



# Preparation of Cannabis Biomass and Crude Extracts with High Neutral Cannabinoid Content

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## ABSTRACT

*Cannabis sativa* L. is a widely known plant belonging to the Cannabaceae family that is rich with diverse bioactive compounds, the most well-known of which are neutral cannabinoids such as delta 9 tetrahydrocannabinol (THC) and cannabidiol (CBD). In the cannabis plant, these compounds are synthesized and accumulated as acidic cannabinoids, but when the biomass is dried, stored, and heated, the acids are gradually decarboxylated into neutral forms. Decarboxylation is, therefore, one of the necessary processes performed in the cannabis industry to provide the desired neutral cannabinoids. However, the suitable temperature and duration of the decarboxylation process for different strains of cannabis biomass and extracts are still unclear. Therefore, the objectives of this study were to compare cannabinoid decarboxylation processes using different temperatures and times to achieve a high yield of neutral-form cannabinoids and to study the pilot-scale feasibility of the selected process. Dried cannabis biomass and cannabis extracts were used in the experiments. The temperatures of decarboxylation were 105°C, 115°C, 130°C, and 145°C with durations between 10 and 60 mins. High-performance liquid chromatography was used for the analysis of the acidic and neutral cannabinoids before and after decarboxylation. The results from the decarboxylation study assisted by the feasibility study suggest that for cannabis biomass, the suitable conditions for CBDA decarboxylation are 130°C for 60 min, and THCA decarboxylation at 145°C for 17 min. For cannabis extracts, the decarboxylation time could be shorter.

**Keyword:** Cannabis sativa; Cannabinoids; Cannabidiol; Degradation of cannabinoids; Decarboxylation; Delta 9 tetrahydrocannabinol

## 1. Introduction

*Cannabis sativa* L. is a plant belonging to the Cannabaceae family and is known as both a medicinal plant and a narcotic drug. Cannabis is rich with diverse compounds exhibiting a range of effects on human physiology. It has gained much attention recently due to its high potential for medicinal uses. Properties of cannabis that might be of therapeutic value include being an analgesic, a muscle relaxant, immune-suppressant, sedative, mood modifier, appetite stimulant, anti-emesis, lowering intraocular pressure, bronchodilator, neuro-protector, and apoptosis inducer in cancer cells [1, 2].

Cannabinoids represent a group of C<sub>21</sub> terpene-phenolic compounds which are large families of metabolites that can interact with many cellular and physiological systems, especially the endocannabinoid system in the body. These constituents are present in acidic form accumulated in the head cells of the glandular hairs (trichomes) which are distributed across the surface of the cannabis plant and are usually concentrated in the female inflorescence. The most realized and studied active cannabinoids are delta 9-tetrahydrocannabinol (THC), and cannabidiol (CBD). Cannabis biomass naturally gradually decarboxylates over time if left alone and its exposure to the elements is enough to turn tetrahydrocannabinolic acid (THCA) gradually into THC, and the THC into cannabinol (CBN) [3, 4]. However, this decarboxylation process is incredibly lengthy, so heat is necessary to accelerate the process [5].

For industry purposes, decarboxylation is a crucial process for producing the desired neutral cannabinoids from cannabis [6]. The starting materials can be cannabis biomass and cannabis extracts. However, the suitable temperature and duration of the decarboxylation process for both types of starting materials are still unclear in the literature. Information regarding the feasible optimal conditions for the decarboxylation

procedure is still not readily available [6-8]. The rationale above leads to the objective of this study which was to determine the optimal temperature and duration of the decarboxylation process that is feasible for the manufacturing process in both cannabis biomass and crude extracts at scale.

## 2. Materials and Methods

### 2.1 Chemicals and reagents

The cannabinoid standard solutions of CBDA and THCA were purchased from Cayman Chemical (USA). CBD and CBN were purchased from THC Pharm GmbH (Germany). Delta 9-THC standard solution was purchased from Lipomed (Switzerland). All HPLC reagents, acetonitrile, methanol, absolute ethanol, and isopropanol were obtained from RCI Labscan Limited (Thailand). Formic acid of 98/100% analytical grade was obtained from Fisher Scientific (UK), ammonium formate 97% from Sigma-Aldrich, and deionized water was obtained from Milli-Q® Reference Water Purification Merck System.

### 2.2 Plant materials

The CBD dominant biomass was a female inflorescence of *C. sativa* RPF3 cultivar aged 120 days. It obtained from the Highland Research and Development Institute (HRDI). The THC dominant biomass was dried female inflorescences of *C. sativa* “Foitong” cultivar aged 120 days. It obtained and authenticated from the Faculty of Science and Technology, Rajamangala University of Technology Phra Nakhon (RMUTP). The cannabis materials were kept at the PNU Herbarium at the Faculty of Science, Naresuan University.

### 2.3 Sample preparation

#### 2.3.1 Cannabis biomass

The cannabis biomass (from section 2.2) was dried in a hot air oven at 50°C for 2 hours then ground to a fine powder with an herbal blender and sieved through a stainless-steel sieve No. 60 (250 µm). The sieved

cannabis biomass was homogenized by mixing and shaking in a container for 10 minutes. The sample was then kept in a firmly closed glass container at  $-20^{\circ}\text{C}$ , in the dark, until further use. This process was repeated individually for each strain.

### **2.3.2 Cannabis crude extract**

A 100 g sample of the dried biomass powder was weighed and macerated with 500 ml of 95% Ethanol and agitated in an orbital shaker for 24 hr. The sample was then filtered, and the filtrate was evaporated under reduced pressure and then any excess water remaining in the filtrate was removed by freeze-drying. The sample was kept in a firmly closed glass container at  $-20^{\circ}\text{C}$  and stored in the dark until further use. This process was repeated individually for each strain.

### **2.4 Decarboxylation experiment**

Three 100 mg samples of powder (Section 2.3.1) and three 100 mg samples of extract (Section 2.3.2) were placed in equal proportions into six separate 3 ml amber glasses. These were then placed into a hot air oven for 60 min at  $105^{\circ}\text{C}$ . Every 10 minutes a bottle of powder and a bottle of extract were removed from the oven for analysis of acidic and neutral cannabinoid contents by HPLC. This procedure was then repeated at  $115^{\circ}\text{C}$ ,  $130^{\circ}\text{C}$ , and  $145^{\circ}\text{C}$ . This process was repeated individually for each strain.

### **2.5 Sample preparation for HPLC analysis**

After the decarboxylation experiment, the biomass (Section 2.3.1) and crude extracts (Section 2.3.2) were prepared by the following steps:

#### **2.5.1 Cannabis biomass**

A 20 mg sample of dried biomass was weighed and transferred into a transport tube and extracted with 5 ml of 80% methanol using an ultrasonicator bath for 15 min at  $25^{\circ}\text{C}$ . The supernatant was filtered through a

0.45  $\mu\text{m}$ -nylon syringe filter and transferred to an LC vial. This process was repeated individually for each treatment group.

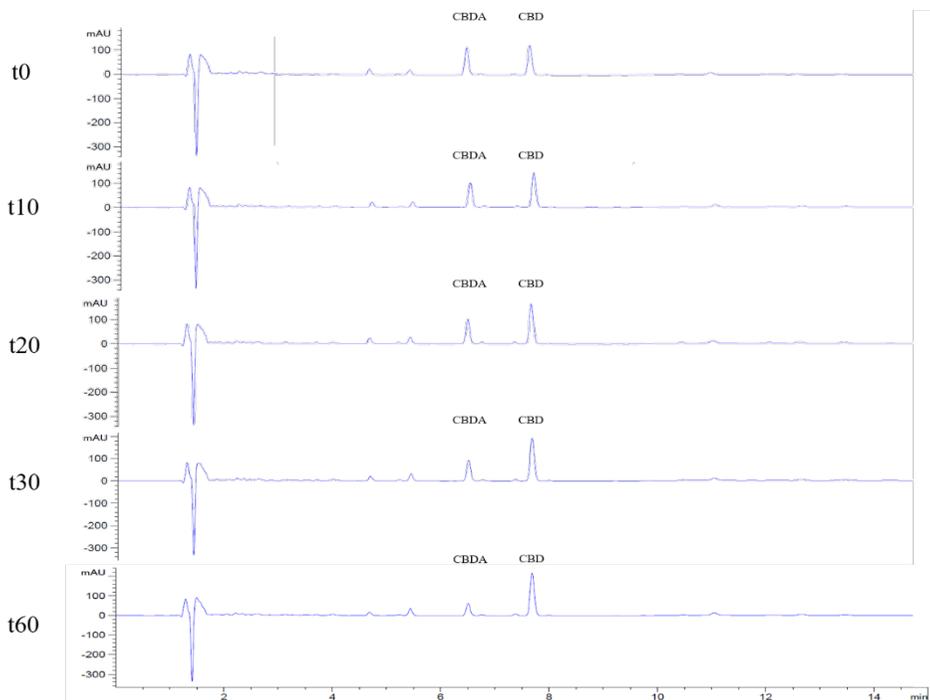
#### **2.5.2 Cannabis crude extract**

A 10 mg sample of homogenized extract was added into a 1.5 ml centrifuge tube and 1 ml of HPLC-grade methanol was added and the sample was mixed with a vortex mixer and prepared to a final concentration of 0.1 mg/ml. The solution was filtered through a 0.45  $\mu\text{m}$ -nylon syringe filter and transferred to an LC vial. This process was performed individually for each treatment group.

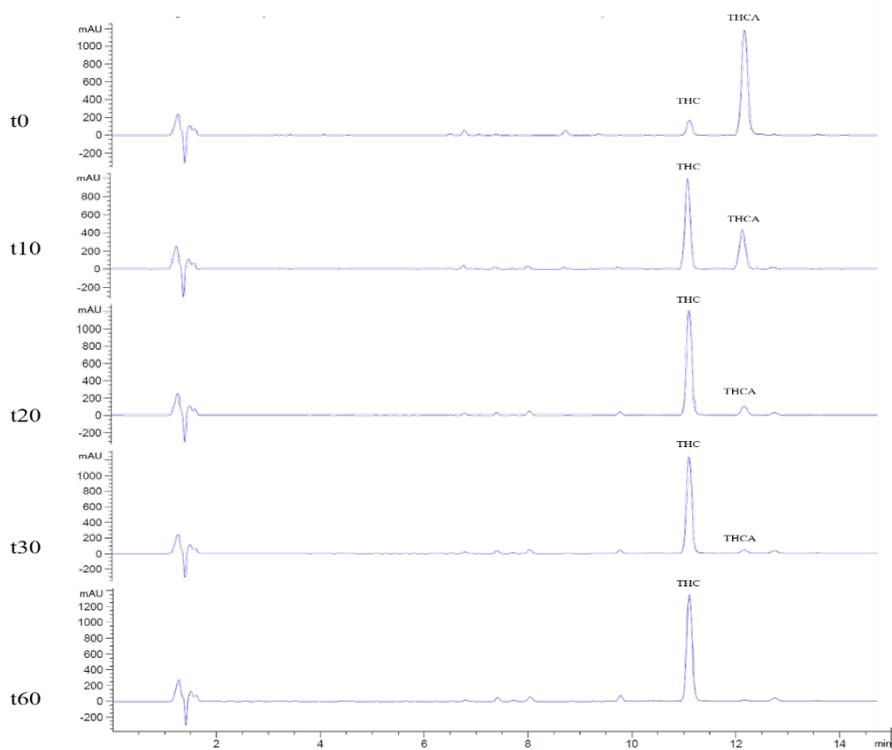
Both cannabis samples were kept in a firmly closed glass container at  $-20^{\circ}\text{C}$  and stored in the dark further use.

### **2.6 Determination of cannabinoids by HPLC**

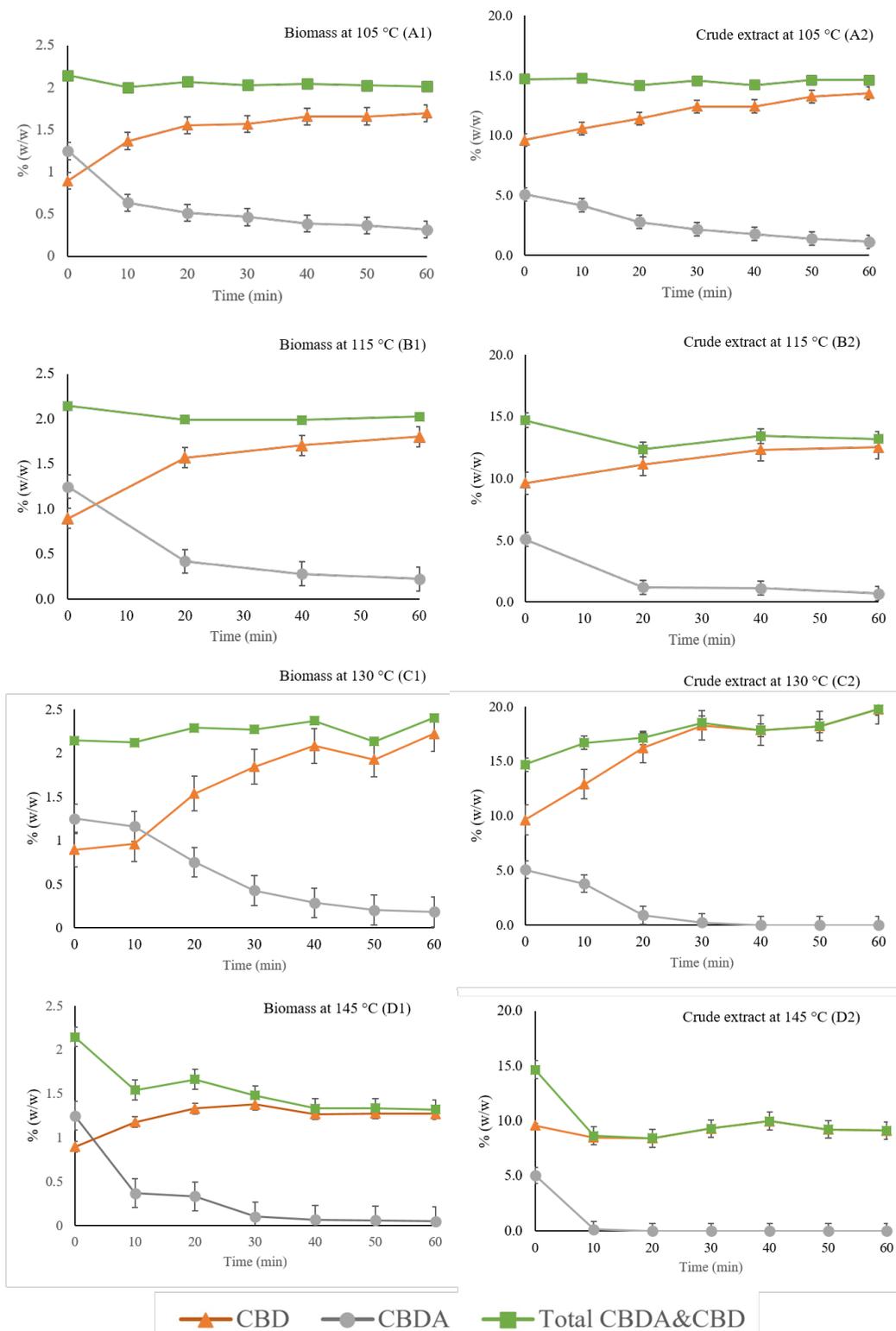
We applied an HPLC method, modified from the American Herbal Pharmacopeia, for the determination of cannabinoids. The modified method was first validated by the Bio-screening Unit, Faculty of Pharmaceutical Science, Naresuan University before we applied it. The HPLC analysis was performed using an Agilent 1260 HPLC/DAD system. The HPLC system comprised a G7129A 1260 vial sampler, a G711A 1260 Quat Pump VL, and a G7115A 1260 DAD WR. Separation of the cannabinoids was achieved using an Agilent Infinity Lab Poroshell 120 EC-C18 column (4.6 $\times$ 5 mm, 2.7 $\mu\text{m}$ ) with a Phenomenex security guard cartridge C18 (4 $\times$ 3.0 mm ID) pre-column. The mobile phase comprised 20 mM of ammonium formate (pH 3.6) as mobile phase A and 0.1% formic acid in acetonitrile with gradient elution mode as mobile phase B. The flow rate was 1.0 ml/min and the injection volume were 5  $\mu\text{l}$ . All samples were carried out at a column temperature of  $40^{\circ}\text{C}$ . The UV detection wavelength was set at 220 nm. The peak was integrated through the Agilent LC open LAB (offline) program.



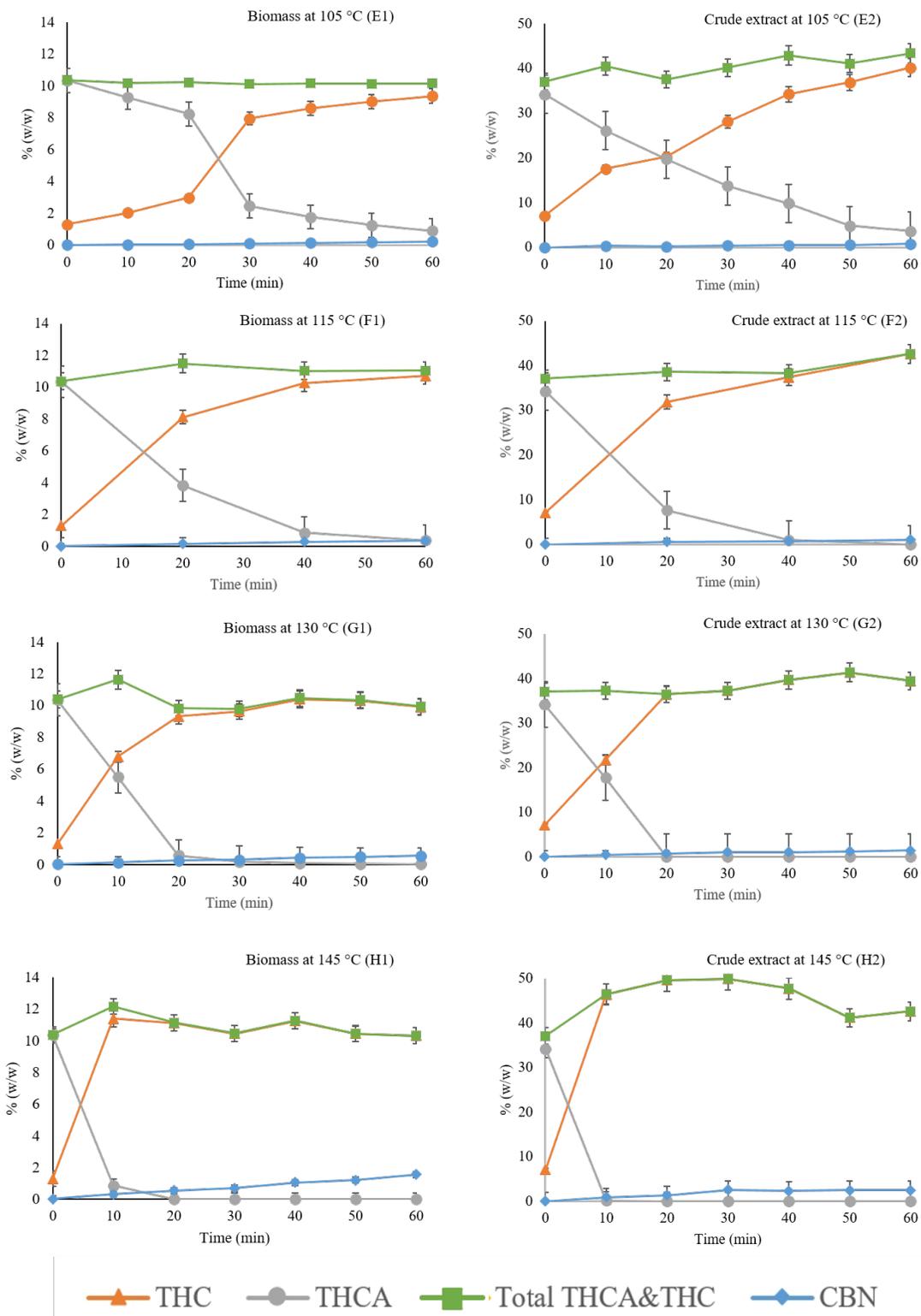
**Fig. 1.** The chromatograms of CBDA and CBD in the cannabis RPF3 cultivar biomass after decarboxylation at 115°C, over 0-60 min.



**Fig. 2.** The chromatogram of THCA and THC in cannabis “Foitong” cultivar biomass after decarboxylation at 115°C, over 0-60 min.



**Fig. 3.** The decarboxylation of CBDA in biomass (left) and crude extract (right) at 105°C (A1, A2), 115°C (B1, B2), 130°C (C1, C2), and 145°C (D1, D2).



**Fig. 4.** The decarboxylation of THCA in biomass (left) and crude extract (right) at 105°C (E1, E2), 115°C (F1, F2), 130°C (G1, G2), and 145°C (H1, H2).

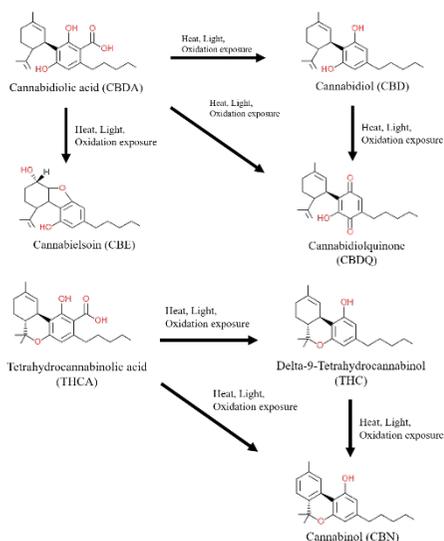
## 2.7 Statistical analysis

Descriptive and inferential statistics were used in this study to provide a summary of data in the form of mean with standard deviation (SD), The coefficients of regression ( $R^2$ ) of the linear graph and the t-test were generated by Microsoft® Excel.

## 3. Results and Discussion

### 3.1 Decarboxylation of CBDA

The representative chromatograms of CBDA and CBD in the cannabis RPF3 cultivar biomass after decarboxylation are shown in Fig. 1. The results for the decarboxylation of the dried biomass and extract are shown in Fig. 3. The content of CBDA diminished over time and as the temperature increased. CBDA was expected to change to CBD by decarboxylation, as can be seen clearly at 105°C, 115°C, and 130°C (Fig. 3(A1-C2)). However, at 145°C, CBD did not significantly increase (Fig. 3(D1-D2)) implying that CBDA and/or CBD might degrade to other compounds at that higher temperature. The possible degradation products previously described include cannabielsoin (CBE) [10, 11] and cannabidiol quinone (CBDQ) [12] as shown in Fig. 5.



**Fig. 5.** The possible degradation products of cannabinoids after the decarboxylation process.

The erasing of the carboxyl group in CBDA and THCA was catalyzed by heat, light, and oxidation exposure [13-18].

The decarboxylation time in the crude extract of both CBD and THC was shorter than in the biomass from each. This was possibly due to the heat easily affecting the acidic cannabinoids in the extract, whereas in the biomass samples, some acidic cannabinoids are still in the glandular trichrome.

### 3.2 Decarboxylation of THCA

The representative chromatograms of THCA and THC in the cannabis “Foitong” cultivar biomass are shown in Fig. 2. The results for the THCA decarboxylation, with heat, in both the biomass and the extract, are shown in Fig. 4. Similar to CBDA, THCA content was converted over time and as the temperature increased (Fig. 4 E1-H2). In all treatments, CBN, one of the degradation products of THC, increased over time and had the highest concentration when treated at 145°C. These results are consistent with the EIHA report [7] and the peaks of THC were only present in the sample for a short time. For instance, the highest THC content was reached at 145°C at 20 min, but the total THC amount was significantly reduced after 40 min. This result is also consistent with the report by Ramirez, C.L. et al. [14] which found that using high temperatures often leads to the degradation of heat-sensitive compounds. THC could transform into CBN [9]. From Fig. 4, the content of CBN increased while THCA content inversely decreased over time. As shown in Fig. 5, THCA can be decarboxylated to THC and can also directly change to CBN with the influence of oxygen, temperature, and UV exposure [15].

It is noted that the cannabis biomass and extract should be kept in an opaque airtight container after the decarboxylation process. According to previous reports [15-17], exposure to light and storage at high

temperatures leads to the loss of cannabinoids, especially in solutions.

### 3.3 The prediction for an appropriate time for CBDA and THCA decarboxylation

The data obtained from decarboxylation of THCA and CBDA in biomass and cannabis extracts at 4 different temperatures (105, 115, 130, and 145 °C) at 4-7 points of time fit to a first order kinetic reaction. The linear equations were calculated by  $\ln$  concentrations of CBDA or THCA versus time (min). The slopes of the linear equations ( $k$ ) at each temperature (Kelvin) are shown in Table 1.

**Table 1.** The slope ( $k$ ) of acidic cannabinoids in biomass at temperatures 105°C, 115°C, 130°C, and 145°C.

1/Temperature (K <sup>-1</sup> )	Slope ( $k$ )	
	CBDA	THCA
2.645*10 <sup>-3</sup>	-0.0196	-0.0461
2.577*10 <sup>-3</sup>	-0.0288	-0.0779
2.481*10 <sup>-3</sup>	-0.0364	-0.1001
2.392*10 <sup>-3</sup>	-0.0537	-0.1202

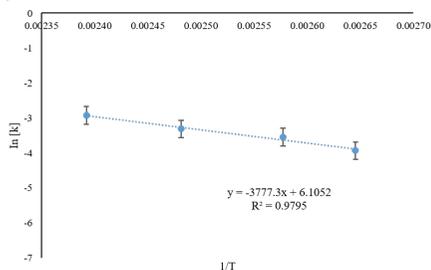
#### 3.3.1 The determination of the predicted equation for CBDA decarboxylation

From

$$y = mx + b, \text{ and } \ln[A] = \ln[A_0] - kt \quad (3.1)$$

$$y = -3777.3x + 6.1052,$$

where the  $y$ -axis is  $\ln[k]$  and  $x$  represents the reciprocal of absolute temperature ( $1/T$ ) of decarboxylation in Kelvin.  $R^2 = 0.9795$  (Fig. 6).



**Fig. 6.** Linear graph between  $\ln[k]$  of CBDA in biomass (Y-axis) and  $1/T$  in Kelvin<sup>-1</sup> unit (X-axis).

For example: At 105°C,  $1/T$  is 0.002645 then insert this value into equation 3.1:

$$\ln[k] = -3.777.3 \times 0.002645 + 6.1052 = -3.886$$

$$k = 0.0205 \text{ min}^{-1}.$$

The prediction time for CBDA decarboxylation at a concentration lower than 10% of the initial concentration ( $t_{10}$ ) at 105°C could be calculated by the following equation:

$$\ln[A]_t = \ln[A]_0 - kt, \quad (3.2)$$

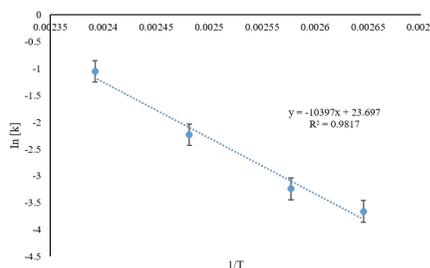
$$t = (\ln[A]_0 - \ln[A]_t) / k, \quad (3.3)$$

$$t_{10} = \ln(0.1) / 0.0205 = 112.32 \text{ min.}$$

For the crude extract, the linear equation is

$$y = -10397x + 23.697, \quad (3.4)$$

$R^2 = 0.9817$  (Fig. 7).



**Fig. 7.** Linear graph between  $\ln[k]$  of CBDA in crude extract (Y-axis) and  $1/T$  in Kelvin<sup>-1</sup> unit (X-axis).

At 105°C, do the same steps for the biomass using Eq. (3.4).

$$\ln[k] = -3.803 \text{ and } k = 0.0223 \text{ min}^{-1},$$

and determine  $t_{10}$  by Eq. (3.3)

$$t_{10} = \ln(0.1) / 0.0223 = 103.25 \text{ min.}$$

The time for the decarboxylation process in the biomass was closely related to the crude extract and the decarboxylation time in the crude extract but was shorter than that of the biomass.

### 3.3.2 The determination of the predicted equation for THCA decarboxylation

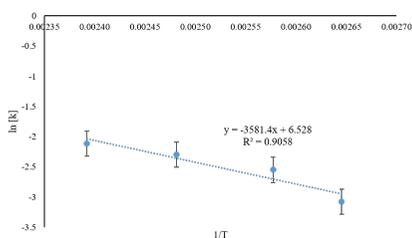
$$y = -3581.4x + 6.528, \quad (3.5)$$

where the  $y$ -axis is  $\ln[k]$  and  $x$  represents the reciprocal of the absolute temperature ( $1/T$ ) of decarboxylation in Kelvin.  $R^2 = 0.9058$  (Fig. 8).

For example: At  $105^\circ\text{C}$ ,  $1/T = 0.002645$  then insert this value into Eq. (3.5):

$$\ln[k] = -3581.4 \times 0.002645 + 6.528 = -2.9448$$

$$k = 0.0526 \text{ min}^{-1}.$$



**Fig. 8.** Linear graph between  $\ln[k]$  of THCA in biomass (Y-axis) and  $1/T$  in Kelvin<sup>-1</sup> unit (X-axis).

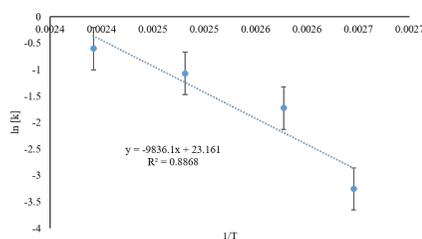
The prediction time for THCA decarboxylation when the concentration is lower than 10% of the initial concentration ( $t_{10}$ ) at  $105^\circ\text{C}$  could be calculated from Eqs. (3.2)-(3.3):

$$t_{10} = \ln(0.1)/0.0526 = 43.78 \text{ min}.$$

For the crude extract, the linear equation is

$$y = -9836.1x + 23.161, \quad (3.6)$$

$R^2 = 0.8868$  (Fig. 9)



**Fig. 9.** Linear graph between  $\ln[k]$  of THCA in crude extract (Y-axis) and  $1/T$  in Kelvin<sup>-1</sup> unit (X-axis).

At  $105^\circ\text{C}$ , the same steps were followed as for the biomass using Eq. (3.6).

$$\ln[k] = -2.855,$$

$$k = 0.058 \text{ min}^{-1},$$

and determine for  $t_{10}$  by Eq. (3.3):

$$t_{10} = \ln(0.1)/0.058 = 39.69 \text{ min}.$$

The prediction equation for THCA decarboxylation was consistent with the CBDA decarboxylation. The decarboxylation time in the crude extract was shorter than that of the biomass.

From Arrhenius equation

$$k = Ae^{-Ea/RT}, \quad (3.7)$$

$$k = \ln[A] - Ea / RT, \quad (3.8)$$

where  $k$  is a specific reaction rate,  $A$  is the pre-exponential factor,  $Ea$  is the activation energy (J/mol),  $T$  is the absolute temperature (Kelvin), and  $R$  is the ideal gas constant (8.31 J/mol K). The plot of the logarithm of the rate constant as a function of  $1/T$  results in a straight line with a negative slope equal to  $Ea/R$ .

From Eqs. (3.1), (3.5), and (3.8),  $Ea$  for the CBDA in the biomass was 31.39 KJ/min·mol and 29.76 KJ/min·mol for the THCA.  $Ea$  for CBDA in the crude extract was 86.39 KJ/min·mol and 81.73 KJ/min·mol for the THCA. This result was also consistent with the report of Perrotin-Brunel et al. [18],  $Ea$  for THCA was 85 KJ/min·mol.

The prediction time of acidic cannabinoid decarboxylation could be adjusted in a range of prediction intervals at 95-105% of the prediction time.

### 3.4 The feasibility of cost management on a pilot scale

The structure of electricity cost was calculated from the equation;

$$\text{Electricity base cost} + FT + VAT \ 7\%. \quad (3.9)$$

The electricity base cost was calculated as a progressive rate (maximum rate > 150 Units/month) at 4.4217 Baht/Unit. The float time (FT), which is a variable factor of the electric bill, changed every 4 months as assigned by Provincial Electricity Authority (PEA) at 0.4801 Baht/unit. The electrical unit was calculated from Kilowatts multiplied by an hour of instrument use.

In Table 2, the electrical power of a hot air oven is shown as 2,800 Watts. The capacity is 1,500 grams per cycle for the biomass and 1,800 grams per cycle for the crude extract. For the CBDA decarboxylation process, the comparison was made at the four temperatures 105°C, 115°C, 130°C,

and 145°C. At 130°C, the duration of the process was 60.61 min which was less than at 105°C. The shortest time for decarboxylation was at 145°C, but this temperature provided the lowest content of total CBD although the net electricity cost was the cheapest at 10.58 Baht.

In the case of THCA decarboxylation, a comparison between all temperatures can be made. At 145°C, the duration of the process was shortest at 17.68 min and consumed 0.825 kW·hr. The net electricity cost was 4.43 Baht and the cost per 1,000 g biomass sample was 2.88 Baht which was almost 60% cheaper than at 105°C.

**Table 2.** The feasible cost for CBDA and THCA decarboxylation in biomass by using a hot air oven.

Working Temperature (± 0.5°C)	CBDA decarboxylation				THCA decarboxylation			
	105°C	115°C	130°C	145°C	105°C	115°C	130°C	145°C
Time of use (min)	112.32	86.9	60.61	43.21	43.78	34.37	24.37	17.68
Unit (kW·hour)	5.24	4.06	2.828	2.02	2.043	1.604	1.137	0.826
Electricity base Cost (Baht)	23.18	17.93	12.50	8.92	9.03	7.09	5.03	3.65
Net Electricity cost (Baht)	27.49	21.27	14.84	10.58	10.72	8.41	5.96	4.43
Cost (Baht per 1,000 g sample)	18.33	14.18	9.89	7.05	7.14	5.61	3.98	2.88

### 3.5 Applications

It is noted that optimal conditions were calculated from the kinetic degradation reaction of acidic cannabinoids and the feasibility relied on power consumption of our equipment. Each manufacturer might have to modify these conditions depending on their equipment. In addition, the quality of biomass and extracts as starting materials have to be considered. Biomass with low cannabinoid levels might not be worth the investment.

### 4. Conclusion

Our study determined suitable conditions for decarboxylation of the two major cannabinoids, CBD and THC, which had not previously been identified. Not only the time and temperature that provided high neutral cannabinoids, CBD and THC, but also the cost of operation was studied for the first time. Our results show that for CBDA cannabis biomass, the appropriate duration

for decarboxylation is 60 min at 130°C and for THCA the duration is 17 min at 145°C. For both CBDA and THCA, the time is shorter for the respective extracts.

The results also demonstrate that longer decarboxylation times at a lower temperature are preferred for CBDA whereas a shorter time at a higher temperature is preferable for THCA. The shorter decarboxylation time means lower electricity cost. However, the high temperature can degrade the sensitive active compounds that must be of concern in the appropriate process for industrial scale. These decarboxylation factors have been identified for each of the cannabinoids and represent useful information for the cannabis industry.

### Abbreviations

CBD	Cannabidiol
CBDA	Cannabidiolic acid
CBN	Cannabinol
THC	Tetrahydrocannabinol

THCA	Tetrahydrocannabinolic acid
CBE	Cannabellsoin
CBDQ	Cannabidiolquinone
EA	activation energy

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