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DART-HRMS triage approach part 2 – Application to the detection of cannabinoids and terpenes in recreational *Cannabis* products

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ABSTRACT

The ambient ionization mass spectrometric technique termed "direct analysis in real time – high-resolution mass spectrometry" (DART-HRMS) has been previously utilized to investigate the presence of cannabinoids in complex matrices such as personal-care products, edibles prepared in-house, certified reference materials, and hemp plant material (the non-psychoactive variety of *Cannabis sativa*). In the study presented here, this proof-of-concept was applied to commercially available retail *Cannabis*-derived products from a recreational *Cannabis* dispensary. Among the retail products analyzed by DART-HRMS were edibles, concentrates, tinctures, topicals, vaporizers, marijuana flower, and pre-rolls comprised of marijuana plant material. Regardless of the type and complexity of the matrix, direct analysis of these materials in their native form readily revealed, as a function of either positive- or negative-ion mode, a range of cannabinoid acids, neutral cannabinoids, and terpenes, including CBGA (nominal *m/z* 361 and 359), THC/CBD (nominal *m/z* 315 and 313), CBN (nominal *m/z* 311 and 309), and eucalyptol (nominal *m/z* 155 and 153), respectively. This was accomplished without any sample preparation steps and permitted avoidance of some of the difficulties typically encountered when utilizing traditional chromatographic approaches for the analysis of cannabinoids in complex matrices. The rapidly obtained chemical information furnished by this approach facilitates assessment of whether further confirmatory testing should be performed, and if so, of what type, thereby avoiding indiscriminate performance of time-consuming and resource-intensive confirmatory testing of all samples.

1. Introduction

The *Cannabis sativa* species contains over 500 compounds, >144 of which are classified as phytocannabinoids (i.e., natural cannabinoids) [1–2]. Other represented molecule classes include flavonoids, fatty acids, and phenols [1,3]. Its two most well-known chemical constituents are Δ^9-tetrahydrocannabinol (THC) and cannabidiol (CBD), which are its major psychoactive and non-psychoactive cannabinoids, respectively. Others include non-psychoactive molecules such as cannabigerol (CBG) and cannabichromene (CBC), as well as Δ^8-THC, an isomer of THC that is also psychoactive. In addition, the acid forms of THC and CBD, commonly known as THCA and CBDA respectively, are particularly prominent in live and freshly harvested *Cannabis* plant material. Over the course of its growth, the cannabinoid and terpene profiles of *C. sativa* change considerably [4].

When *C. sativa* plant material is extracted and/or processed in other ways, it is not uncommon for it to be added to or combined with other ingredients that increase the complexity of the resulting matrix even further. Examples include commercially prepared edibles/beverages, topicals/personal-care products, and vape products, among numerous others. Adding to this broad range of products are those that are "homemade", such as the various concoctions that are prepared by combining *Cannabis*-derived materials with food and beverage ingredients, which increase the complexity of the final material. Consequently, when these samples must be analyzed (e.g., in forensic analysis for cannabinoid concentrations; independent laboratory testing for pesticides, etc.), nuanced and complex multi-step sample preparation protocols are usually required. This challenge also makes development of standard operating procedures that can be used uniformly across forensic laboratories difficult to develop. In a recent investigation of improvements that can be applied for both hemp and marijuana *Cannabis* variety analysis conducted in a laboratory setting, the National Institute of Standards and Technology (NIST) observed as recently as 2020 that the approaches used by forensic and *Cannabis* testing laboratories for the analysis and quantification of cannabinoids vary considerably [5]. This challenge is anticipated to become more

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intractable because of the ever-increasing range of new matrices presented for analysis, and emphasizes the need for more consistent and standardized analysis protocols.

One potentially viable approach that could address the issue of complex matrix analysis standardization, and which could offer considerable time and resource savings, is to utilize direct analysis in real time – high-resolution mass spectrometry (DART-HRMS) [6]. The use of this technique as a screening method for forensic purposes has increased in recent years because molecules of interest can be rapidly detected through either direct analysis of the material in its native form (e.g., leaves, stems, roots, powders, tinctures, capsules, and other herbal products) or with minimal sample preparation [7–12]. The ability to screen for small-molecules of interest in very complex matrices without the need for sample pretreatment steps is an important time-saving benefit. Furthermore, the screening advantages that it offers enable more rapid decision-making regarding the need for an optimal approach to more targeted confirmatory analysis and quantification of specific compounds (e.g., cannabinoids, terpenes, pesticides etc.). Accordingly, a DART-HRMS-based method demonstrating proof-of-concept for the rapid detection of cannabinoids in complex matrices, including hemp plant material (the non-psychoactive variety of *C. sativa*), certified reference materials (CRMs), personal-care products, and mock edibles prepared in-house, such as baked goods, chocolates, and gummy candies (i.e., fruit chews) was developed [13]. The method, which also investigated the instrument detection limit (IDL) for THC and CBD, not only revealed the presence of cannabinoids despite the complexity of the matrices within which these compounds were infused, but also the absence of cannabinoids in experimental controls [13]. While it demonstrated success as a triage approach for mock samples, its utility in the analysis of real world commercially available retail *C. sativa* products sold at recreational dispensaries was not demonstrated. Therefore, as an extension of the previously reported work, the research presented here investigated the application of DART-HRMS as a triage approach for commercial *Cannabis* products available through the Adult-Use Menu of a recreational *Cannabis* dispensary. For the samples analyzed in this study, the vendor website provided information such as cannabinoid content, terpene content, branding, etc. In addition to their genetic and metabolomic profiles, marijuana strains have been shown to be distinguishable by the presence and relative abundances of both terpenes and cannabinoids [14]. In particular, the terpene profiles of both hemp and marijuana contribute to their overall organoleptic properties, and hence, to consumer preferences. Thus, the terpene molecules in marijuana flower and vape products were also investigated by DART-HRMS, thereby offering an additional dimension of analysis to the reported method.

2. Materials and methods

2.1. Chemical standards

Eucalyptol, β-caryophyllene, (-)-caryophyllene oxide, α-guaiene and α-pinene analytical standards were purchased from Cayman Chemical (Ann Arbor, MI, USA). Polyethylene glycol (PEG 600) and Fomblin Y were purchased from Sigma Aldrich (St. Louis, MO, USA). Cannabidivarin (CBDV), tetrahydrocannabidivarin (THCV), Δ^8-tetrahydrocannabinol (Δ^8-THC), cannabichromene (CBC), cannabicitran (CBT), cannabinodiol (CBND), cannabielsoin (CBE) and tetrahydrocannabidivarinic acid (THCVA) were also purchased from Cayman Chemical. Cannabichromenic acid (CBCA) was purchased from Cerilliant Corporation (Round Rock, TX, USA). Nitrogen and ultra-high purity helium gas were purchased from AirGas (Albany, NY, USA).

2.2. Recreational retail Cannabis products

A range of representative items were purchased from a dispensary in Massachusetts (Garden Remedies Marijuana Dispensary, Melrose, MA, USA), where retail products for medicinal purposes and adult-use (i.e., recreational-use) are offered. All products analyzed were purchased from the Adult-Use Menu, as opposed to the Medical Menu which is restricted to patrons with Medical Marijuana cards. Products available on the Adult-Use Menu fell under one of the following categories: Edibles, Concentrates, Tinctures, Vaporizers, Topicals, Flower, and Pre-Rolls. Subcategories within the Edibles list included chocolates, drinks, capsules/tablets, chews, and cooking/baking items. Sample(s) from each category and subcategory were purchased and analyzed in this study. Fig. 1 presents images of all the products from the non-flower categories, with several insets providing additional information that appeared on the product label and/or close-ups of the material inside the packaging (e.g., a single fruit chew, sample of liquid from inside the bottle, etc.). Three types of marijuana flower from different brands were obtained: Snowdog (Berkshire Roots), Dr. Lime #10 (Garden Remedies), and Wonka Bars (Nature's Heritage). Images of these flower samples are shown in Supplementary Fig. 1.

2.3. Sample preparation

2.3.1. Chemical standards

CBDV ($[C_{19}H_{26}O_2 + H]^+$ *calc.* 287.2011; $[C_{19}H_{26}O_2 - H]^-$ *calc.* 285.1855), THCV ($[C_{19}H_{26}O_2 + H]^+$ *calc.* 287.2011; $[C_{19}H_{26}O_2 - H]^-$ *calc.* 285.1855), Δ^8-THC ($[C_{21}H_{30}O_2 + H]^+$ *calc.* 315.2324; $[C_{21}H_{30}O_2 - H]^-$ *calc.* 313.2168), CBC ($[C_{21}H_{30}O_2 + H]^+$ *calc.* 315.2324; $[C_{21}H_{30}O_2 - H]^-$ *calc.* 313.2168),), and CBT ($[C_{21}H_{30}O_2 + H]^+$ *calc.* 315.2324; $[C_{21}H_{30}O_2 - H]^-$ *calc.* 313.2168) standards were obtained as certified reference materials (CRMs) at a concentration of 1 mg/mL in methanol. THCVA ($[C_{20}H_{26}O_4 + H]^+$ *calc.* 331.1909; $[C_{20}H_{26}O_4 - H]^-$ *calc.* 329.1753) and CBCA ($[C_{22}H_{30}O_4 + H]^+$ *calc.* 359.2222; $[C_{22}H_{30}O_4 - H]^-$ *calc.* 357.2066) were also acquired as CRMs, at a concentration of 1 mg/mL in acetonitrile. CBE ($[C_{21}H_{30}O_3 + H]^+$ *calc.* 331.2273; $[C_{21}H_{30}O_3 - H]^-$ *calc.* 329.2117) and CBND ($[C_{21}H_{26}O_2 + H]^+$ *calc.* 311.2011; $[C_{21}H_{26}O_2 - H]^-$ *calc.* 309.1855) standards were obtained as 1 mg in 100 μL of acetonitrile and methanol solutions, respectively. Eucalyptol ($[C_{10}H_{18}O + H]^+$ *calc.* 155.1436) and α-pinene ($[C_{10}H_{16} + H]^+$ *calc.* 137.1330) were acquired as 10 mg neat oils. The β-caryophyllene ($[C_{15}H_{24} + H]^+$ *calc.* 205.1956) standard was received as a 100 mg neat oil. The (-)-caryophyllene oxide ($[C_{15}H_{24}O + H]^+$ *calc.* 221.1905) standard was received in crystalline form (100 μg). Lastly, α-guaiene ($[C_{15}H_{24}O + H]^+$ *calc.* 221.1905) was obtained as a 500 μg/mL in chloroform standard. All cannabinoids and terpenes were analyzed directly by DART-HRMS as received without any sample pretreatment or dilution.

2.3.2. Recreational retail Cannabis products

Edibles, *C. sativa* flower, concentrates and tinctures were analyzed in their native forms without any sample pretreatment steps prior to analysis by DART-HRMS. For samples that were sold as multiples of individual units (such as fruit chews and capsules), three individual pieces were analyzed in a single DART-HRMS acquisition and averaged to provide a spectrum representative of the multiple pieces. To analyze the pre-rolls, the wrapping was unfurled to expose the *Cannabis* contents, which were then presented to the DART gas stream for analysis.

2.4. DART-HRMS mass spectral data acquisition and analysis

A DART-SVP ion source (IonSense, Saugus, MA, USA), coupled to a JEOL AccuTOF high-resolution mass spectrometer (Peabody, MA, USA), was used for all mass spectral analyses, which were performed using ultra-high purity helium at a DART gas temperature of 350 °C and flow rate of 2 L min^{-1}. In positive-ion mode, the following mass spectrometer settings were used: ring lens voltage, 5 V; orifice 1 voltage, 20 V; orifice 2 voltage, 5 V; peak voltage, 600 V; and detector voltage, 2000 V. The following mass spectrometer settings were used in negative-ion mode: ring lens voltage, −5 V; orifice 1 voltage, −20 V; orifice 2 voltage, −5 V;

Fig. 1. Twenty-five (25) recreational *Cannabis* products including edibles, concentrates, vaporizers, tinctures, topicals, and pre-rolls. Images with additional visuals of the products, if applicable, are shown in the insets.

peak voltage, 600 V; and detector voltage, 2000 V. Samples were analyzed by DART-HRMS at one of two locations: (1) the University at Albany – State University of New York (SUNY) in Albany, NY; or (2) IonSense Inc. in Saugus, MA. The DART ion source at the University at Albany was operated at a gird voltage of 250 V in positive-ion mode and −250 V in negative-ion mode. Alternatively, the DART ion source at IonSense used grid voltages of 350 V/-350 V in positive- and negative-ion modes, respectively. Both instruments had a resolving power of 6000 full width at half maximum (FWHM).

Data were collected over a mass range of *m/z* 60–1000 using PEG 600 and Fomblin Y as mass calibrants in positive- and negative-ion modes, respectively. All mass spectral calibration, spectral averaging, background subtraction, and peak centroiding were conducted using the TSSPro 3.0 software from Shrader Software Solutions (Grosse Pointe, MI, USA). Data collected using the DART-HRMS instrument at UAlbany were translated and calibrated prior to data processing. All recreational *Cannabis* products were analyzed at IonSense, and the raw data files were calibrated, processed, and evaluated at UAlbany using previously reported methods [13]. For samples analyzed at IonSense, a reference mass in PEG 600/Fomblin Y was applied to the data after file translation during the calibration and data processing steps [15]. The mass spectral data were processed using the Mass Mountaineer software suite (RBC Software, Portsmouth, NH, USA). Although the method previously utilized a ±5 millimass unit (mmu) mass tolerance [13], incorporating the use of a reference mass when calibrating raw data files from an alternate DART-HRMS instrument prompted the slight increase in the mass tolerance to ±10 mmu. This increase still allows for the differentiation of high-resolution masses. In alignment with the IDL and peak intensity threshold cutoff of 100 ion counts previously reported [13], peak intensities consistent with cannabinoids that fell below the cutoff were not reported in order to avoid potential false positives.

The labels of several of the products displayed test results, or provided QR codes which were linked to more detailed reports that listed further information, such as cannabinoid profiles (obtained using high-performance liquid chromatography-photodiode array detector (HPLC-PDA)) and terpene profiles (acquired using headspace gas chromatography – tandem mass spectrometry (GC–MS/MS)), among other independent laboratory test results. This provided the opportunity to assess the veracity of the claims on the product labels using DART-HRMS as a triage approach for detection of compounds whose masses aligned with what would be anticipated for various cannabinoids and terpenes. For example, the Nature's Heritage Wonka Bars Flower provided a QR code that linked to a report featuring heavy metal analysis, microbial contaminants analysis, pathogenic bacteria results, mycotoxins result, residual solvent results, pesticides results, and vitamin E acetate results, in addition to quality assurance (QA) and quality control (QC) results. Of relevance to this study were the cannabinoid and terpene profiles provided in this report, which included the results from testing panels of 11 cannabinoids and 10 terpenes.

All products were screened in triplicate by DART-HRMS in both ionization modes under soft ionization conditions with orifice 1 voltages of 20 V (positive-ion mode) and −20 V (negative-ion mode). Replicates were averaged to produce a mass spectrum representative of the respective sample. Chemical standards and recreational *Cannabis* products were analyzed by swabbing or inserting the closed end of a melting point capillary tube (Fisher Scientific, Pittsburgh, PA, USA) into the sample and presenting the coated surface of the tube to the heated DART gas stream.

3. Results

3.1. Cannabinoid standards

It has previously been shown that CBN ($[C_{21}H_{26}O_2 + H]^+$ *calc.* 311.20211; $[C_{21}H_{26}O_2 - H]^-$ *calc.* 309.1855), THC/CBD ($[C_{21}H_{30}O_2 + H]^+$ *calc.* 315.2324; $[C_{21}H_{30}O_2 - H]^-$ *calc.* 313.2168), CBG ($[C_{21}H_{32}O_2 + H]^+$ *calc.* 317.2481; $[C_{21}H_{32}O_2 - H]^-$ *calc.* 315.2324), THCA/CBDA ($[C_{22}H_{30}O_4 + H]^+$ *calc.* 315.2324; $[C_{22}H_{30}O_2 - H]^-$ *calc.* 313.2168), and CBGA ($[C_{22}H_{32}O_4 + H]^+$ *calc.* 361.2379; $[C_{22}H_{32}O_4 - H]^-$ *calc.* 359.2222), in the form of reference standards, are readily detected by DART-HRMS analysis in both positive- and negative-ion modes [13]. Nine additional cannabinoid standards that have not been previously reported to have been detected by DART-HRMS (i.e., Δ^8-THC, CBC, CBCA, CBDV, CBE, CBND, CBT, THCV, THCVA,) were analyzed. The DART-HR mass spectra collected in positive- and negative-ion modes for these cannabinoids are shown in Supplementary Figs. 2 and 3. In summary, each features a peak consistent with the protonated and deprotonated masses of the indicated cannabinoids in positive- and negative-ion modes, respectively. For example, when the cannabinoid CBDV was analyzed by DART-HRMS, peaks at *m/z* 287.1984 and 285.1869 were detected in positive- and negative-ion modes, respectively. These masses are within 5 mmu of the calculated protonated and deprotonated masses shown above.. This confirmed that all cannabinoids (both neutral and acid forms) utilized in this study can be detected by DART-HRMS.

3.2. Terpene standards

The following five terpenes were analyzed by DART-HRMS in positive-ion mode: (1) α-pinene; (2) eucalyptol; (3) α-guaiene; (4) β-caryophyllene; and (5) (-)-caryophyllene oxide. These were selected to represent various classes of terpenes (e.g., monoterpenes, monoterpenoids, sesquiterpenes, and sesquiterpenoid oxides) known to be present in *C. sativa*. As shown in Fig. 2, a peak consistent with the protonated mass of the indicated terpene (within 5 mmu) was detected for each. Analysis of these terpenes in negative-ion mode was not informative, as their corresponding deprotonated precursors did not appear (data not shown).

3.3. Recreational Cannabis products

Representative DART mass spectra collected in positive-ion mode of samples categorized as edibles (multiple subcategories), tinctures, vaporizers, topicals, or pre-rolls are shown in Fig. 3. The DART mass spectra collected in positive-ion mode for all the additional products analyzed under these categories are shown in Supplementary Fig. 4, with mass spectra for all non-flower products analyzed in negative-ion mode presented in Supplementary Fig. 5. Table S1 shows the mass spectral data obtained when the recreational *Cannabis* products were screened by DART-HRMS in positive-ion mode. Data demonstrating the detection of cannabinoids by DART-HRMS in negative-ion mode using the ±10 mmu tolerance are shown in Table S2. Masses that were consistent within ±10 mmu of those cannabinoids and/or terpenes listed on the product label are included in Tables S1 and S2. Assignments of cannabinoids and/or terpenes were made on the basis of detecting *m/z* values consistent with the high-resolution masses of molecules reported on the product labels. DART-HR mass spectra collected in negative-ion mode were found to be suboptimal for the detection of terpenes, when compared to the spectra of molecules that contain acidic protons which are more readily deprotonated.

3.3.1. Edibles

DART-HRMS analysis of two chocolate bars (Milk Chocolate and Dark Chocolate) yielded a peak consistent with that of the protonated mass of THC at nominal *m/z* 315 in positive-ion mode. However, only the milk chocolate bar also produced a peak consistent with deprotonated THC at *m/z* 313.2216 in negative-ion mode. Similarly, in positive-ion mode, a peak at *m/z* 315 was detected in each of the fruit chew flavors (Sour Blueberry, Watermelon, and Apple Martini), which is consistent with the presence of THC reported on their product labels. However, analysis of these samples in negative-ion mode furnished little information with regard to detecting cannabinoids: a peak consistent with the mass of deprotonated THC at *m/z* 313 that was above the 100-

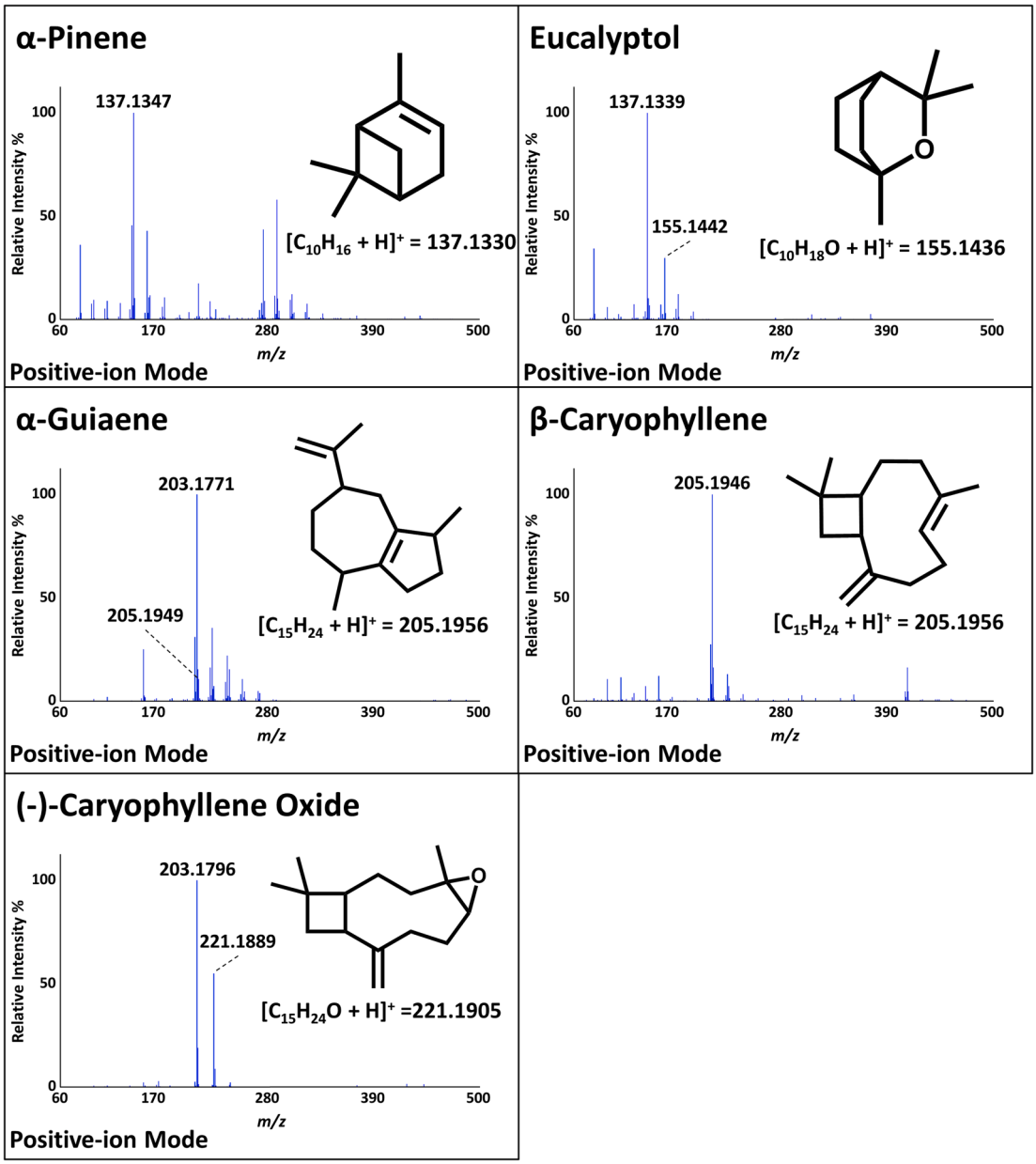

Fig. 2. DART-HR mass spectra (collected in positive-ion mode), structures, $[M + H]^+$ chemical formulas, and corresponding masses of terpenes reported in some *Cannabis* products (e.g., flower, concentrates).

ion count IDL threshold was not detected any of these samples.

The following three seltzer beverages were analyzed: (a) Achieve Drink – Raspberry Lime; (b) Celebrate Drink – Lemon Lime; and (c) Dream Drink – Jam Berry. All three beverages reported the presence of THC and the absence of THCA, CBD, and CBDA. Peaks at nominal *m/z* 315 and 313 were detected in positive- and negative-ion modes, respectively, in each beverage. However, in negative-ion mode, the intensity of the *m/z* 313 peak in the Dream Drink fell below the 100-ion count IDL threshold.

The two *Cannabis* capsule products (i.e., G-Caps) analyzed in this study were indicated by the vendor to contain several cannabinoids, many of which were detected by the DART-HRMS method and are featured in Tables S1 and S2. The THC G-Caps were reported to contain THC, CBG, CBN, and CBC. Peaks consistent with all four cannabinoids were detected in negative-ion mode, while in positive-ion mode, the only peak of interest for which a mass was detected was THC/CBC at *m/z* 315.2338. Of the 11 cannabinoids listed on the 1:1 Hybrid G-Caps product label, peaks consistent with cannabinoid acids (i.e., THCA/CBDA, CBNA,) were absent from the DART mass spectra obtained when these capsule contents were analyzed in both ionization modes. However, if the percentages of these cannabinoids portrayed on their product labels are accurate (i.e., 0.01 %, 0.01 %, and 0.02 %, respectively, implying their presence in only trace amounts), then the absence of their representative peaks is not surprising.

3.3.2. Concentrates

A variety of concentrates produced by various extraction approaches were analyzed by DART-HRMS, including kief, hash, rosin, sauce, wax, and sugar. Both ionization modes revealed the presence of cannabinoids in each. Their DART mass spectra collected in positive-ion mode are shown in Fig. 4. The mass spectrum of the Lava Cake Wax revealed the greatest number of peaks consistent with the presence of the protonated cannabinoids listed on the product label (i.e., THC/CBC (*m/z* 315.2348), CBG (*m/z* 317.2425), THCA/CBDA (*m/z* 359.2227), and CBGA (*m/z*

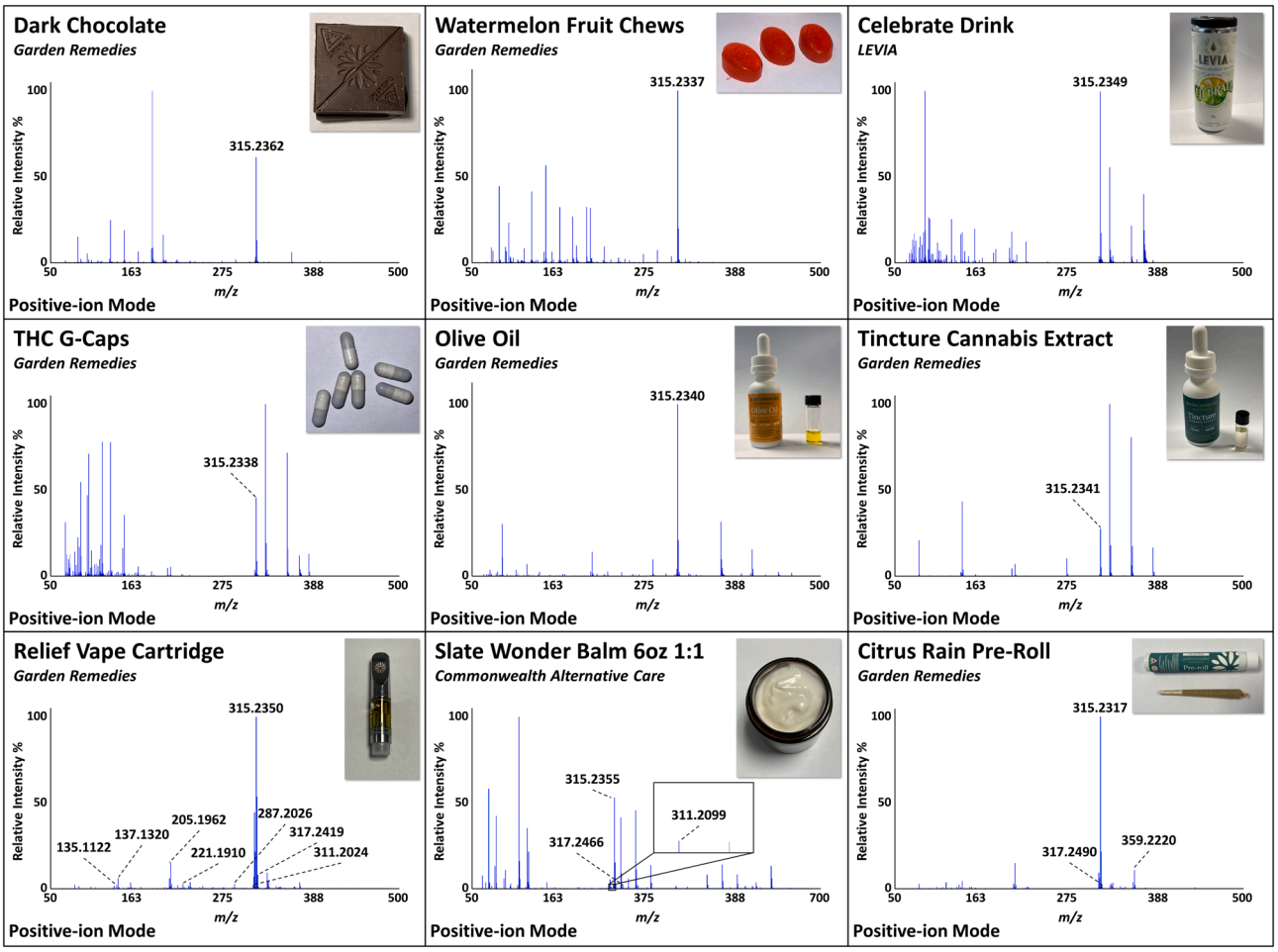

Fig. 3. DART-HR mass spectra of recreational *Cannabis* products analyzed in positive-ion mode. Peaks consistent with reported cannabinoids and terpenes are labeled. Images of the corresponding products are shown in the insets.

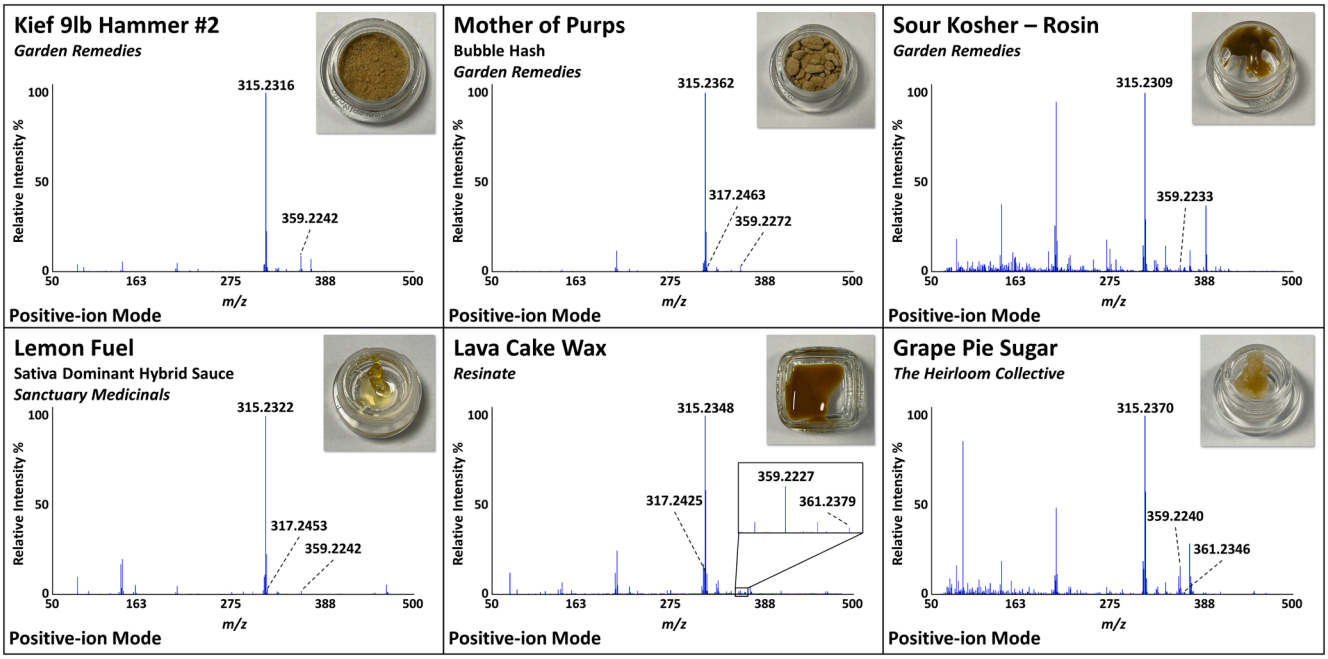

Fig. 4. DART-HR mass spectra of *Cannabis* concentrates analyzed in positive-ion mode. Peaks consistent with reported cannabinoids are labeled. Images of the corresponding concentrates are shown in the insets.

361.2379)). Analysis of the Lemon Fuel – Sativa-dominant Hybrid Sauce in negative-ion mode, which is presented in Supplementary Fig. 5, revealed the most peaks consistent with the presence of cannabinoid precursors (in deprotonated form) listed on the product label (i.e., THCV (*m/z* 385.1891), CBN (*m/z* 309.1837), CBD/THC/$^{\Delta 8}$-THC/CBT (*m/z* 313.2113), CBG (*m/z* 315.2267), and THCA (*m/z* 357.2048). Cannabinoids detected in the remaining concentrates are listed in Tables 1 and S2.

3.3.4. Tinctures

When analyzed by DART-HRMS, the CBD Tincture revealed peaks at *m/z* 315.2341 and 313.2116 in positive- and negative-ion modes, respectively, and no peaks consistent with other cannabinoids were detected above the 100-ion count IDL threshold. This is consistent with what would be expected if the tincture was prepared using only CBD and was not spiked with any other cannabinoids.

3.3.5. Vaporizers

For the single vaporizer cartridge product that was analyzed by DART-HRMS, masses consistent with the presence of all the cannabinoids listed on the product label were detected in either positive- or negative-ion mode by DART-HRMS (Table S1). Protonated precursor peaks consistent with THC/CBD/CBC/CBT (*m/z* 315.2350), CBG (*m/z* 317.2419), THCV (*m/z* 287.2026), and CBN (*m/z* 311.2024) were detected. While a peak consistent with the presence of protonated THCA was not detected in positive-ion mode, its deprotonated counterpart in negative-ion mode was readily detected as a strong peak (*m/z* 357.2070). Other cannabinoids detected in negative-ion mode include THC/CBD/CBC/CBT (*m/z* 313.2177), CBG (*m/z* 315.2283), and CBN (*m/z* 309.1858). The vape cartridge sample was also listed as containing terpenes, and peaks that aligned with the protonated precursors of several terpenes were detected in positive-ion mode (Table S1).

3.3.5. Topicals

The Slate Wonder Balm – 6 oz (1:1 THC:CBD) was reported to contain THC/CBD, CBG, and CBN. Peaks consistent with each of these cannabinoids were detected at *m/z* 315.2355, 317.2466, and 311.2099, respectively, in positive-ion mode. Peaks at *m/z* 313.2144 and 309.1861 consistent with deprotonated THC/CBD and CBN, respectively, were detected in negative-ion mode. However, a high-resolution mass consistent with deprotonated CBG was not observed.

3.3.6. Marijuana flower

The following three marijuana flower samples were analyzed by DART-HRMS in both ionization modes: (a) Snowdog – Hybrid; (b) Dr. Lime #10 – Sativa; and (c) Wonka Bars – Indica. In all cases, THC and THCA were detected in both ionization modes. Other cannabinoids detected between the two ionization modes included CBG, CBGA, and CBCA. In addition, protonated molecules consistent with the masses of monoterpenes ($C_{10}H_{16}$), sesquiterpenes ($C_{15}H_{24}$), and/or sesquiterpenoids ($C_{15}H_{24}O$) were observed in all flower strains. Representative positive- and negative-ion mode spectra are shown in Fig. 5 and Supplementary Figure 6, respectively.

3.3.7. Pre-Rolls

Four pre-rolls comprised of different strains of marijuana were analyzed by DART-HRMS: (a) 9 lb Hammer #2; (b) Big D Energy; (c) Citrus Rain; and (d) Skunk Hero. Similar to the flower samples, peaks in the pre-rolls whose *m/z* values were consistent with those of cannabinoids such as THC, CBG, THCA, and CBCA were detected in both ionization modes (Tables S1 and S2).

4. Discussion

The DART-HRMS triage approach for the detection of cannabinoids and terpenes in commercially available *Cannabis* products proved successful, despite the variety and complexity of the matrices that were surveyed. Overall, the presence of multiple peaks peculiar to the matrix did not preclude the ability to readily detect cannabinoids or terpenes of interest. This was most notable for samples classified as edibles. Sugars, fats, lipids, flavoring agents, and other ingredients are used in the preparation of these products, and their presence is reflected in their DART-HRMS chemical profiles. In positive-ion mode, these ingredients did not interfere with the observation of THC/CBD (nominal *m/z* 315). However, in negative-ion mode, the ability to observe THC (nominal *m/z* 313) was matrix dependent, and it was difficult to detect in the fruit chew, chocolate, and beverage samples in particular. This contrasted with other matrix types such as concentrates, flower and pre-rolls, in which the presence of THC/CBD at *m/z* 313 was readily observed. The matrix-dependent difficulty of detecting cannabinoids in negative-ion mode was consistent with previous observations where edible candies prepared in-house were analyzed. The results for DART-HRMS analysis of samples in which THC and CBD had been infused, including fruit chews (i.e., gummy candies), dark chocolate, semi-sweet chocolate and white chocolate are presented in Supplementary Figure 7. The spectra appearing in the left panels represent control samples that did not contain THC or CBD. Those in the middle panels represent samples into which THC was infused, while those on the right contained CBD. The results show that with the exception of THC- and CBD-infused dark chocolate, no peaks consistent with the presence of THC and CBD were detected in the candies where these compounds were known to be present. Since THC/CBD could be readily detected when analysis was performed in positive-ion mode, the results indicate that the absence of a peak at *m/z* 313 in negative-ion mode does not necessarily mean that there is no THC or CBD present. Thus, for these high-sugar matrices, effective screening by DART-HRMS requires that the analysis be performed in positive-ion mode.

There were a few instances when the DART-HRMS data acquired did not fully align with the list of cannabinoids reported on the product labels. For example, the product information for the Apple Martini Chew

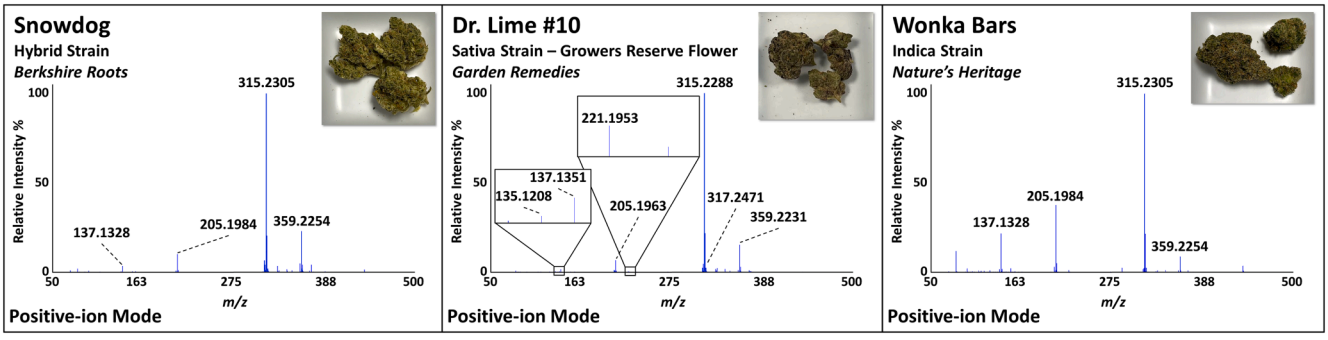

Fig. 5. DART-HR mass spectra of *Cannabis* flower strains analyzed in positive-ion mode. The base peak (i.e., *m/z* value with the highest relative intensity) in each sample was nominal *m/z* 315, which is consistent with the protonated mass of THC. Images of the corresponding flower samples are shown in the insets.

indicated that testing performed to detect THC, THCA, CBD, CBDA and Δ^8-THC (which would exhibit peaks for the protonated precursors at nominal *m/z* 315 (THC, CBD, and Δ^8-THC) and 359 (THCA, CBDA)) revealed the presence of only THC. However, in our hands, analysis of this material by DART-HRMS showed not only a peak at *m/z* 315.2345 which would be expected for THC, but also a peak at *m/z* 359.2244. Since the mass at *m/z* 359 is consistent with the presence of THCA/CBDA, but the product label indicated that neither of these compounds was detected, the observation of this peak in DART-HRMS analysis might indicate that it corresponds to another known isomer of THCA/CBDA that might be present, such as CBCA and cannabicyclolic acid (CBLA).

This type of scenario can occur even with products that were subjected to a comprehensive cannabinoid analysis. For example, CBN and its acid counterpart CBNA ($C_{22}H_{26}O_4$) are two of the cannabinoids listed as "not detected" among a panel of 17 other cannabinoids examined in the Sour Kosher – Rosin product. However, DART-HRMS analysis in positive-ion mode revealed peaks at *m/z* 311.1960 and 355.1938, which are consistent with the respective protonated masses of CBN and CBNA. Negative-ion mode analysis of this product revealed corroborating results: high-intensity peaks at *m/z* 309.1879 and 353.1771 consistent with deprotonated CBN and CBNA, respectively, were detected. A similar situation occurs with cannabinodiol (CBND), an isomer of CBN. Although there is a standard available for this cannabinoid, analysis for its presence was not included in the independent laboratory testing for any of the products surveyed in this study. Therefore, it is possible that this cannabinoid is present in Sour Kosher – Rosin, as well as in other products (e.g., Lava Cake Wax and 9 lb Hammer #2 – Kief) that also exhibited peaks at nominal *m/z* 311 and 309 in positive- and negative-ion modes, respectively.

Just as both CBN and CBNA naturally occur in *C. sativa*, CBND and its acid form (cannabinodioloic acid—CBNDA) can also be found. Thus, the presence of CBNDA in situations where CBNA was not tested for or was reported as "not detected", could explain the peaks observed at *m/z* 355 and 353 in positive- and negative-ion modes, respectively. While there are commercial standards available for CBND, to the best of our knowledge, there is no commercial standard available for CBNDA at the writing of this report. Therefore, DART-HRMS analysis of a CBNDA standard could not be conducted. Thus, in addition to the need for comprehensive testing panels, this observation stresses the necessity for chemical standards manufacturers to keep pace with the acquisition of novel forensically relevant natural products derived from psychoactive plants.

In cases where cannabinoids were listed as present (according to product labels) but were not detected by DART-HRMS, it is possible that complex edible and plant matrices may interfere with their detection. Four products (two concentrates and two pre-rolls) reported the presence of THCVA ($C_{20}H_{26}O_4$) (the cannabinoid acid form of THCV) at levels between 0.1 and 0.4 % (approx. 0.02–0.03 mg/serving in concentrates and 1–4 mg/g of plant material). This translates to less than roughly 3 μg of THCVA present on the capillary tube during DART-HRMS acquisitions, which falls below the IDL threshold set for these experiments. However, a high-resolution peak consistent with protonated/deprotonated THCVA was not detected in any of the commercial products in either ionization mode. DART-HRMS analysis of a THCVA analytical standard revealed that the protonated/deprotonated precursor for this cannabinoid can be detected in both positive- and negative-ion modes, respectively. Therefore, while it is clear that this cannabinoid can be detected by DART-HRMS, it is also possible that its signal is significantly suppressed when it is present in certain matrices.

Although not consistent with the high-resolution mass of THCVA, peaks at nominal *m/z* 331 and 329 in positive- and negative-ion modes, respectively, were detected in multiple concentrates, pre-rolls, edibles, tinctures, and flower samples. No other cannabinoids were listed on the product labels that would correspond to these *m/z* values. As it turns out, the cannabinoid cannabielsoin (CBE) ($C_{21}H_{30}O_3$) has a calculated protonated mass of *m/z* 331.2273 and a deprotonated mass of *m/z* 329.2116. The peaks detected in these products at nominal *m/z* 331 and 329 are all within 10 mmu of these high-resolution masses, in contrast to the average 41 mmu difference between the observed *m/z* values and the calculated protonated/deprotonated masses of THCVA. In this regard, it is notable that both THCVA and CBE were confirmed to be detectable by DART-HRMS in both positive- and negative-ion modes.

Several methods have been devised for the detection and quantification of cannabinoid and terpene molecules. Gas chromatography (GC) coupled with either a flame-ionization detector (FID) or mass spectrometer (MS) is a popular choice for *Cannabis* analysis [16]. However, pitfalls of these GC-based methods include the possible degradation of cannabinoids in the GC injector port and column, and the necessity to derivatize samples that contain both neutral and acid forms of cannabinoids prior to sample injection in order to provide accurate results. HPLC – tandem mass spectrometry (HPLC-MS/MS) has been used to determine cannabinoid concentrations following supercritical fluid extraction (SFE) of *Cannabis* plant materials [17]. HPLC-diode array detection (HPLC-DAD) in combination with GC–MS techniques to monitor cannabinoid and terpene content, respectively, for analysis of plant material acquired at various points during the growth phase of *C. sativa* plants has also been reported [4]. HPLC has been used for the analysis of cannabinoids in gummy candies and brownies [18], as well as for cannabinoid quantification in commercial *Cannabis* consumer products, such as food, beverages, vapes, tinctures/oils, powders, and supplements (in combination with DAD) [19,20]. Several tandem mass spectrometry techniques have also been used for various qualitative and/or quantitative investigations of cannabinoids in complex matrices, including the following: (1) brownie marijuana edibles with UPLC-MS/MS;[21] (2) consumer products including plant materials, oils and cosmetics by LC-MS/MS;[22] and (3) *Cannabis* plant material, distillates, concentrates, food, and cosmetics by LC-UV-MS/MS and UHPLC-UV-MS/MS [23,24]. In addition to using UHPLC-MS to analyze cannabinoids in edibles in forensic casework [25], UPLC coupled with photodiode-array detection (PDA) and MS has also been used to analyze *Cannabis* plant materials and edibles [26]. Lastly, electrospray ionization-LC/MS (ESI-LC/MS) has demonstrated success with the identification and quantification of numerous natural cannabinoids in *Cannabis* extracts to obtain the overall phytocannabinoid metabolite profile [16].

While the LC-based methods circumvent the risk of thermal decomposition of cannabinoids that can occur during analyses by GC, they remain time-consuming, and significant sample pretreatment steps are still required prior to LC analysis. Sample preparation approaches for extracting cannabinoids from edibles and/or beverages (prior to analysis by HPLC) include the QuEChERS extraction protocol [27] and use of matrix-removal cartridges [28]. However, successful application of these tools for the vast range of complex matrices that may require analytical investigation, such as those surveyed in this study and available at recreational dispensaries, has not been demonstrated.

The complex matrices examined in this work have proven challenging to analyze when interrogated by traditional chromatographic approaches; materials containing fats, oils, and both simple and complex carbohydrates are notorious for adhering to columns, clogging syringes, and causing workflow interruptions because of the need to address maintenance issues due to dirtied instruments. Although no carryover was observed between DART-HRMS acquisitions in this study, frequent cleaning of the outside of orifice 1 is recommended when analyzing samples that could cause potential contamination in subsequent runs, a process that takes under a minute and does not require the instrument to be shutdown (outside of routine instrument maintenance). The advantage of DART-HRMS requiring only very small amounts of sample, is that it minimizes the chances of complex matrices causing contamination that results in the appearance of spurious peaks in subsequent runs. However, as with other mass spectrometric methods, contamination of the mass analyzer would require that the instrument be shut down for

cleaning.

This study was prompted in part by the desire to reduce the number of samples that are needlessly subjected to time-consuming, expensive and resource-intensive confirmatory testing protocols (when they do not contain scheduled molecules or other compounds of interest), so that confirmatory testing can be reserved for those instances where there is reason to believe that molecules of concern (e.g., cannabinoids, terpenes) are present. The results revealed that while a broad range of cannabinoids and terpenes were successfully detected by DART-HRMS when in the form of CRMs and when they were infused within a range of complex matrices, it was also clear that some matrices affect the ability to detect these compounds of interest. For ease of reference, a summary of the matrix types and the ability to detect cannabinoids and terpenes infused within them by DART-HRMS, in both ionization modes, are presented in tabular form in Table 1.

There have been DART-HRMS studies that have successfully utilized multiple orifice 1 voltages, in which collision-induced dissociation (CID) conditions are implemented [29,30]. However, the generation of protonated and deprotonated precursor molecules under soft ionization conditions (orifice 1 voltage of 20 V/-20 V) was found to be successful for the developed triage approach described here. Furthermore, the utilization of CID conditions would result in the fragmentation of *all* of the hundreds of molecules contained within the matrix, which could generate spectra of such complexity as to make it challenging if not impossible to presumptively detect the cannabinoids of interest. Although the DART-HRMS method presented here does not focus on distinguishing between cannabinoid isomers (e.g., THC and CBD) or terpene isomers (such as α-pinene and limonene), this deficiency is offset by its ability to rapidly detect *Cannabis*-related molecules with no sample preparation required, a feature that confers particular advantages. Furthermore, this triage approach would be beneficial when instituted prior to launching time-consuming confirmatory techniques (which themselves vary from state to state depending on the legal status of THC, CBD, and other cannabinoid isomers). The *Cannabis* industry and the products within it will continue to evolve and the number of new products on the illicit market is anticipated to expand, regardless of the legal status of *Cannabis* and products derived from it. Experience has shown not only that these materials are likely to increase in complexity, but also that the reliance on conventional methods for their analysis is disadvantageous because of the nuanced method development required for each new matrix. Therefore, implementing the triage method demonstrated here, prior to launching confirmatory testing would benefit numerous laboratory types, including forensic (state and county) and federal laboratories by saving time, resources, and funds. Furthermore, this approach and its successful application to retail recreational products sets the foundation for the extension of DART-HRMS methods to the differentiation of cannabinoid isomers by including a derivatization step, in order to achieve an additional measure of confirmation.

5. Conclusions

Direct analysis of a broad range of recreational *Cannabis* products in their native forms by DART-HRMS readily revealed the presence of cannabinoids, with only a few occurrences where the matrix affected the ability to detect them, primarily in negative-ion mode. To avoid the potential observation of false positive results for THC/CBD detection, the presence of THC/CBD was based on observation of peaks consistent with their high-resolution masses at m/z 315.2324 and 313.2168 in positive- and negative-ion modes, respectively, that were above the instrument detection limit (IDL) cutoff of 100 ion counts. The simultaneous detection by DART-HRMS of terpene molecules provided an additional dimension of discrimination to the triage approach. The results show that this method can be deployed for the rapid analysis of cannabinoids and terpenes in commercial products to provide preliminary information that will increase sample analysis efficiency by informing not only the need for further confirmatory tests, but also the

Table 1
Summary of results obtained from the DART-HRMS screening of recreational *Cannabis* products. The detection of cannabinoids/terpenes refers to the presence/absence of peaks consistent with the calculated protonated/deprotonated mass.

Category	Matrix Type	DART Ionization Mode	Observations
Edibles	Chocolate	Positive-ion mode	• THC was readily detected in each type of chocolate
		Negative-ion mode	• Difficulty detecting THC some types of chocolate
	Fruit Chew	Positive-ion mode	• THC was readily detected in each flavor
		Negative-ion mode	• Difficulty detecting THC in all flavors
	Beverage (Seltzer)	Positive-ion mode	• THC was readily detected in each flavor
		Negative-ion mode	• Difficulty detecting THC in some flavors
	Capsule (G-Caps)	Positive-ion mode	• Detected all cannabinoids reported to be present at levels $>$ 0.03 % (CBDV, CBD, CBG, THC, CBC, CBT) • Did not detect most cannabinoids reported to be present at levels $\leq$ 0.02 % (CBDA, CBN, CBNA, THCA) • CBG was detected in multiple samples, but below the 100-ion count IDL threshold • CBN was detected in one sample but fell below the 100-ion count IDL threshold
		Negative-ion mode	• Detected all cannabinoids reported to be present at levels $\geq$ 0.02 % except CBNA
	Olive Oil	Positive-ion mode	• THC was readily detected
		Negative-ion mode	• THC was readily detected
Concentrates	Rosin	Positive-ion mode	• Detected reported cannabinoids (CBDA, THC, THCA, CBCA, CBT) except CBG, CBGA, and THCVA
		Negative-ion mode	• Detected all reported cannabinoids (CBDA, CBGA, CBG, THC, THCA, CBCA, CBT) except THCVA
	Wax	Positive-ion mode	• Detected all reported cannabinoids (THCA, THC, CBDA, CBGA, CBG, CBN, CBC)
		Negative-ion mode	• Detected all reported cannabinoids (THCA, THC, CBDA, CBGA, CBG, CBN, CBC)
	Kief	Positive-ion mode	• Detected all reported cannabinoids (THC, THCA, CBGA) • CBGA was detected but fell below the 100-ion count IDL threshold
		Negative-ion mode	• Detected all reported cannabinoids (THC, THCA, CBGA)
	Sugar	Positive-ion mode	• Detected all reported cannabinoids (THC, THCA, CBGA)
		Negative-ion mode	• Detected all reported cannabinoids (THC, THCA, CBGA)
	Sauce	Positive-ion mode	• Detected all reported cannabinoids (CBG, CBD, THC, Δ^8-THC, THCA, CBT) except THCV and CBN
		Negative-ion mode	• Detected all reported cannabinoids (CBD, THC, Δ^8-

(*continued on next page*)

Table 1 (*continued*)

Category	Matrix Type	DART Ionization Mode	Observations
			THC, THCA, CBT, THCV, CBN) except CBG
	Hash	Positive-ion mode	• Detected most reported cannabinoids (CBG, THC, THCA, CBCA); did not detect THCVA or CBGA
		Negative-ion mode	• Detected all cannabinoids reported to be present at levels $>$ 0.02 % (CBGA, THC, THCA, CBCA) • Did not detect cannabinoids reported to be $\leq$ 0.02 % (CBG, THCVA)
Tinctures	CBD Tincture	Positive-ion mode	• CBD was readily detected
		Negative-ion mode	• CBD was readily detected
Topicals	Balm	Positive-ion mode	• Detected all reported cannabinoids (THC, CBD, CBG, CBN)
		Negative-ion mode	• Detected most reported cannabinoids (THC, CBD, CBN) except CBG
Vape Products	Vaporizer	Positive-ion mode	• Detected all cannabinoids reported to be present at levels $\geq$ 0.02 % (CBG, CBD, THCV, CBN, THC, CBC, CBT) except THCA • Several reported terpenes were detected ($C_{10}H_{14}$, $C_{10}H_{16}$, $C_{15}H_{24}$, $C_{15}H_{24}O$) • Some reported terpenes were not detected ($C_{10}H_{18}O$, $C_{15}H_{26}O$)
		Negative-ion mode	• Detected all reported cannabinoids (CBG, CBD, CBN, THC, THCA, CBC, CBT) except THCV • No peaks consistent with reported terpenes were detected
Plant Material	Pre-roll	Positive-ion mode	• When reportedly present, THC, THCA, CBG, and CBCA were readily detected • THCVA was not detected in any samples • CBGA was either not detected or fell below the 100-ion count IDL threshold
		Negative-ion mode	• When reportedly present, THC, THCA, CBCA, and CBGA were readily detected • THCVA was not detected in any samples • CBGA was either not detected or fell below the 100-ion count IDL threshold
	Flower	Positive-ion mode	• When reportedly present, THC, THCA, and CBCA were readily detected • CBG was detected but did not always fall above the 100-ion count IDL threshold • CBGA was either not detected or fell below the 100-ion count IDL threshold • Several reported terpenes were detected ($C_{10}H_{14}$, $C_{10}H_{16}$, $C_{15}H_{24}$) • Several reported terpenes were not detected ($C_{10}H_{18}O$, $C_{15}H_{26}O$)
		Negative-ion mode	• Several terpenes were only occasionally detected ($C_{15}H_{24}O$) • When reportedly present, THC, THCA, CBCA, and CBGA were readily detected • CBG was detected in all but one of the samples • No peaks consistent with reported terpenes were detected

nature of the confirmatory tests that should be performed. Future applications of the developed DART-HRMS triage method may include screening for pesticides and residual solvents in complex matrices. Fields outside of forensic science may also benefit from the method, such as the medicinal, environmental, and agricultural industries, including the cultivation of *C. sativa*.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

Data will be made available on request.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.forc.2023.100469.

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