaping CBD and other cannabinoids are not well understood, particularly the emissions of harmful or potentially harmful compounds (HPHCs) such as carbonyls. While recent work in the literature characterized select chemical constituents of vaped aerosols from cannabis- and hemp-derived e-liquids,[13, 20, 21] these studies focused on surveying commercial products that have complex proprietary formulations for which it is challenging to extract fundamental insights about the chemistry of the cannabinoids alone. A systematic characterization of the chemical transformations that occur during the vape aerosolization process from highly controlled solutions (e.g., pure cannabinoids in solvents) is needed in the literature to inform on the chemical origins of HPHCs and aid in risk assessment, consumer choices, and regulatory considerations of cannabinoid e-liquid ingredients.

This research examines the aerosol mass generation and chemical composition of vaped aerosols from five natural and synthetic cannabinoids (**Fig. 1**): CBD, H2CBD (8,9-dihydrocannabidiol), H4CBD (1,2,8,9-tetrahydrocannabidiol), CBG (cannabigerol), and CBDA (cannabidiolic acid). Furthermore, we compare the cannabinoid content of the vaped aerosol to the unvaped e-liquid to gain insights into thermal transformations and efficiency of cannabinoid delivery. Each of these cannabinoids and synthetic cannabinoids are known to have therapeutic effects, including anti-convulsant, anti-inflammatory, antioxidant, and other beneficial properties.[22-26] H2CBD and H4CBD, in particular, have modified terpene moieties and thus do

not have the ability to act as a substrate in the acid catalyzed conversion of CBD to Δ^9-THC.[14] H2CBD and H4CBD have comparable pharmacology to CBD,[24, 25] and thus might offer similar health benefits while reducing the risk of unwanted side effects.

2. Experimental

2.1 Generation of Aerosol

All e-liquids were prepared at 50 mg/mL in 30% a propylene glycol (99%, Sigma-Aldrich) 70% vegetable glycerin (≥99.5%, Sigma-Aldrich) mixture by volume (i.e., 30:70 PG/VG), which is comparable to commercially available e-liquids.[1,2] Solutions were stored at 2-8 °C prior to use. A refillable VaporessoXROS2 pod device (Shenzhen Smoore Technology Limited, Shenzhen, China) was used for aerosol generation, which allows for precise control of the e-liquid formulation. The vaping apparatus and sampling protocols have been described in detail previously.[27] Briefly, 0.8 Ω kanthal (FeCrAl alloy) mesh coils, a puffing air flow of 2.0 ± 0.2 L/min, a 2 s puff, and a puff volume of 65 ± 5 mL were used.[28] E-cigarette pods that had been filled with 2 mL e-liquid were weighed before and after vaping to assess gravimetric mass loss of the e-liquid per 30 puffs. The total aerosol mass per puff was calculated as the difference in mass of the e-liquid reservoir divided by the number of puffs that were generated.

2.2 Collection and Analysis of Carbonyls and Cannabinoids by HPLC-HRMS.

The methods for the collection and analyses of carbonyls from vaping aerosols used in this work have been described previously.[11, 13, 27] Briefly, 2,4-dinitrophenylhydrazine (DNPH) cartridges (350 mg DNPH, Supelco, Inc., Bellefonte, PA) were used to sample the aerosols produced from the vaped samples. The collection efficiency of samples with DNPH cartridges was determined to be ≥98% based on carbonyl analyses of three cartridges sampled in series.[11] All samples were collected in triplicate. 30 puffs were collected on the cartridge for each e-liquid, such that the derivatization agent remains in excess. Cartridges were extracted at ≥97% efficiency[11] with 2 mL of liquid chromatography-mass spectrometry (LC-MS) grade acetonitrile (Fisher Scientific) and unvaped e-liquids were diluted at 1:5 volume in LC-MS grade methanol (Fisher Scientific) prior to high-performance liquid chromatography-high-resolution mass spectrometry (HPLC-HRMS) analysis. Separation for both carbonyl-DNPH and cannabinoids was done on an Agilent 1100

HPLC using an Agilent Poroshell EC-C18 column (2.1 mm×100mm, 2.7μm, 120 Å) coupled to a linear trap quadrupole-Orbitrap (LTQ-Orbitrap) mass spectrometer (ThermoCorp., Waltham, MA) at a mass resolving power of 30,000 m/Δm at m/z 400. Formaldehyde, acetaldehyde, acetone, acrolein, propionaldehyde, diacetyl, methacrolein, butyraldehyde, glyoxal, and methylglyoxal DNPH hydrazones were calibrated and quantified with commercial analytical standards (AccuStandard, primary standards in acetonitrile). Acetic acid and glycolaldehyde DNPH hydrazone standards were prepared. The other carbonyls and organic acids reported in this work (e.g., **Table S1**) were quantified using theoretical calculations of relative sensitivity in the electrospray ionization (ESI) negative mode ionization and ratioed to measured sensitivities of commercial standards.[29] The total mass loss from the device was used to quantify aerosol mass.

Standard solutions of the pure CBD (GVB Biopharma, >99% purity), H2CBD (synthesized, >98% purity), H4CBD (synthesized, >99% purity), CBG (synthesized, 96% purity), and CBDA (obtained from a local cannabis grower, >98% purity) were used to quantify their LC-HRMS peak areas. A commercial standard of the CBD hydroxyquinone (HU-331, Cayman Chemicals, > 95% purity) was used to quantify all hydroxyquinones in this work. Concentrations of each carbonyl, organic acid, cannabinoid, or cannabinoid hydroxyquinone were normalized by the amount of aerosol mass lost.

2.3 Syntheses of Standard Compounds H2CBD[24] and H4CBD[30] were synthesized and purified as described previously. CBG was synthesized as follows: Olivetol (6.0 g, 33.3 mmol) and geraniol (6.0 mL, 5.38 g, 34.9 mmol, 1.05 equiv) were combined in hexane (50 mL). The mixture was stirred at 35 °C until it became homogeneous at which point activated alumina (24 g) was added portionwise. The temperature of the bath was increased to 90 °C and most of the hexane was removed by distillation. The resulting slurry was stirred at 90 °C for 18 h. After cooling to room temperature, the mixture was extracted three times with dichloromethane (100 mL) and the extracts were concentrated under vacuum. The residue (6.6 g of crude CBG, ~95.5% by GC) was purified by column chromatography (silica gel, dichloromethane/hexane 2/3) to give CBG (5.7 g, 54%) as a white solid. NMR spectroscopic data matched those in a previous report.[31]

3. Results and Discussion

Authentic standards of CBD, H2CBD, H4CBD, CBG, and CBDA (**Fig. 1**) enabled an investigation of how chemical structure modifies aerosol mass and composition in e-cigarette vaping for these cannabinoids. CBD, H2CBD, and H4CBD differ from each other by one sequentially fewer C=C double bond in the terpene fragment of the molecules. CBDA is different from CBD by the presence of a carboxylic acid group on the aromatic ring. And CBG is different from CBD by the acyclic nature of the terpene. The range of concentrations of CBD in PG/VG solvent from commercial e-liquids is vast: the CBD concentrations labelled on commercial vape products range from 3 – 1000 mg/mL and were analyzed to be in the range of 0.6 – 417 mg/mL.[32] We chose a concentration of 50 mg/mL of cannabinoid in PG/VG e-liquid for investigation. Representative HPLC-HRMS chromatograms showing the quantification of both carbonyls and cannabinoids in the PG/VG control, unvaped e-liquid, and vape aerosol are shown for H2CBD (**Fig. 2**).

Table 1: Quantitative data for the aerosol mass and aerosol composition of the control (PG/VG only) experiment and five sample experiments, each of 50 mg/mL of cannabinoid in PG/VG. Errors represent one standard deviation from triplicate collections and analyses. Quantitation of the parent cannabinoid, and conversion to CBD, the hydroxyquinone product of the cannabinoid, and total carbonyls have been normalized to the aerosol mass in mg that was collected for each replicate. The data in μg/mg can be converted to mg/mL using an assumed density of 1.18 g/mL for the aerosol. Data for the unvaped samples are reported per mL volume of the e-liquid. The data for total carbonyls represent a summation of 15 carbonyls and 2 organic acids quantified in this work (Table S1). Asterisks (*) represent statistical significance compared to the control ($p < 0.01$) using one-way ANOVA. Not detected (n.d.) indicate signals below the detection limit.

Vape Aerosol Sample	Aerosol mass (mg/puff)	Parent Cannabinoid	Conversion to CBD	Conversion to Hydroxyquinone	Conversion to Carbonyls	Hydroxyquinone, Unvaped (mg/mL solution)
			(μg/mg aerosol)			
PG/VG control	5.8 (± 0.3)	n.d.	n.d.	n.d.	0.6 (± 0.2)	n.d.
CBD	8.6 (± 0.2)*	101 (± 29)	n.d.	0.20 (± 0.05)	5.6 (± 2.0)	0.05
H2CBD	8.6 (± 1.2)*	112 (± 40)	1.3 (± 0.6)	0.44 (± 0.28)	3.5 (± 1.0)	0.01
H4CBD	8.2 (± 0.4)*	102 (± 20)	n.d.	1.29 (± 0.50)	2.7 (± 1.2)	0.22
CBG	9.2 (± 0.5)*	107 (± 26)	n.d.	0.30 (± 0.14)	3.2 (± 1.1)	0.03
CBDA	7.8 (± 0.6)*	50 (± 17)	15.8 (± 1.8)	0.0003 (± 0.0001)	2.1 (± 0.3)	0.0001

3.1. Aerosol mass and cannabinoid transfer efficiency We found that the addition of cannabinoids to PG/VG solvent at 50 mg/mL enhances the aerosolization yield of the e-liquid (**Table 1**). Each of the cannabinoid samples produced more aerosol mass compared to the PG/VG control with a strong statistical significance using one-way ANOVA ($0.0001 < p < 0.01$). However, aerosol mass formation from the five cannabinoid samples were not statistically significant from

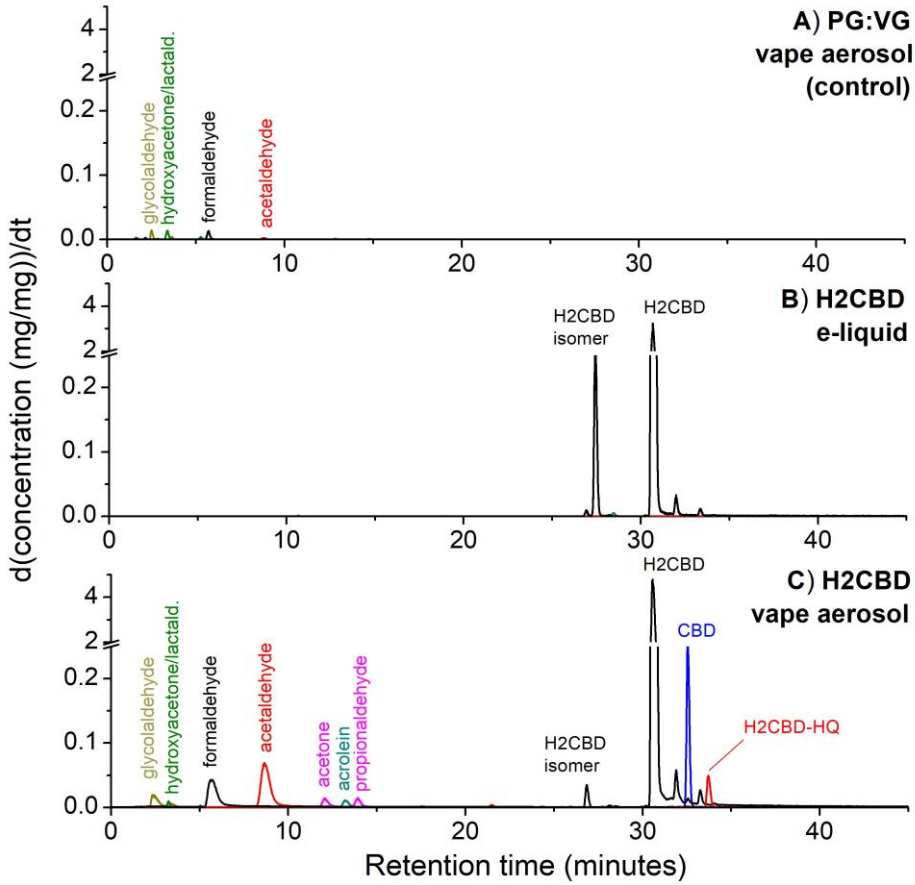


Figure 2: Representative HPLC-HRMS extracted ion chromatograms for (A) PG/VG control vape aerosol, (B) unvaped e-liquid of 50 mg/mL H2CBD in PG/VG, and (C) vape aerosol of 50 mg/mL H2CBD in PG/VG. Peaks are normalized for their sensitivity in the analytical procedure, extraction solvent volume, and aerosol mass collected or e-liquid mass. All scales are identical, note the break in the vertical axis. The unnormalized version of this figure is shown in the Supplement (Fig. S1).

each other (i.e., each individual value compared to the mean of the five samples ($p > 0.18$)). This suggests that while the addition of the $C_{21\text{-}22}$ cannabinoids aids in the formation of inhalable aerosols, the specific cannabinoid structures are not highly influential in the aerosolization process. This result may not be surprising, given that aerosolization is thought to be controlled by vapor pressure,[33] wherein compounds with higher vapor pressure preferentially partition to the gas phase rather than the condensed particles. The vapor pressure of CBD (~ 6 x 10^{-6} Torr) [33] is lower than glycerol (~ 1 x 10^{-4} Torr)[34] at 20 °C, which would support an increase in aerosol formation upon addition of CBD to PG/VG. The vapor pressures of cannabinoids are not well understood relative to each other; however, the difference between the cannabinoids under study is apparently insignificant for the outcome of aerosol mass generation from vaping.

A solution of 50 mg cannabinoid per mL of 30:70 PG/VG has an average density of 1.18 g/mL (assuming 0.96 g/mL for CBD,[35] 1.04 g/mL for PG and 1.26 g/mL for VG), which equates to ~ 44 µg cannabinoid/mg solvent in the e-liquid. Compared to the e-liquid cannabinoid mass concentration, the cannabinoid content of the aerosol is enhanced by a factor of 1.5 – 2.5 (**Table 1**). This can be rationalized by the higher potential of the cannabinoids to condense in particles compared to the solvent, thus potentially concentrating the cannabinoid in the aerosol. A significant portion of PG and VG has been shown to exist in the gas phase upon aerosolization.[11] **Figure 2** shows that, compared to the unvaped e-liquid, the vape aerosol contains a slightly different distribution of cannabinoid-derived compounds, but that the highest signal is that of the parent cannabinoid by an approximate order of magnitude when aerosolized from the device used in this work. Thus, most of the mass of the parent cannabinoid is conserved and transferred to the aerosol from the e-liquid under the tested vaping conditions. A recent investigation using 2 – 20 mg/mL of CBD in PG/VG found a lower transfer efficiency of CBD to the aerosol (50 – 70%).[36] This discrepancy is unclear, but may be due to the different e-cigarette device and cannabinoid concentrations used. CBDA is found in the aerosol under the study conditions at 50 µg/mg or ~59 mg/mL. This is similar to its e-liquid concentration; however, a substantial fraction of the parent cannabinoid was converted to CBD (~19 mg/mL). This decarboxylation phenomenon is well researched as this is the route of forming CBD from CBDA in hemp.[37, 38] The kinetics are sensitive to temperature,[39] and are shown here to be relatively efficient in a fourth-generation vape device at the measured coil temperature of ~120 °C.[27] There is also a small conversion of H2CBD to CBD due to oxidation occurring in the vape process (~ 1%, **Table 1, Fig. 2C**). This oxidative dehydrogenation is somewhat surprising, although it is possible that the heated metal environment of the vaping coil provided sufficient catalysis.[40]

Notably, we did not observe conversion from CBD to THC, even though our HPLC-HRMS method is able to quantify Δ^8-, Δ^9-, and Δ^{10}-THC. A recent study suggested that CBD is a precursor to THC in e-cigarettes;[15] however, that study did not use an e-cigarette device or a PG/VG based e-liquid. Instead, a quartz pyrolysis set up was used with a platinum heating coil and a CBD solution in methanol at temperatures of 200-500 °C. Platinum is known to be a highly reactive catalyst;[41] however, platinum (or any precious metal) coils are not available in commercial e-cigarette devices. The most common coil types are kanthal, stainless steel, or nichrome.

Interestingly, lower temperatures produced higher signals of the Δ^9-THC under both inert and oxidative conditions in Czégény et al.,[15] likely due to the decomposition of THC at higher temperatures. In addition, we also did not observe cannabinol or cannabichromene in our study using an authentic e-cigarette device with a relevant e-liquid. The fourth-generation e-cigarette device in this work uses a kanthal coil with a measured coil temperature of 120 °C.[27] It is possible an e-cigarette device with higher coil temperature, a different coil type, or a different CBD e-liquid may be able to access the decomposition channels described in Czégény et al.;[15] however, our study conditions were not able to reproduce the outcomes described in that work.

3.2. Oxidations to Hydroxyquinones

CBD is known to oxidize to a hydroxyquinone (CBD-HQ in this work, but also referred to as HU-331) under oxidative conditions such long term storage in air.[16] Love et al. showed that CBD-HQ is formed via vaping using CBD distillate and flavored e-liquid on an authentic vaping device.[17] The CBD-HQ has biological properties that may be useful in cancer therapies such as inhibiting angiogenesis and promoting apoptosis of endothelial cells.[42] It was however also shown to induce cellular stress pathways in the lung by altering protein function via Michael addition.[17] This work explores whether the same HQ-forming reaction in vapes occurs with other cannabinoids and how chemical structure may alter the yields of the bioactive hydroxyquinones (HQs). We found that all tested cannabinoids formed HQs except for CBDA, for which the preferred reactive pathway in e-cigarettes is decarboxylation to produce CBD (**Fig. 3, Table 1**). In agreement with Love et al.,[17] we found that HQ yields are only

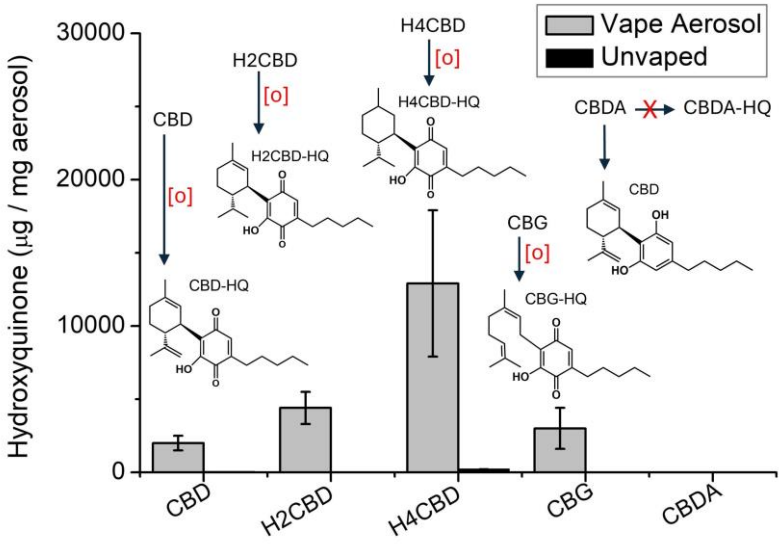


Figure 3: Quantitative yields of hydroxyquinones (HQ) from the oxidation of the five cannabinoids under study. Chemical structures of the HQ are shown for all transformations except that of CBDA, which does not form the HQ but instead decarboxylates to CBD.

significant in the vape aerosol, and negligible in the unvaped e-liquids. For CBD e-liquid, the CBD-HQ mass percent found in this work (~ 0.2 ± 0.5%, relative to CBD) compares well to the ~ 0.1 % CBD-HQ observed from the CBDFx flavored e-liquid tested by Love et al using a different e-cigarette device.[17] At the highest yield, for H4CBD-HQ, the HQ mass is roughly 1% of the parent cannabinoid. While the hydroxyquinone yields are not high, they are not trivial for a compound with bioactive effects. Although the CBD-HQ (HU-331) has been the topic of numerous studies in regards to its cytotoxic and antiangiogenic properties,[43] the biological effects of the H2 and H4 analog hydroxyquinones have not yet been investigated. However, Kogan et al. found that the reduction of double bonds has a minimal influence on activity, which may suggest similar effects of the H2- and H4- HQs compared to the CBD-HQ. Comparatively, the CBG-HQ (HU-1006) did not demonstrate significant biological activity toward a series of cell lines.[43]

Interestingly, we found that HQ yield increased with a decreasing number of double bonds in the cannabinoid structure. We discuss in **Section 3.3**. that the double bonds on the terpene moiety of cannabinoids are oxidized by the hydroxyl (OH) radicals produced in the vaping process,[44-46] which go on to fragment to carbonyls in a process similar to the oxidative reactions occurring in the atmosphere or in combustion. The more double bonds in the terpene moiety of the cannabinoid, the more likely it is that oxidation will occur at those sites instead of the benzene ring to produce the HQ, given that the OH radical oxidation of aliphatic alkenes is faster than with benzene. Indeed, for the series of CBD, H2CBD, and H4CBD where all else is equal except for the number of double bonds on the terpene moiety, we see an inverse correlation between the total carbonyls yields and the HQ yields (**Table 1**). CBG has a similar HQ yield to CBD, but a lower carbonyl yield.

3.3. Formation Yields of Carbonyls and Organic Acids

It is established that the vaping process in e-cigarettes produces harmful and potentially harmful carbonyl toxicants, derived from the oxidative thermal decomposition of organic compounds in the e-liquid such as the PG/VG solvent itself,[11, 12, 29, 47, 48] flavorant additives,[49-52] THC, and vitamin E acetate,[13] among other ingredients that may be found in commercially available vape cartridges. The chemical mechanisms that form carbonyls in e-cigarettes include heat-induced dehydration and radical reaction pathways via H abstraction and addition by OH radicals.[11, 12, 53, 54] In particular, Li et al. showed that the carbonyls expected to form via thermal dehydration had an exponential

(Arrhenius) temperature trend and those expected to be formed from radical reaction pathways displayed a linear temperature dependence in their formation.[11] Thus, it is expected that the cannabinoid additives to PG/VG solvent will also decompose into carbonyls via thermal and radical pathways.

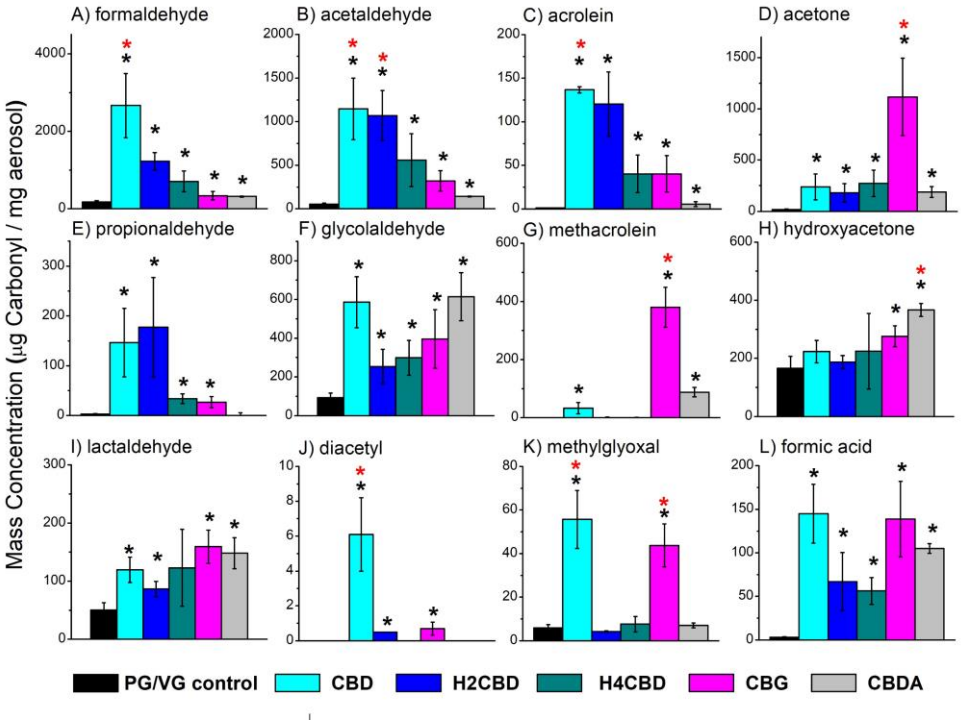


Figure 4: Mass concentrations of carbonyls (µg) detected per mg aerosol. Black asterisks denote quantities of carbonyls in a sample that are statistically significant compared to the PG/VG control ($p < 0.05$). Red asterisks denote quantities of carbonyls in a sample that are statistically larger than the mean value among the five samples ($p < 0.05$). Statistics were performed using one-way ANOVA with four degrees of freedom between groups.

Fifteen carbonyls and two organic acids were identified by their accurate masses and retention times in HPLC-HRMS and quantified by chemical standards or as described previously.[29] **Table S1** reports these data in full for the five cannabinoid samples and the PG/VG control. **Figure 4** shows the aerosol mass concentration of eleven select carbonyls and one organic acid, for which the aerosol mass concentrations are the highest. The are a number of notable observations, which are discussed below.

Firstly, the quantities of most of the carbonyls observed in the samples are significantly higher compared to the control, as noted by the black asterisks in **Figure 4** and the total carbonyl data in

Table 1 (~ 0.6 mg/mg in the PG/VG control vs. 2.1-5.6 mg/mg in the samples). This demonstrates that carbonyls are formed in the vaping process directly from every cannabinoid under study, although the total quantity and distribution of carbonyl products differs for each one. Hydroxyacetone is an exception; the major source of this compound is the PG and VG solvent (**Fig. 4H**), with statistically insignificant sources from CBD, H2CBD and H4CBD. Even for CBDA, which yielded the highest amount of hydroxyacetone, more than half can be accounted for by solvent chemistry.

Chemically specific trends may be ascertained from the carbonyls data, for which statistically higher formation yields compared to the mean of the five samples are denoted with a red asterisk in **Figure 4**. The decreasing total carbonyl production trend of CBD > H2CBD > H4CBD is mirrored for formaldehyde, acetaldehyde, and acrolein. In particular, CBD produces significantly higher aerosol mass-normalized yields of formaldehyde, acetaldehyde, and acrolein compared to the mean of the five samples (**Fig. 4 A, B, C**). This likely suggests that the exocyclic double bond of the terpene moiety in CBD is a significant source of formaldehyde and other carbonyls. However, H4CBD produces a fairly high yield of carbonyls in some cases, for example the acetaldehyde yield of H4CBD is half that of CBD, suggesting carbonyl formation can also come from oxidation at saturated carbon. CBD is also a significant source of diacetyl and methylglyoxal (**Fig. 4 J, K**), although the absolute production of these two carbonyls is lower compared to the others under study.

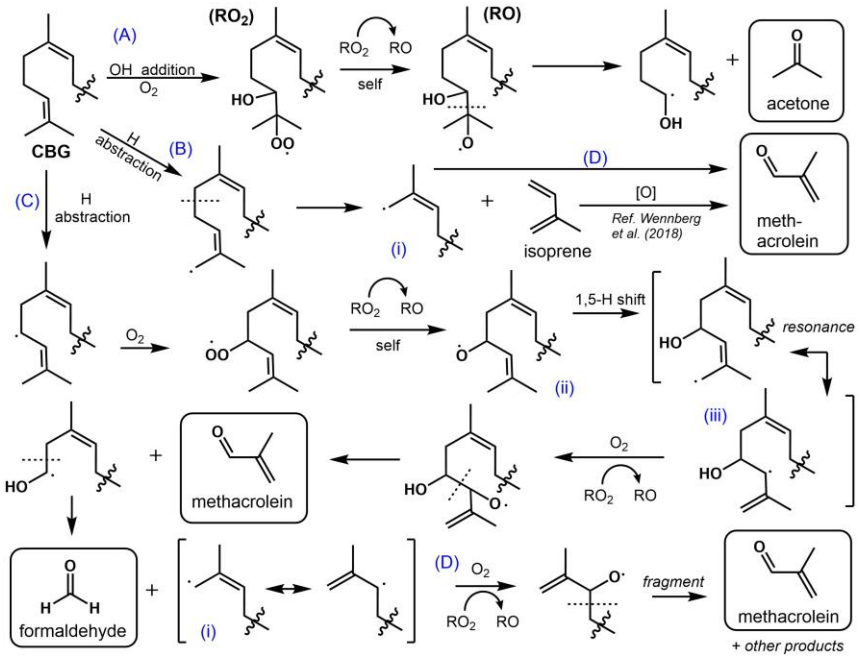
The data suggest that CBG produces particularly high yields of acetone, methacrolein, and methylglyoxal, all of which are statistically higher than the mean of the five samples (**Fig. 4 D, G, K**). The acetone yield from CBG is especially high, a factor of 4-6 greater than any other cannabinoid in this study. CBG has a terpene moiety that is most closely related to myrcene, while CBD's terpene moiety resembles limonene. In agreement with this work, a study of OH oxidation of various terpenes in the gas phase also found that acetone is formed in much higher yields from myrcene (~ 0.36 – 0.45) compared to limonene (< 0.03),[55] suggesting that the structure of the terpene moiety influences product formation in the aerosolization process of vaping. A similar study for the formation of methacrolein or methylglyoxal was not found for comparison.

Methacrolein has also been observed as a major degradation product of CBG and myrcene in vaping and dabbing, the production yield for which increases with temperature.[56 57]

3.4. Proposed Chemical Mechanisms

The reactions that form carbonyls in e-cigarettes are understood to follow the classical aerobic radical oxidation mechanisms that occur in the atmosphere,[58] in aqueous and organic solutions,[59] and in vivo.[60] These are "cascade" reactions that rapidly generate, propagate, and terminate radicals. It is important to note that numerous chemical reaction channels are available during the vaping process for cannabinoids; however, we propose only select fragmentation reaction pathways that may support the observations shown in **Figure 4**.

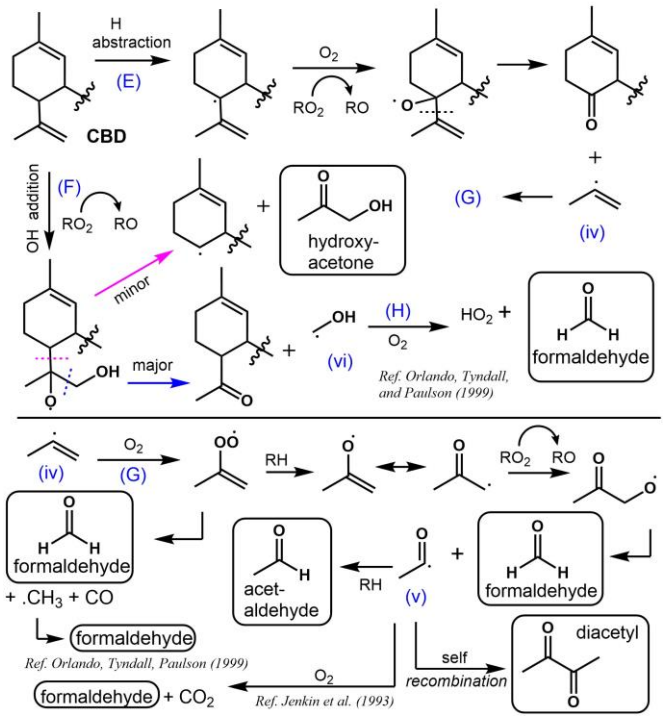
Scheme 1 shows that the addition of OH radical to a double bond or abstraction of H from an allylic site of CBG will form an alkyl (R) radical, which can add molecular oxygen to form an alkylperoxy radical (RO_2).[59, 61-63] The RO_2 is reduced to an alkoxy radical (RO)[64] upon reactions with other peroxy radicals[65] or reductants in the solution. The H abstraction may be initiated by OH, R, RO_2, RO or other radicals in solution.[59, 66, 67] The RO_2 + RH reaction forms hydroperoxides (ROOH).[59] Our work did not assess hydroperoxide yields but this may be important to quantify for future research as hydroperoxides are oxidants. The RO radical may isomerize via hydrogen shifts, fragment via β-scission, or produce a carbonyl upon abstraction of H by molecular oxygen (-HO_2).[64, 68] Scission is preferred if the radical on the RO is tertiary, but also possible for secondary sites.[64] We also show alkyl radical decomposition into a



Scheme 1: Abridged OH-initiated oxidation of CBG, showing plausible radical addition and abstraction pathways towards the formation of acetone, methacrolein, and formaldehyde.

carbon-centered radical and a closed shell molecule;[69] this can be particularly fast if the product radical is allylic due to resonance stabilization.[70]

The addition of OH radicals at the "fishtail" moiety of CBG (-C=CH(CH_3)$_2$) allows for a straightforward pathway toward acetone formation via the tertiary RO radical[71] (**Scheme 1**, A). Only the addition site forming the tertiary radical is shown in **Scheme 1**, although acetone could be formed at either addition site on the fishtail, in addition to other viable mechanisms that are not shown. The formation of methacrolein from CBG during vaporization has been suggested via a stable isoprene intermediate,[56, 72] as methacrolein is a known oxidation product of isoprene.[73] However, the chemical mechanism for the formation of isoprene from either CBG or myrcene is not well understood, along with whether there is a direct decomposition channel to methacrolein. In reactions B and C (**Scheme 1**), we propose isoprene and methacrolein production via H abstraction at allylic sites of CBG. The allyl radical formed in B is proposed to fragment into another allyl radical (**i**) and isoprene, which can then oxidize to methacrolein via multiple pathways.[73] Radical **i** can add oxygen and undergo RO_2/RO chemistry to produce methacrolein directly (pathway D). Alkoxy radical **ii** follows from the H abstraction in C. This radical is proposed to isomerize via a 1,5-H shift[74] to allylic radical **iii**. Further RO_2/RO chemistry of **iii** is proposed to produce methacrolein and formaldehyde, among other products.

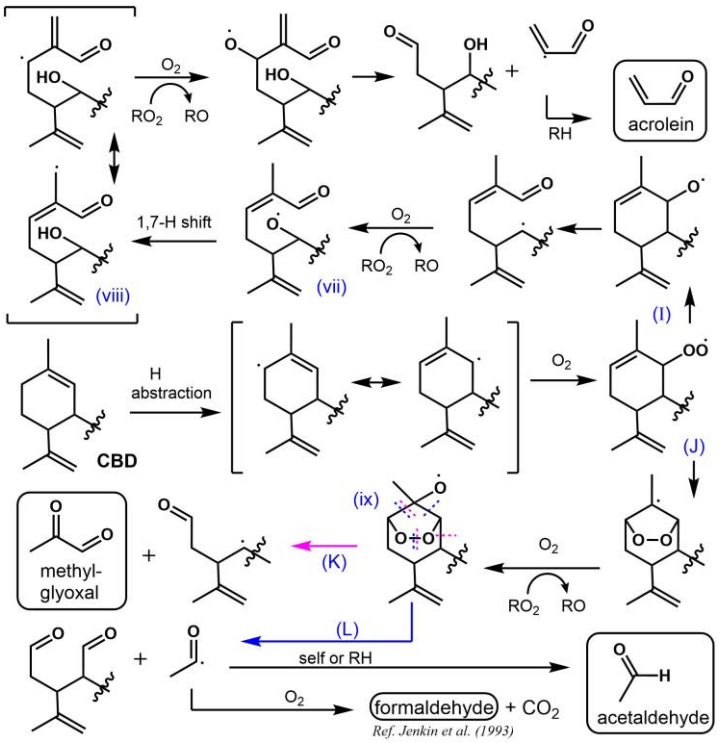


Scheme 2: Abridged OH-initiated oxidation of CBD, showing radical addition and abstraction pathways at the exocyclic double bond of the terpene moiety that leads to the formation of formaldehyde, acetaldehyde, diacetyl, and a minor route to hydroxyacetone.

CBD forms a statistically higher yield of formaldehyde, acetaldehyde, acrolein, methylglyoxal, and diacetyl compared to the other samples. **Scheme 2** illustrates proposed (E) H abstraction and (F) OH addition routes to

give formaldehyde, acetaldehyde, and diacetyl. CBD has a double bond in a different location on the fishtail (-CH-C(=CH_2)CH_3) compared to CBG, which alters its product distribution. In particular, the fishtail of CBD's limonene structure can fragment into the methylvinyl radical (**iv**), which produces formaldehyde alongside coproducts upon exposure to oxygen (**Scheme 2**, G).[75] An intermediate in the methylvinyl oxidation chain is the acetyl radical (**v**).[75] Acetyl radicals rapidly add oxygen to form the acetylperoxy ($CH_3C(O)O_2^{\cdot}$) radical, which will generate formaldehyde + CH_3 + CO in air (**Scheme 2**).[76] CH_3 radicals also eventually produce formaldehyde.[76] This may help explain the especially high formaldehyde yields from CBD (**Fig. 4A**). To a lesser extent, acetyls can also disproportionate[77] or abstract H from the solvent[78] to form acetaldehyde. There is also a recombination reaction of acetyl that forms diacetyl; this reaction is fast in the absence of oxygen, but represents only a minor pathway in air.[79] The minor recombination of acetyl radicals may explain the small, but statistically significant production of diacetyl from CBD. Another source of formaldehyde is the hydroxymethyl radical (**vi**), formed along multiple reaction pathways in the chain oxidation of CBD and the other cannabinoids (**Scheme 2**, H).[75]

The relatively high production yields of acetaldehyde and acrolein from CBD and H2CBD, which is reduced significantly for the other cannabinoids, suggest a source of these aldehydes from the endocyclic double bond of the limonene moiety of CBD and H2CBD. As these mechanisms have not been reported in the literature, we propose some plausible routes in **Scheme 3**. H abstraction at an allylic carbon within the ring forms an initial RO_2 radical that can be (I) reduced to the RO radical or (J) cyclize to a bicyclic



Scheme 3: Abridged OH-initiated oxidation of CBD, showing plausible radical addition and abstraction pathways at the endocyclic double bond of the terpene moiety that leads to the formation of acetaldehyde, acrolein, methylglyoxal, and formaldehyde.

ROOR radical.[62,80] The RO radical formed in I opens the ring to an aldehyde and alkyl radical, which is eventually converted to another RO (**vii**). It is possible that a 1,7-H shift of **vii**, which requires only slightly more activation energy compared to the facile 1,5-H shifts of alkoxy radicals,[81] will produce the allylic radical **viii**. Further reaction is shown to produce acrolein via decomposition to an alkenyl radical. This is a more endothermic scission compared to analogous reactions that form alkyl radicals;[82] however, the reaction might be feasible due to the high temperatures produced by the vaping coils. More readily accessible paths to acrolein are not apparent. Pathway J that forms the ROOR radical may produce alkoxy radical **ix**, which can decompose to either (K) methylglyoxal or (L) formaldehyde and acetaldehyde, alongside other coproducts.

4. Conclusions The therapeutic properties of CBD and some other cannabinoids are well documented; however, whether there is a net benefit for vaping as a use scenario for cannabinoids is debatable. Compared to the oral consumption of cannabinoid edibles and oils, vaping introduces CBD and other cannabinoids directly into the lungs, which increases the magnitude and rate of bioavailability[83] and may have anti-inflammatory effects.[84] However, complex or negative effects on lung cells and tissues have also been noted in the literature.[19,85] This work also shows that a non-negligible fraction of the cannabinoids (depending on chemical structure) oxidizes to bioactive hydroxyquinones (up to ~ 1%) or decomposes to HPHC carbonyls (approximately 3 – 6%) using a fairly low-temperature fourth-generation vaping device with ~ 0.8 Ω coil resistance. Conversion of CBD to THC, however, was not observed under the conditions of our study.

The chemical structure of the cannabinoid (and arguably, any vape liquid ingredient) substantially influences the emissions of HPHCs, which alters the biological impacts of the vape aerosol and underscores the need to consider each cannabinoid ingredient individually. Particularly, for CBD, the relatively high emissions of toxic formaldehyde, acetaldehyde, acrolein, diacetyl, and methylglyoxal observed in this work may be concerning. This is consistent with the findings of Leigh and Goniewicz, where CBD vape aerosols were observed to be more cytotoxic to bronchial epithelial cells compared to CBD-free e-cigarettes, regardless of flavorants.[86] Further research into the fundamental toxicant emission profile of each cannabinoid in vapes, and the other ingredients they may be mixed with, may enable more thorough risk assessment to better inform consumer

and regulators on the public health impacts of the emerging trend of cannabis vaping. It may also be beneficial to further study how vaping synthetic analogues of CBD may affect human health, as they have similar pharmacology[24, 25] but produce fewer carbonyls. Finally, it would also be worthwhile for future research to characterize the vaping conditions and devices that maximize cannabinoid delivery and minimize side-products.

5. Supporting Information Tabulated data for aerosol mass concentrations of carbonyls and acids; raw extracted ion chromatograms for the PG/VG control, unvaped H2CBD e-liquid, and H2CBD vape aerosol.

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