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RESEARCH PAPER

Thermal stability of cannabinoids in dried cannabis: a kinetic study

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Abstract
This study was undertaken to quantitatively explore the effect of temperature on the degradation of cannabinoids in dried cannabis flower. A total of 14 cannabinoids were monitored using liquid chromatography and tandem mass spectrometry in temperature environments from −20 to +40 °C lasting up to 1 year. We find that a network of first-order degradation reactions is well-suited to model the observed changes for all cannabinoids. While most studies focus on high-temperature effects on the cannabinoids, this study provides high-precision quantitative assessment of room temperature kinetics with applications to shelf-life predictions and age estimates of cannabis products.

Keywords Cannabis · Stability of cannabinoids · Bayesian kinetic modeling

Introduction

A number of countries have established medicinal cannabis programs and a handful have also legalized cannabis for adult recreational purposes. Regulated cannabis markets typically have stringent testing requirements to ensure the safety of consumers. In addition to measuring cannabinoid and terpene levels, which define the desired properties of the product, cannabis is generally tested for a wide variety of other chemicals including pesticides, mycotoxins, mold, bacteria, and heavy metals.

Determination of cannabinoid levels for regulatory purposes, also known as measuring "potency," calls for measurements of the major cannabinoids such as the Δ^9-tetrahydrocannabinol (THC), cannabidiol (CBD), and their carboxylic acid precursors (THCA, CBDA). Over 100 other minor cannabinoids are known and some of them are part of mandatory testing in jurisdictions such as New Hampshire or California. Mostly, however, the minor cannabinoid profile is used for branding or exploratory research purposes.

A feature common to acid cannabinoids is that they undergo decarboxylation. Although this is well-known, it is generally viewed as inconsequential because the degradation product of THCA is an active ingredient. Some regulations take this into account and require reporting the total THC equivalent which is the sum of Δ^9-THC and Δ^9-THCA defined as $m(\text{THC}) + 0.877m(\text{THCA})$ [1]. However, the decomposition of cannabinoids does not stop with decarboxylation; there is ample evidence [2, 3] (supported by the results of this study) showing that THC levels too can decrease over time thus further adding to the overall loss of total THC.

Many studies have been devoted to better understand the degradation of cannabinoids [2, 3]. This helps to provide evidence-based considerations for the shelf-life of cannabis and is an important part of metrology surrounding cannabis testing in general. A variety of cannabinoid ratio markers are employed to perform chemical characterization of cannabis [4]. As an example, the CBN to THC ratio is used as a marker of age [5], and the CBDA to CBD ratio is used to evaluate storage conditions [6].

Despite the interest in cannabinoids, many studies devoted to measurements of cannabinoids do not distinguish between the carboxylic cannabinoids and their decarboxylated analogues. Unlike liquid chromatography, gas chromatography is known to induce decarboxylation in the injection port [7]. Such conversion is often incomplete and therefore comparing the cannabinoid measurements by gas

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and liquid chromatography might not be reliable. While others employ a decarboxylation step prior to analysis, such methods can provide biased results.

This study provides precision measurements of cannabinoids along with a long-term stability study of these compounds in dried cannabis material using isotopic internal standards. This work was made possible with the development of a cannabis reference material, which had sufficient homogeneity to allow for detection of small changes in cannabinoid levels across samples at different storage conditions.

Experimental

Cannabis material

The cannabis material used in this study was produced by blending two strains of *Cannabis sativa*. One strain contained mostly THCA/THC and the other CBDA/CBD. Both strains were blended to achieve typical cannabinoid levels (see Table 1) using a two-stage blending process using food blenders while ensuring that the material remained at ambient temperature. In both stages, blending was followed by passing the material through a 355-µm sieve. The sieved cannabis material was homogenized by hand-mixing and shaking.

Determination of cannabiniods by LC-MS/MS

The cannabinoid method employed has been described elsewhere [8] and was adapted to yield higher precision and accuracy for this work by using narrower calibration ranges. The cannabinoids were extracted from 200 mg cannabis samples by vortex-mixing with methanol-water mixture (80:20 volume ratio). The cannabis samples were extracted sequentially four times (10 mL each time). After centrifugation, the supernatants were combined (40 mL), vortex-mixed, and an aliquot was diluted 100-fold in methanol (we refer to this sample as the diluted cannabis extract).

The LC-MS/MS system consisted of a HPLC (1290 Infinity I, Agilent) coupled to a triple quadrupole mass spectrometer (TSQ Quantiva; Thermo Scientific). Chromatographic separation was carried out on C18-Amide bonded phase column (Ace-3, 100 mm × 2.1 mm i.d. with 3 µm particle size; Advanced Chromatography Technologies, Aberdeen Scotland) maintained at 40 °C and mobile phases consisting of water/formic acid and acetonitrile/formic acid both mixed in 1000:1 volume ratio. The MS/MS detection of cannabinoids was performed via electrospray ionization in positive ion mode using quasi-molecular ion to product ion transitions as outlined elsewhere [8]. The total chromatographic run time was 21 min (see Fig. 1). External calibration standard solutions of cannabinoids were prepared gravimetrically in methanol in four separate groups to decrease possible cannabinoid inter-conversion bias. Standards were prepared at three levels: at half, double, and same levels of cannabinoids expected in the diluted cannabis extract. THC-d_3 (Cerilliant; Round Rock, TX, USA) was used as internal standard for THC and THCA, CBD-d_3 (Cerilliant) for CBD and CBDA, and CBN-d_3 (Cerilliant) was used as internal standard for all other cannabinoids.

Table 1 Cannabinoids studied in this work along with their tentative certified mass fraction values and their 95% uncertainties in the dried cannabis NRC certified reference material

Cannabinoid	Symbol	w, mg/g
Δ^9-Tetrahydrocannabinol	THC	60 ± 4
Δ^9-Tetrahydrocannabinolic acid	THCA	125 ± 6
Cannabidiol	CBD	9.1 ± 0.8
Cannabidiolic acid	CBDA	24 ± 1
Cannabigerol	CBG	2.1 ± 0.1
Cannabigerolic acid	CBGA	4.3 ± 0.2
Cannabinol	CBN	2.9 ± 0.6
Cannabinolic acid	CBNA	2.0 ± 0.2
Cannabichromene	CBC	1.2 ± 0.1
Cannabichromenic acid	CBCA	1.9 ± 0.1
Tetrahydrocannabivarin	THCV	0.30 ± 0.02
Tetrahydrocannabivarinic acid	THCVA	0.49 ± 0.03
Cannabidivarin	CBDV	0.046 ± 0.004
Cannabidivarinic acid	CBDVA	0.13 ± 0.01

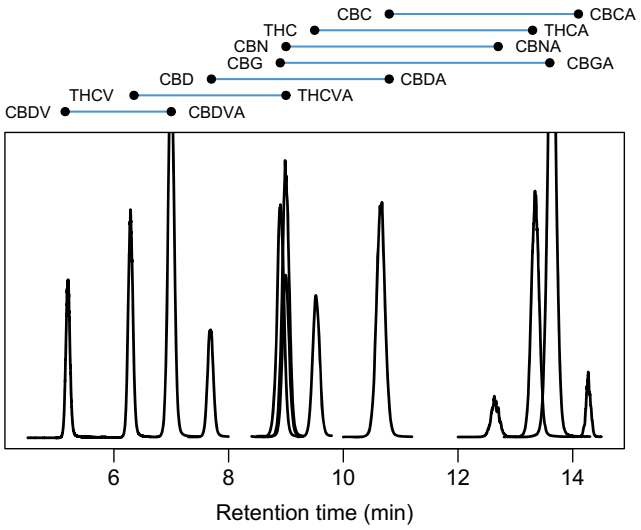

Fig. 1 A representative LC-MS/MS chromatogram of a 14-cannabinoid mixture each at 1.0 µg/mL. The image shown is a composite of nine separate chromatograms each corresponding to a unique MS/MS transition

Unweighted ordinary linear regression was used for calibration with peak area ratio of cannabinoid and internal standard as the response variable. In all cases, calibration curves had $R^2 \geq 0.99$ resulting in a typical combined relative measurement uncertainty of 2% for all cannabinoids.

Stability study design

An accelerated isochronous stability study [9] was conducted with two units of the dried cannabis NRC certified reference material (CRM) stored at each of the temperature levels (−20 °C, +4 °C, +20 °C, +32 °C, +37 °C, and +40 °C) for up to 52 weeks in 66-L microbiological incubators (Isotemp, Fisher Scientific) with ±0.2 °C stability and whose temperature was also monitored with calibrated thermometers. Two additional samples were stored at −80 °C serving as the control environment. At each time point, the CRM units were removed from storage and allowed to equilibrate to room temperature for 1 h. Each CRM unit was then mixed by hand and two 200-mg sample aliquots were transferred into clean 15-mL polypropylene tubes with the exact sample masses recorded. The CRM units were then closed and returned to the appropriate storage temperature whereas the weighed cannabis aliquots were stored at −80 °C until the completion of the 50-week term, when they were analyzed on the same day. Additional study was done afterwards to provide data for +30 °C and +40 °C. For this, a pooled sample from three units of the CRM were subsampled for +30 °C (1.0 g), +40 °C (1.0 g), and −80 °C control level (0.5 g). At appropriate time points, two 100-mg sample aliquots were transferred into clean polypropylene tubes and stored at −80 °C until analysis.

The overall dataset consisted of 924 observations involving seven cannabinoids in their carboxylic and decarboxylated forms (Table 1). Considering that the mass of cannabis material is not conserved during the storage of cannabis due to the release of CO_2 as a result of decarboxylation of its components, all samples were weighed after being held at the various temperature environments and all measurement results are expressed as mass fractions of cannabinoids relative to the mass of cannabis at the time of analysis.

Sample homogeneity

Cannabis plants can be extremely inhomogeneous with respect to their cannabinoid content and dried materials require thorough blending [10]. To evaluate the homogeneity of the cannabis sample with respect to its cannabinoid content, we conducted measurements of 14 cannabinoids from 10 CRM units. Uncertainty due to homogeneity, the combination of the between- and within-unit random effects, averaged to 2%, ranging from 1% (CBGA) to 4% (CBN). Thus, the cannabis CRM was shown to be homogeneous at the level of measurement uncertainty. Nevertheless, the effects of the homogeneity was incorporated in our statistical model.

Results

Kinetic model of cannabinoid stability

Many cannabinoids are aromatic carboxylic acids which are capable of decarboxylation in dried cannabis [11]. The conversion of THCA into THC over time is an example of such a process. Thus, we consider the following idealized consecutive pseudo first-order reaction system to model the changes of cannabinoids:

$$\mathrm{A} \xrightarrow{k_\mathrm{A}} \mathrm{N} \xrightarrow{k_\mathrm{N}} \ldots \tag{1}$$

Here, A refers to the cannabinoid in carboxylic form, N refers to its decarboxylated analogue, and Y is the unknown degradation product of N. As an example, tetrahydrocannabinolic acid (A = THCA) converts into tetrahydrocannabinol (N = THC). We also consider the formation of cannabinol (CBN) and cannabinolic acid (CBNA) as shown in Fig. 2.

Additionally, the conversion of CBD to THC has been described in the presence of acids at high temperatures [12], but this reaction is unlikely to occur to any significant extent at normal temperatures. In addition, we have not observed the formation of Δ^8-THC in this study. Although other inter-conversions of cannabinoids can occur in plants, such as CBGA → CBDA or CBGA → THCA [13], these enzymatic processes are unlikely to occur in dried plant material. In addition, due to trace amounts of cannabicyclol (CBL) we also disregarded the conversion of CBC to CBL [14].

The measurement models are based on the above chemical reactions and can be expressed in a system of ordinary differential equations assuming first-order kinetics.

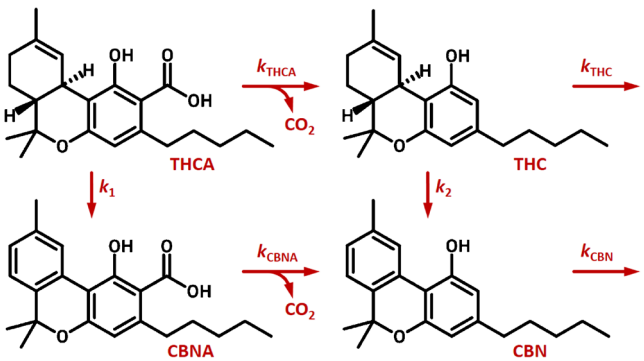

Fig. 2 Decarboxylation and degradation pathways involving THC considered in this work

In the simplest two-component model, the decarboxylation of cannabinoids, shown in Eq. 1, can be described using the following system of differential equations:

$$\begin{aligned} \frac{dc_{\mathrm{A}}}{dt} &= -k_{\mathrm{A}}c_{\mathrm{A}} \\ \frac{dc_{\mathrm{N}}}{dt} &= +k_{\mathrm{A}}c_{\mathrm{A}} - k_{\mathrm{N}}c_{\mathrm{N}} \end{aligned} \tag{2}$$

The Arrhenius equation has been widely used to model the temperature effect on the rate of chemical reactions:

$$\begin{aligned} \ln k_{\mathrm{A}}(T) &= a_{\mathrm{A}} + b_{\mathrm{A}}/T \\ \ln k_{\mathrm{N}}(T) &= a_{\mathrm{N}} + b_{\mathrm{N}}/T \end{aligned} \tag{3}$$

Thus, for example, the stability of CBDA and CBD in cannabis with respect to time and temperature can be described using a kinetic model with four parameters a_{CBDA}, b_{CBDA}, a_{CBD}, and b_{CBD}. Our kinetic model was developed with the aim of studying cannabinoid changes under storage conditions in dark conditions and does not take into account other physical influences such as the humidity, bacterial activity, pH changes, or light, which might play significant roles in other applications.

Model fitting

Given the complexity of the measurement model, we have adopted a Bayesian multi-curve fitting using the Markov chain Monte Carlo method [15, 16]. The reaction rate constants are parameters of differential equations which require integration in order to obtain the concentration of substances at any given time and temperature. This can be achieved using either numerical integration methods, or Eq. 2 can be integrated analytically to obtain an explicit measurement equation. For simple two-compound systems, such as CBDA-CBD, the closed-form expression of the system of consecutive first-order chemical reactions is as follows:x

$$\begin{aligned} c_{\mathrm{A}} &= c_{\mathrm{A},0} \cdot \mathrm{e}^{-k_{\mathrm{A}}t} \\ c_{\mathrm{N}} &= c_{\mathrm{A},0}(\mathrm{e}^{-k_{\mathrm{A}}t} - \mathrm{e}^{-k_{\mathrm{N}}t})\frac{k_{\mathrm{A}}}{k_{\mathrm{N}}-k_{\mathrm{A}}} + c_{\mathrm{N},0} \cdot \mathrm{e}^{-k_{\mathrm{N}}t} \end{aligned} \tag{4}$$

The Bayesian model expresses the observed cannabinoid concentrations with observational equations which explain them probabilistically in terms of the Arrhenius parameters and their uncertainties, the uncertainty arising from the temperature control, as well as the uncertainty due to measurement of the cannabinoids. In addition, we allow for a small variability in the initial cannabinoid levels across the various samples as a result of imperfect homogeneity of the material.

Overall, our approach seeks not to find the best fits to each and every kinetic profile. Rather, the fitting involves finding the values of the Arrhenius parameters that best fit the entire data over all temperature environments.

Fitting complex nonlinear kinetic models is often faced with difficulties that necessitate parameter transformation or scaling [17], whereas Bayesian methods naturally handle parameter estimates in nonlinear models [18]. Additionally, the Bayesian framework provides uncertainty distributions for all model parameters and any derived quantities. As an example, one can readily evaluate and make predictions for the total THC content (sum of THCA and THC), ratio of THCA to THC, or the ratio of THC to CBD, while seamlessly accounting for parameter uncertainties, constraints imposed by the model, or the correlations between parameters.

Given the complexity of the analytical expressions, we employed numerical methods to solve (integrate) the system of differential equations and to find the best estimates of all parameters that fit the data. The three most common open-source options for Bayesian inference are BUGS, JAGS, and STAN, all of which involve Markov chain Monte Carlo methods. We chose STAN largely due to its ability to handle differential equations [19]. The calculations were performed in R using the package "rstan" to interface with STAN [20]. Computational codes discussed in this manuscript are provided in the Supplementary Information (ESM).

Bayesian analysis requires prior probability distributions for all parameters. We have adopted diffuse priors to express vague information about all parameters with common-sense boundaries (all mass fractions must be positive and all reaction rates must increase with temperature). It takes 1–2 h to complete the standard fitting routine for CBDA-CBD (2.5 GHz CPU with 8-core processor). While this approach is significantly more demanding than conventional curve-fitting, Bayesian methods provide the most complete picture of the model parameters and their probability distributions. The fitted kinetic models for all cannabinoids were incorporated into an interactive web application in order to facilitate the exploration of the results (see ESM).

The initial values for model parameters were obtained by pre-fitting the kinetic models to data using R package "mkin" [21] whereas additional analytical calculations developed in this work were aided by *Mathematica* v.10.0.

Discussion

We performed a stability study of seven pairs of cannabinoids in a dried cannabis material stored in dark environments at temperatures ranging from −20 to +40 °C for up to 1 year. Samples stored at −80 °C were treated as reference and all results are summarized in the ESM. We performed Bayesian model fitting, and Fig. 3 shows the changes in the mass fraction of THC, CBD, and CBC at + 40 oC.

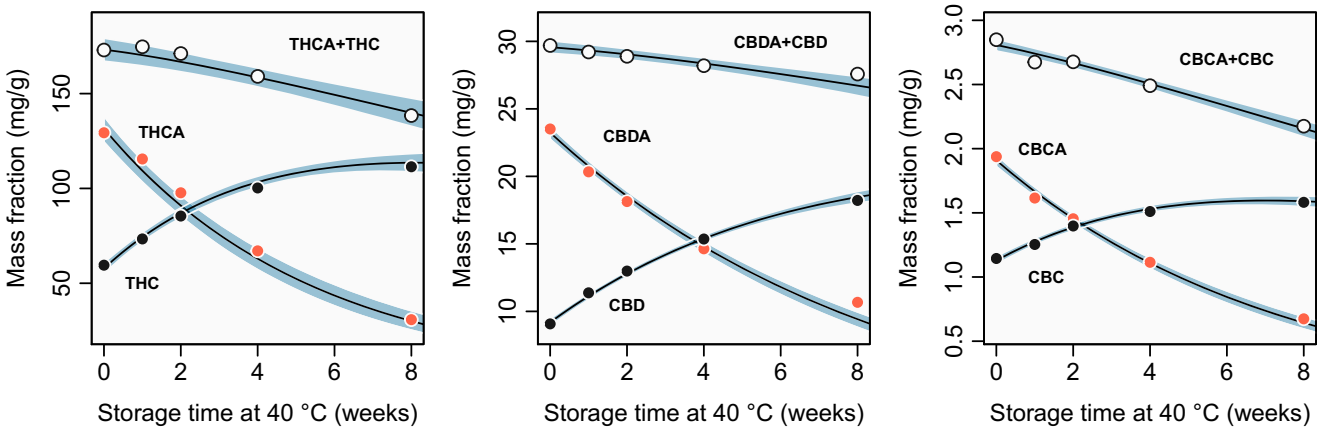

Fig. 3 Kinetic degradation profiles of THCA-THC, CBDA-CBD, and CBCA-CBC in dried cannabis reference samples stored at +40 °C. The total cannabinoid equivalent (upper lines) is defined, for example, as $m_{\mathrm{THC}} + m_{\mathrm{THCA}}(M_{\mathrm{THC}}/M_{\mathrm{THCA}})$. Black curves represent the best fit of the kinetic model and the surrounding blue segments are the 95% credible intervals

In order to further simplify the kinetic model, we have treated CBN as stable product at the temperatures considered here ($k_{\mathrm{CBN}} = 0$). This is in line with our measurements and the observation that CBN remains the prevalent cannabinoid in century-old dried cannabis samples [3].

Figure 4 shows the relationship of the decarboxylation rate constants as a function of temperature (the Arrhenius plot). The analysis of these results shows that decarboxylation rate constants of all seven cannabinoids analyzed are mostly indistinguishable from one another. Thus, given the complexity of the THC-CBN kinetic network, one can impose this observation (i.e., $k_{\mathrm{A,THCA}} = k_{\mathrm{A,CBNA}}$) to facilitate the model fitting for THC.

The observed changes in the mass fraction of cannabinoids align well with the simple first-order kinetic model. We also note the clear opposing trends in the decay of cannabinoid acid forms and the rise of the decarboxylated analogues. These two processes can, and indeed do, cancel each other out: when stored at +40 °C for 2 weeks (Fig. 3), the total THC equivalent remains nearly unaffected despite the significant loss of THCA. This interplay further demonstrates that the term "THC" remains too ambiguous without explicit mention of the acid precursor.

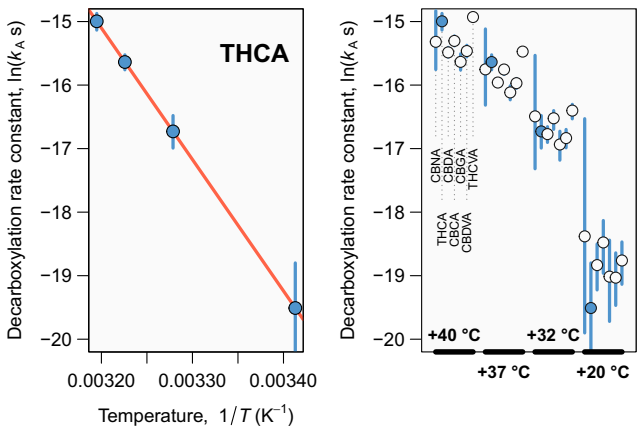

Fig. 4 Decarboxylation rate constants of THCA (left) and other cannabinoids (right) in dried cannabis reference material. Vertical lines represent the 95% credible intervals

The shelf-life of cannabis

The half-life of a carboxylic cannabinoid (A) is the time in which half of it is decarboxylated. Given first-order decay of A, the time at which its levels are at a fraction h (such as 85%) of its initial value is $t_{\mathrm{S}} = -\ln h/k_{\mathrm{A}}$. Generally speaking, we find that the 85% shelf-life ($h = 0.85$) of cannabinoids doubles with each 5 °C reduction in the storage temperature.

Of high practical interest is also the minimum duration, t_{S}, at which the total amount of a cannabinoid has decayed to a certain amount, such as 15%, below its original value. For THC, as an example, such shelf-life (shown in Fig. 5) is obtained by solving the following expression for t_{S}:

$$\frac{n_{\mathrm{THCA}}(t_{\mathrm{S}}) + n_{\mathrm{THC}}(t_{\mathrm{S}})}{n_{\mathrm{THCA}}(t=0) + n_{\mathrm{THC}}(t=0)} = 0.85 \tag{5}$$

In the early cannabis stability studies, Lerner showed that the THC content of cannabis decreases at the rate of $3-5\%$ per month at room temperature [22]. Similarly, Zamengo et al. showed recently that the average THC degradation in the first 100 days is 12% at 22 °C (or $3-4\%$ per month) [23]. Our study is in general agreement with these estimates and puts the average monthly THCA+THC degradation rate at 2% at 20 °C. While room temperature is indeed unsuitable for storage of cannabis standards, we have observed that even storage at +4 °C fails to maintain a reasonable long-term stability (Fig. 5).

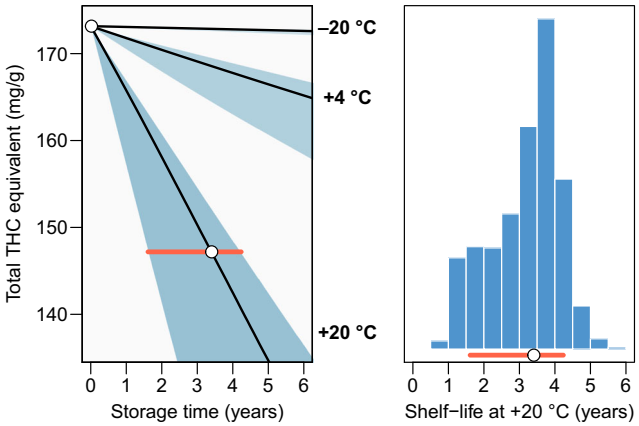

Fig. 5 Predicted changes of the total THC equivalent in dried cannabis stored at −20 °C, +4 °C, and +20 °C (left) and predicted shelf-life (85%) distribution of the total THC equivalent at +20 °C (right). Segments around the best-fit model lines represent the 90% credible intervals

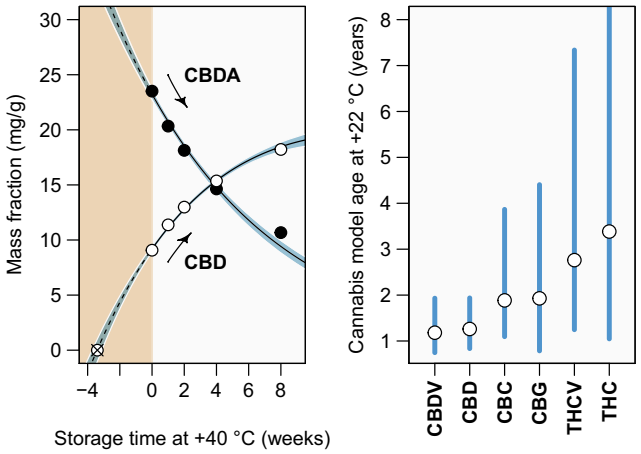

Fig. 6 The principle of the cannabis model age calculation, exemplified with CBDA-CBD measurements of the cannabis CRM stored at + 40 °C (left). The model age is obtained by extrapolating the CBD curve to zero. The figure to the right shows the + 22 °C model age estimates of our cannabis CRM as calculated from the measurements of acid/decarboxylated cannabinoid ratios of six cannabinoids

The age of cannabis

Whereas the shelf-life calculation aims to predict the subsequent changes after the sample analysis, a useful application of the kinetic modeling is to estimate the age of cannabis. We start with the assumption that cannabinoids are present in vivo only in their acidic forms (THCA, CBDA, etc.), which are subsequently decarboxylated upon drying [13, 14, 24]. As a result, the ratio of acid-to-decarboxylated form of a cannabinoid provides an internal clock for the age of cannabis whereby the model age of a cannabis sample is defined as the duration (at a given constant temperature) required to reach the observed amount ratio of the decarboxylated and acid forms of a cannabinoid, $R_{\mathrm{N:A}}$. The system of first-order linear differential equations represented in Eq. 1 and Fig. 2 can be solved analytically to obtain a closed-form expression for the cannabinoid levels as shown in Eq. 4. Solving the latter for the cannabis model age, t_0, gives

$$t_0 = \frac{1}{\Delta k} \ln\left(1 + R_{\mathrm{N:A}} \frac{\Delta k}{k_{\mathrm{A}}}\right) \approx \frac{R_{\mathrm{N:A}}}{k_{\mathrm{A}}} \tag{6}$$

where $\Delta k = k_{\mathrm{A}} - k_{\mathrm{N}} + k_1 - k_2$. (Note that $k_1 = k_2 = 0$ for all cannabinoids except THCA/THC and Eq. 6 is not valid for CBNA/CBN although applicable expressions can be derived.) Measurements of six cannabinoid ratios in the cannabis CRM provide consistent model age estimates as shown in Fig. 6. The contextual knowledge about the provenance of the CRM puts its age estimate to approx. 2 years, which is in agreement with our model age estimates.

Given that THCA and THC are known to oxidize to CBNA and CBN over time, the CBN:THC ratio has been used to infer the age of cannabis samples [5]. Notably, Ross and Elsohly have shown that a simple linear relationship is observed between the cannabis storage duration (t) and the CBN:THC ratio ($R_{\mathrm{CBN:THC}}$), $t \approx 30\ R_{\mathrm{CBN:THC}}$ years, at room temperature [5]. Although this work is ambiguous on the exact meaning of "THC" and "CBN," if we interpret them as total equivalents, our results align very well with this classical "UN formula."

The system of differential equations represented in Fig. 2 can be solved to obtain expressions for the cannabis model age from the ratios involving CBN/CBNA and THCA/THC. For example,

$$t_0 = \frac{1}{k_1} \ln(1 + R_{\mathrm{CBNA:THCA}}) \tag{7}$$

which gives the model age of 57 weeks at 22 °C for our cannabis CRM. However, using the ratio of total CBN and total THC, by extrapolation to zero, suggests markedly lower model age of our CRM, t_0 = 39 weeks. The reasons for this discrepancy are unclear and it remains to be seen which of these age estimates is more robust when applied to a variety of cannabis samples.

Comparison with other studies

Many investigations have been devoted to decarboxylation of cannabinoids in dried cannabis [6, 11, 25, 26], focusing on the high-temperature (ca. 100 °C) and short duration (minutes) domain. By contrast, our study focuses on lower temperatures (ca. 20 °C) and longer time periods (weeks), which is possible, in part, due to the availability of a homogeneous cannabis reference material combined with high-precision LC-MS/MS measurements.

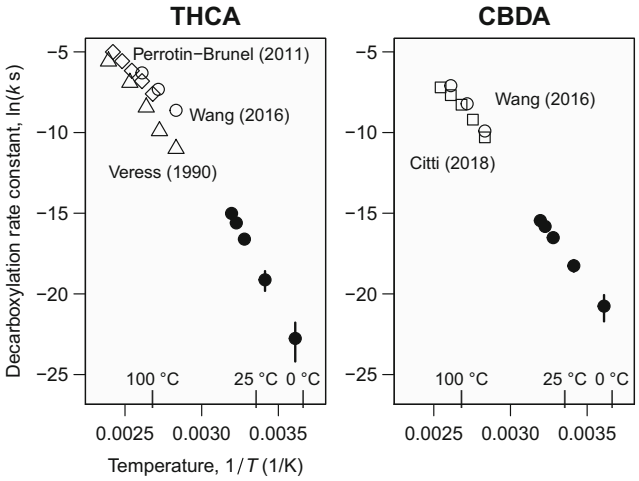

Fig. 7 Compilation of THCA and CBDA decarboxylation rate constants reported in the literature [6, 11, 25, 26]. Results from this work are shown with black circles with 95% uncertainty bars

While there is a reasonable agreement of the decarboxylation rate constants from these studies (see Fig. 7), we note that the interpretation of cannabinoid measurements is challenging due to the fact that many studies do not distinguish between the cannabinoids in their acid and decarboxylated forms. In fact, some legislative documents still suffer from a similar lack of specificity, which has led to many concerns [27].

Conclusion

Our study explores the behavior of dry cannabis at storage conditions near room temperature. To this effect, we have conducted high-precision measurements of seven pairs of cannabinoids and shown that a simple first-order kinetic model is able to explain the changes of both major and minor cannabinoids under a variety of storage conditions up to +40 °C. The decarboxylation rate constants agree well with other recent studies conducted at higher temperatures, which suggests the wider applicability of our kinetic model to a variety of cannabis samples with applications to shelf-life estimates and cannabis age calculations. The results from our study could help inform cannabis regulators in setting degradation thresholds or shelf-lives, and could lay the framework for standardization of stability testing in the cannabis industry [28, 29].

It is not trivial to apply this modeling approach to typical hemp or cannabis samples as measuring small changes in cannabinoid levels stored at different temperature conditions requires highly homogeneous samples. While preliminary results indicate that there could be differences in cannabinoid stability across various cannabis strains, work is underway to elucidate the source of this variability.

Supplementary Information The online version contains supplementary material available at (https://doi.org/10.1007/s00216-020-03098-2).

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

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