Brazilian Journal of Analytical Chemistry
***Pre-publication – Accepted after peer review***
doi: 10.30744/brjac.2179-3425.AR-72-2025

BrJAC

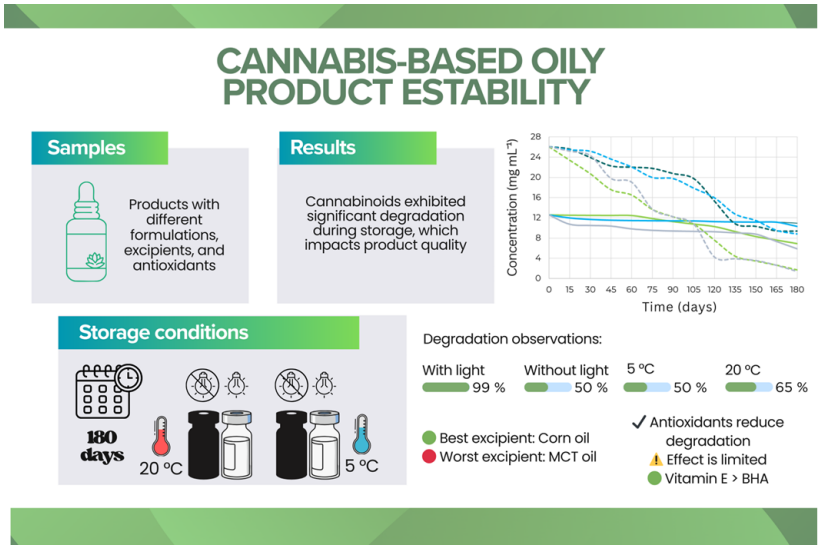
***ARTICLE***

# Evaluation of the Stability of Cannabidiol and delta-9-tetrahydrocannabinol in Cannabis-based Oily Product: Effects of Light, Temperature, Excipients and Antioxidant Additives

**Aldo Sindulfo Barboza Valdez[1], Jeisson Brandway Blanco Castañeda[1], Nédice Borges Cardoso Rastely[1], Wagner Ferreira[1], Francisney Pinto Nascimento[2], Aline Theodoro Toci[1]***

*[1]Laboratório de Estudos Interdisciplinares do Meio-Ambiente e Alimentos (LEIMAA), Universidade Federal da Integração Latino-Americana (UNILA) . Avenida Tancredo Neves, 6731, Foz do Iguaçu, PR, Zip Code 85867-970, Brazil*

*[2]Laboratório de Cannabis Medicinal e Ciência Psicodélica (LCP), Universidade Federal da Integração LatinoAmericana (UNILA) . Avenida Tarquinio Santos Ave, 1000, Foz do Iguaçu, PR, Zip Code 85870-650, Brazil*




Due to the potential therapeutic effects of cannabis-based oily products and the increasing number of studies in this field, several producer associations have emerged in recent decades. Oral administration of formulations in oily excipients has been the most commonly used therapeutic route. However, the susceptibility of cannabinoids, such as delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD), to environmental factors is well known, and studies on the stability of cannabis-based oily products remain scarce. Therefore, research that supports associations in improving product quality and ensuring reliability is crucial. With these considerations, the objective of this study was to conduct a stability study of cannabis-based oil products containing CBD and THC under different storage conditions for 180 days. For the first time, the effects of temperature, light, excipients, and additives were evaluated together. Cannabinoid

**Cite:** Valdez, A. S. B.; Castañeda, J. B. B.; Rastely, N. B. C.; Ferreira, W.; Nascimento, F. P.; Toci, A. T. Evaluation of the Stability of Cannabidiol and delta-9-tetrahydrocannabinol in Cannabis-based Oily Product: Effects of Light, Temperature, Excipients and Antioxidant Additives. *Braz. J. Anal. Chem.* (Forthcoming). http://dx.doi.org/10.30744/brjac.2179-3425.AR-72-2025

**Submitted:** August 1, 2025; **Revised:** January 19, 2026; **Accepted:** January 30, 2026; **Published online:** February 2026.

This article was submitted to the BrJAC special issue on the 21st ENQA and 9th CIAQA.

determination was performed using a validated HPLC-DAD methodology. Both CBD and THC were best preserved in corn and sesame oil, while medium-chain triglycerides were the worst excipient, reaching losses of 99%. Light was the most significant storage variable. In all samples, regardless of any other variable, the highest degradation rates were observed in the presence of light, for both CBD and THC. However, temperature exhibited less uniform behavior compared to light. Overall, the highest THC degradation occurred at 20 °C. The presence of antioxidants was not effective as expected. In sesame oil, lower degradation percentages of up to 10% were observed in samples containing butylhydroxyanisole. Regarding vitamin E, in general, the degradation rate was 2 to 11% and 3 to 22% lower than in samples without the vitamin, for CBD and THC, respectively. The addition of antioxidants shows promise but requires further study.

**Keywords:** cannabis-based oily products, cannabidiol, delta-9-tetrahydrocannabinol, photodegradation, cannabinoid stability

## INTRODUCTION

In medicinal cannabis treatments, the predominant route of administration is oral, through oils, solutions, and formulated capsules.[1] This preference is due to its slow absorption, prolonged effect, precise dosing, and greater safety and convenience for the patient.[2] Given that cannabinoids are lipophilic compounds, their incorporation into oily vehicles is ideal, with vegetable oils being the most commonly used carriers. Among these, corn, sunflower, sesame, and olive oils are frequently employed, as well as medium-chain triglycerides (MCT), the latter derived from coconut oil.[3]

Beyond their pharmaceutical form, it is important to consider how these compounds act. Cannabinoids are bioactive compounds that interact with the endocannabinoid system, an endogenous signaling network present in various tissues, especially in the central nervous system, which regulates functions such as pain, inflammation, sleep, appetite, and mood.[4,5] Among the main cannabinoids, cannabidiol (CBD) and delta-9-tetrahydrocannabinol (THC) stand out, both found in high concentrations in the flowers of *Cannabis sativa* L.[6]

The growing interest in their clinical applications has also driven the advancement of scientific research. In Brazil, Dr. Elisaldo Carlini was a pioneer in clinical studies on medicinal cannabis, standing out with more than 30 publications in the field. In 1980, he led one of the first studies that demonstrated the potential of CBD in controlling seizures in epileptic patients.[7]

As science has progressed, regulatory frameworks have also been developed to allow access to these treatments. In Brazil, since 2015, the National Health Surveillance Agency (ANVISA) has authorized the import and domestic production of cannabis-based medications under medical prescription. In 2019, Resolution RDC No. 327 established a stricter regulatory framework, limiting THC content to 0.2% and setting high standards of quality and safety.[8] Even so, access remains limited, which has led to the emergence of patient associations that produce medicinal products through artisanal or semi-automated methods, with judicial authorization for cultivation, extraction, and distribution.

Once in the hands of the patient, another key aspect is the product's stability, as it determines its efficacy over time. Cannabinoid molecules are susceptible to isomerization and oxidation under various factors.[9] Variables such as light, temperature, humidity, and oxygen exposure can accelerate degradation, reducing potency and generating less active secondary products, such as cannabinol (CBN), a derivative of oxidized THC.[10]

This can be explained by the chemical structure of THC and CBD themselves (Figure 1), which feature regions highly sensitive to ultraviolet light and oxidation, such as conjugated double bonds and hydroxyl groups. Light exposure can cause bond breakage and the formation of free radicals, initiating chain reactions that degrade the original molecule. For this reason, protecting formulations from these factors is essential to preserve their integrity.[11]

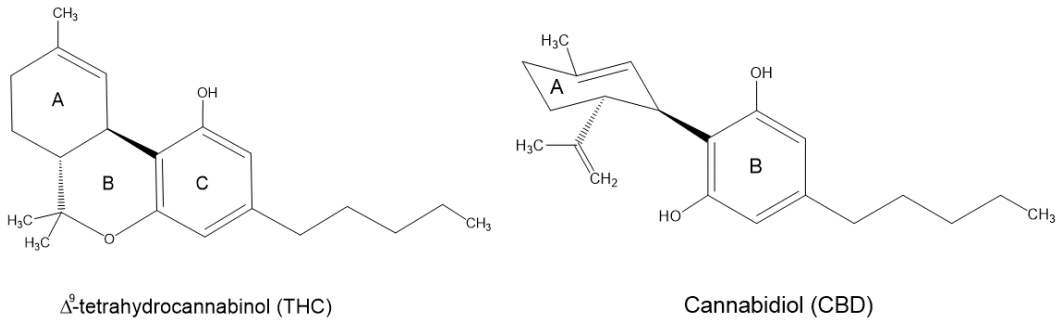



**Figure 1.** Chemical structures of THC and CBD.

Despite its relevance, the stability of cannabinoids in oily products based on medicinal cannabis has been scarcely studied. Nevertheless, some works have provided valuable information. Pacifici and collaborators[12] evaluated the stability of THC and CBD in olive oil over a 14-day period at 25 °C and 4 °C. They reported a degradation of 28% for THC and 20% for CBD at 25 °C, while at 4 °C the loss was 20% for both compounds.

Raslan-Jaramillo *et al*.,[13] in turn, studied oily extracts in coconut and sunflower oils. After 28 days of storage, both THC and CBD showed losses of less than 2% under refrigeration (4 ± 2 °C) or freezing (-20 ± 2 °C). Under room temperature (22 ± 2 °C) and light-protected conditions, CBD degraded by 5%, whereas THC degradation was 1.5%. In contrast, under light exposure at room temperature, THC lost 9% in three days, and CBD more than 19% in just one day, highlighting their instability under such conditions.

In oily extracts, Trofin *et al*.,[14] reported a 21.6% THC loss over one year under refrigeration and darkness, and 83.8% after four years. Under light and room temperature conditions, THC degraded by 23.2% in one year and by 89.9% over four years. CBD also degraded, with losses between 11.03% and 13.45% in the first year, depending on the storage conditions.[13]

In this context, the present study aimed to investigate the degradation of THC and CBD in cannabis-based oily products from Brazilian associations. The extracts were subjected to different storage conditions simulating real-life scenarios of temperature, light exposure, and storage time by patients. Additionally, the influence of the type of excipient and the presence of antioxidant additives on the stability of the compounds was evaluated.

## MATERIALS AND METHODS

### *Samples*

Twelve samples provided by Brazilian medicinal cannabis associations were analyzed. Their characteristics are described in Table I.

**Table I.** Chemical profile and characteristics of the Cannabis-based oily product analyzed

| Sample | Company | Excipient | Additive | CBD (mg mL$^{-1}$) | THC (mg mL$^{-1}$) |
|---|---|---|---|---|---|
| 1.a | A | MCT* | Vitamin E | 12.5 | 12.4 |
| 1.b | A | MCT* | none | 12.5 | 12.4 |
| 2.a | A | MCT* | Vitamin E | 25.9 | nd |
| 2.b | A | MCT* | none | 25.9 | nd |
| 3.a | A | MCT* | Vitamin E | nd | 28.2 |
| 3.b | A | MCT* | none | nd | 28.2 |
| 4.a | B | EVO** | Vitamin E | 4.8 | 9.5 |
| 4.b | B | EVO** | none | 4.8 | 9.5 |

(continued on next page)

**Table I-contd.** Chemical profile and characteristics of the Cannabis-based oily product analyzed

| Sample | Company | Excipient | Additive | CBD (mg mL$^{-1}$) | THC (mg mL$^{-1}$) |
|---|---|---|---|---|---|
| 5.a | B | EVO** | Vitamin E | 11.6 | nd |
| 5.b | B | EVO** | none | 11.6 | nd |
| 6.a | B | EVO** | Vitamin E | nd | 14.9 |
| 6.b | B | EVO** | none | nd | 14.9 |
| 7 | C | Corn oil | none | 21.1 | 19.2 |
| 8 | C | Corn oil | none | 21.4 | nd |
| 9 | D | Corn oil | BHA*** | 49.3 | 40.5 |
| 10 | D | Corn oil | none | 40.8 | 34.5 |
| 11 | D | Sesame oil | BHA*** | 41.9 | 34.2 |
| 12 | D | Sesame oil | none | 42.5 | 37.0 |

Notes: *Medium-chain triglycerides; **Extra virgin olive oil (0.5% acidity); ***Butylated hydroxyanisole. Vitamine E was added for experimental purposes, while the samples containig BHA were obtained with the compound already incorporated.

### *Storage conditions*

Sample storage was performed by placing 2 mL of each sample in 4 mL glass vials and storing them for 180 days, under controlled temperature conditions (5 and 20 °C) and in the presence or absence of light (Figure 2). In six samples (numbers 1a, 2a, 3a, 4a, 5a and 6a, as shown in Table I), 10 mg of vitamin E (equivalent to 1000 IU) was added.

Prepared sample vials were placed in custom-designed boxes under controlled temperature and light conditions. Boxes measuring 25 × 15 cm were made of pine plywood for 20 ± 1 °C storage (air-conditioned room) and cardboard for 5 ± 1 °C storage (refrigeration). Each box contained internal strips with 18 light-emitting diodes (LEDs) (3 mm) arranged within a 17 × 10 cm area, emitting white light in the 400–700 nm range. This illumination was selected for its common household use and low heat generation, minimizing interference with the system's internal temperature. Samples that were to be stored in the dark were covered with black tape to prevent light from reaching them. The samples were measured at the beginning of storage (time zero) and every 15 days, totaling 12 points.

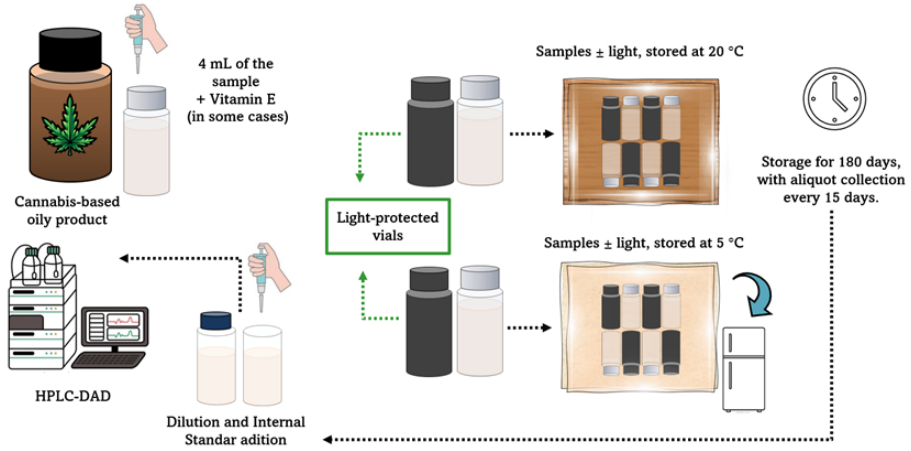



**Figure 2.** Experimental design to evaluate the stability of cannabinoids CBD and THC for 180 days.

### *CBD and THC quantification by HPLC-DAD*

The determination of CBD and THC was performed according to the methodology proposed by Zivovinovic,[15] with some modifications. High-performance liquid chromatography (HPLC) coupled to a diode array detector (Ultimate 3000, Thermo®, Germany) was used, equipped with a quaternary pump 5600, an Accela 5600 autosampler, and a diode array detector (PDA Accela, 20 Hz, Thermo®, Germany). Data were processed using the Chromeleon 7.3.2 software (Thermo® Fisher Scientific). A C18 chromatographic column (250 × 4.6 mm, 5 µm particle size; ACE HPLC Columns, USA) was used at a constant temperature of 30 °C. Analytes were eluted in gradient mode with solvents (A) water with 0.1% formic acid and (B) acetonitrile with 0.1% formic acid, following the program: 30% A (2 min); 28.7% A from 2 to 4.5 min; 5% A from 4.5 to 6 min (held until 10 min); and back to 30% A from 10 to 20 min. The flow rate was 0.8 mL/min, and the injection volume was 5 µL. Detection was performed at a wavelength of 220 nm. THC and CBD were identified by comparing their spectra with those of reference standards and by their retention times.

### *Method validation*

The quantification method for CBD and THC was validated prior to commencement of storage. The validation was conducted in accordance with the guidelines of the ICH (Harmonized Tripartite Guideline, 2005),[16] DOQ-CGCRE-008 from INMETRO[17] and ANVISA (RDC 166/2017 and RDC 899/2003)[18] through the determination of the selected parameters: selectivity, linearity, homoscedasticity, matrix effect, limits of detection (LOD), limits of quantification (LOQ) and precision.

### *Calibration curve*

The following analytical standards were used: (−)-(6aR,10aR)-6,6,9-trimethyl-3-pentyl-6a,7,8,10a-tetrahydro-6H-benzo[c]chromen-1-ol with 2-[(1R,6R)-3-methyl-6-prop-1-en-2-ylcyclohex-2-en-1-yl]-5-pentylbenzene-1,3-diol (Dr. Ehrenstorfer, Germany). The calibration curve was prepared from an initial stock solution at a concentration of 200 µg $mL^{-1}$. The analytical curve was constructed by diluting the stock solution to obtain seven concentration points (0.5; 1; 2; 5; 10; 15 and 20 µg $mL^{-1}$). As the matrix effect was significant, the dilution solution contained 0.5% of a mix of oils in ethyl acetate and acetonitrile 1:1. The internal standard used was caffeine at a concentration of 100 µg $mL^{-1}$ at each point of the calibration curve.

### *Sample preparation*

At each storage period, 50 µL of sample was aliquoted and diluted in 1.5 mL vials, according to the initial sample concentration, generally 600 to 4000 times, with a 1:1 solution of ethyl acetate and acetonitrile, both HPLC grade. To each vial, 100 µL of the internal standard solution was added.

### *Statistical analysis*

The normality of the data was verified by the Shapiro-Wilk test. The data were subjected to analysis of variance by ANOVA ($p \leq 0.05$), and in cases of significance, Tukey's test ($p \leq 0.05$) was used to compare the means. Both were performed with the Statistica software (StatSoft, version 14.1.0.8). To compare the slopes of the calibration curves, Student's *t*-test and F-test were used.

## RESULTS AND DISCUSSION

The samples selected for the study are real samples available on the market for cannabis therapy in Brazil. In a pilot study conducted by our research group (unpublished data), it was found that the presence of more than one cannabinoid and the oily excipient used in the medicinal extract could influence the degradation rate. These hypotheses have also been raised in a few other studies.[14,19-21] Therefore, we selected real samples available on the market for cannabis therapy in Brazil, with different excipients, one or two cannabinoids, and the addition of an antioxidant. However, this last parameter was found in only a single collaborating company, or some samples may not have this information on their packaging. It should be noted that these extracts are controlled by regulatory agencies and are subject to controlled revenue,

so that, in order to carry out the research, it was necessary to prove the companies' collaboration and permission from ANVISA (No. 16/2023 and 18/2022).

Due to the numerous variables involved, controlled and inherent to the samples, the analysis of the results was divided into two sections. The first seeks to evaluate variables intrinsic to the samples, such as the excipient, number of cannabinoids, and antioxidants, and the second, controlled variables, such as temperature and light.

### *Method validation*

Chromatography was employed in such a way that CBD and THC did not co-elute, thus ensuring the selectivity of each compound (Figure 3), in accordance with the guidelines followed.[16]

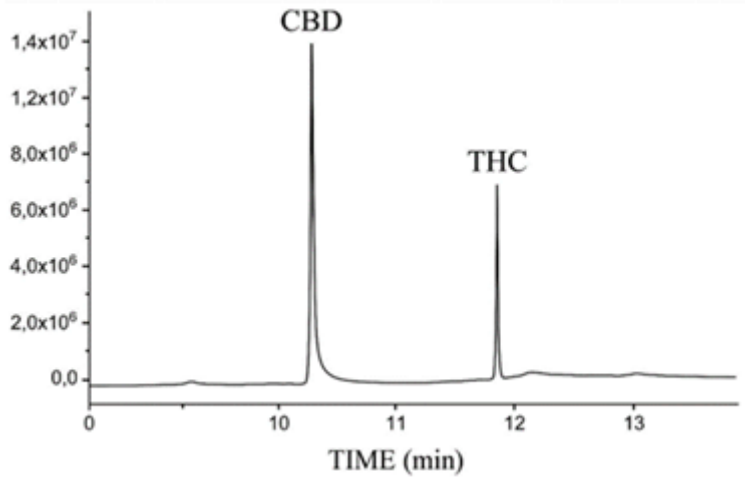



**Figure 3.** Chromatogram showing CBD and THC at 220 nm.

Suppression of the calibration curve slope was observed when the analysis was performed in the matrix (0.5% oil mixture), compared to the solvent, showing a slope ratio of 63.1% (see Figure S1 in the supplementary material). Consequently, statistical analyses using the F-Snedecor test and Student's *t*-test, applied to assess the equality of slopes based on the comparison of residual variances, indicated a statistically significant difference between the models ($p < 0.05$), evidencing the occurrence of a matrix effect (see Tables S2 and S3 in the supplementary material). Accordingly, all other analytical parameters were determined using matrix calibration. The calibration curves showed confirmed linearity for THC and CBD, based on the correlation coefficients obtained (R values) and the homoscedasticity of the system (residual dispersion) (see Table S4 in the supplementary material).

The limits of detection (LOD) and quantification (LOQ) ranged from 0.57 to 3.43 μg $mL^{-1}$, values well below the concentrations found in the analyzed extracts, indicating the adequacy of the method. Lower limits have previously been reported (LOD = 0.07 and LOQ = 0.22 μg $mL^{-1}$ for CBD).[22] However, in this study, the determination of these parameters was performed from the analytical curve, making the values dependent on the chosen working range. Higher values than those obtained here have also been described in the literature, such as in the study by Carvalho *et al*.,[23] who reported LODs ranging from 0.20 to 0.22 mg $mL^{-1}$ and LOQs of 0.59 to 0.66 mg $mL^{-1}$ for CBD and THC, respectively.

Precision, evaluated through intraday repeatability, showed relative standard deviation (RSD%) values between 0.61% and 4.34% across the seven levels of the calibration curve, which is considered acceptable according to the established limits (up to 5.3%)[17] (see Table S5 in the supplementary material).

### *Effect of variables intrinsic to the cannabis-based oily products during storage*

All samples showed degradation of the cannabinoids CBD and THC over 180 days (6 months) of storage, with percentages ranging from 13.1 to 94.6% and 9.1 to 99.7%, respectively (Table II). There was

no significant difference in the degradation profiles over the months among the excipients (Figure 4); only a more pronounced decrease in levels was observed at 45 days for sesame oil and at 15 days for corn oil (Figures 4c and 4d).

The highest degradation rates were found in the MCT excipient for both analytes (Table II). In these samples, both the pure CBD and the pure THC samples achieved degradation rates above 30% (samples 2 and 3, Table II). However, when the sample contains both analytes (sample 1), THC degradation is higher than CBD under specific conditions. For example, in sample 2b, under conditions without additive, with light and 20 °C, degradation reached 94.6% for CBD. However, in sample 1b, under the same conditions, degradation was 53.4% for CBD and 97.4% for THC (Table II). This behavior was also observed by Trofin *et al.*,[14] who carried out a study on the storage of two oily samples under two conditions: protected from light at 5 °C and with indirect natural light at 22 °C. They found that THC was more susceptible (approximately 9% and 11%, respectively) than CBD (approximately 5% and 6.5%, respectively) over 6 months of storage. Some other studies, with resinous products or in solvents, also report greater susceptibility to storage of THC compared to CBD.[19,20,21] The greater susceptibility of THC appears to be intrinsic to its chemical structure, as it has a cyclic ring (ring B, Figure 1) prone to oxidative processes.[24,25,26]

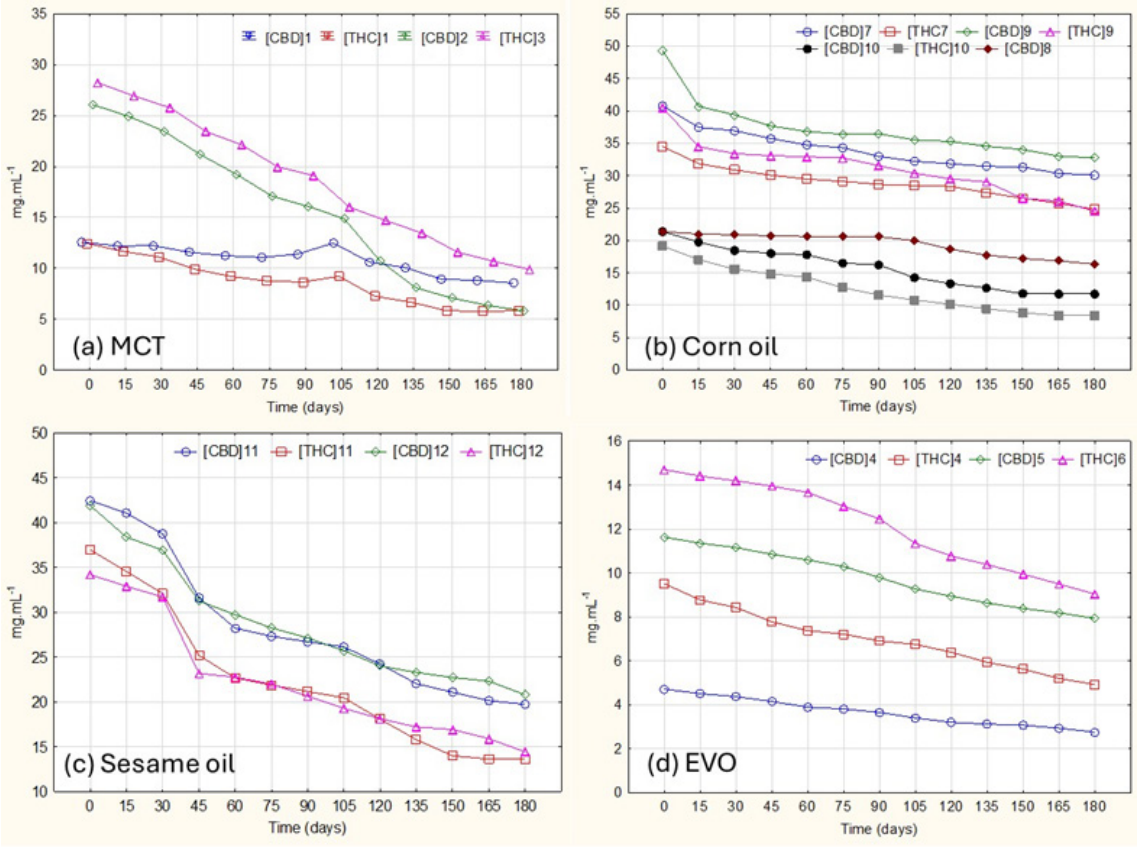



**Figure 4.** Least squares means for CBD and THC concentrations of cannabis-based oily products in different oils over 180 days.

Although the results reported by Troffin *et al.*[14] corroborate our findings, the degradation rates were much lower than ours. However, few sample characteristics were provided, except that the oil was very viscous. It is generally agreed that viscosity is a parameter that affects the rate of numerous reactions, and Grafström *et al.*,[20] evaluating the storage of resinous samples, also found lower rates, with 11.8% degradation for THC, and CBD remained stable over four years under ambient light and a temperature of 20-22 °C.

On the other hand, the lowest degradation rates were observed for corn oil, for both CBD and THC, with variations of 15% to 37.7% and 20% to 49.9% (samples 8, 9, and 10) (Table II), with the exception of sample 7, which was more outlier, reaching 54.8% and 74.5%. One possibility for this behavior could be the acidity of this sample, as acidity is known to increase the oxidative processes of cannabinoids[24]. However, due to the quantity of samples provided, we cannot verify this hypothesis.

Regarding the oil composition, MCT is a purified coconut oil that contains only saturated medium-chain triglycerides (100% capric and caprylic acid), while corn oil, among the four oils studied, has the highest percentage of polyunsaturated acids (linoleic acid), ranging from 53 to 60% (Table III). The high susceptibility of polyunsaturated fatty acids to oxidation is well reported in the literature and is primarily due to the greater number of double bonds in their structure, which facilitates free radical attack and the propagation of oxidative reactions, especially in the presence of light and heat.[27,28] Thus, comparing MCT with corn oil, we can assume that the polyunsaturated fatty acids in corn oil acted as sacrificial molecules, preventing the sharp degradation of CBD and THC. Or, in other words, we can say that the excipient itself acted as an antioxidant.

Sesame oil, in turn, showed the smallest variability in the degradation percentages between CBD and THC, ranging from 47.8 to 54.8% and 47.7 to 71.3%, respectively (samples 11 and 12) (Table II). In this oil, CBD also showed the most similar degradation percentages to THC, except for the most aggressive conditions for THC, with light and 20 °C. Our results diverge from a recent study by Orallo *et al*.,[29] who evaluated the stability of full-spectrum samples in sesame oil for 1 year at 25 °C and found no significant changes in the composition of CBD and THC. Sesame oil also has high levels of polyunsaturates (38-48% linoleic), but in lower quantities compared to corn oil (Table III), which explains why this oil showed a higher or equivalent degradation percentage compared to corn oil.

In olive oil, degradation rates ranged from 19 to 55% and 9 to 77% for CBD and THC, respectively (samples 4, 5, and 6; Table II). This oil showed the greatest variability across the various variables and samples. Unlike MCT oil, samples containing only CBD showed similar or even lower rates (19 to 48.8%, sample 5b) compared to samples containing both analytes (25.5 to 55.3%, samples 4a and 4b). However, THC, as in the other oils, showed the highest degradation rates, reaching 77.5%, although with considerable variability across storage conditions.

**Table II.** CBD and THC (mg $mL^{-1}$) at baseline and after 180 days of storage, with their respective % degradation, in cannabis-based oily products under different oil types and storage conditions

| Sample | Excipient/ additive | Storage condition | | Concentration (mg $mL^{-1}$) Begining (Time 0) | | Concentration (mg $mL^{-1}$) After 180 days | | Degradation (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Light | T (°C) | CBD | THC | CBD | THC | CBD | THC |
| 1.a | MCT/ Vitamin E | With | 5.0±1 | 12.6 ± 0.03 | 12.5 ± 0.05 | $5.70^{c}$ ± 0.11 | $0.80^{c}$ ± 0.04 | 55.0 | 93.3 |
| | | None | | | | $10.3^{a}$ ± 0.08 | $10.0^{b}$ ± 0.11 | 17.8 | 19.9 |
| | | With | 20±1 | | | $5.30^{d}$ ± 0.14 | $0.04^{d}$ ± 0.04 | 58.0 | 99.7 |
| | | none | | | | $10.5^{a}$ ± 0.10 | $10.5^{a}$ ± 0.12 | 16.5 | 15.7 |
| 1.b | MCT/ None | With | 5.0±1 | 12.6 ± 0.03 | 12.5 ± 0.05 | $6.90^{c}$ ± 0.12 | $1.80^{b}$ ± 0.02 | 45.3 | 85.7 |
| | | none | | | | $10.9^{a}$ ± 0.15 | $10.6^{a}$ ± 0.74 | 13.1 | 14.7 |
| | | With | 20±1 | | | $5.90^{d}$ ± 0.11 | $0.30^{c}$ ± 0.01 | 53.4 | 97.4 |
| | | none | | | | $10.3^{b}$ ± 0.05 | $10.1^{a}$ ± 0.11 | 18.4 | 19.3 |
| 2.a | MCT/ Vitamin E | With | 5.0±1 | 26.1 ± 0.28 | nd | $2.90^{c}$ ± 0.01 | nd | 88.9 | nd |
| | | none | | | | $10.0^{a}$ ± 0.01 | | 61.5 | |
| | | With | 20±1 | | | $2.90^{c}$ ± 0.06 | | 88.7 | |
| | | none | | | | $9.50^{b}$ ± 0.10 | | 63.6 | |

(continued on next page)

**Table II-contd.** CBD and THC (mg mL$^{-1}$) at baseline and after 180 days of storage, with their respective % degradation, in cannabis-based oily products under different oil types and storage conditions

| Sample | Excipient/ additive | Storage condition | | Concentration (mg mL$^{-1}$) Begining (Time 0) | | Concentration (mg mL$^{-1}$) After 180 days | | Degradation (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Light | T (°C) | CBD | THC | CBD | THC | CBD | THC |
| 2.b | MCT/ None | With | 5.0±1 | 26.1 ± 0.28 | nd | 1.70$^{c}$ ± 0.08 | nd | 93.5 | nd |
| | | none | | | | 9.40$^{a}$ ± 0.04 | | 64.1 | |
| | | With | 20±1 | | | 1.40$^{d}$ ± 0.03 | | 94.6 | |
| | | none | | | | 8.80$^{b}$ ± 0.01 | | 66.3 | |
| 3.a | MCT/ Vitamin E | With | 5.0±1 | nd | 28.2 ± 0.04 | nd | 2.60$^{c}$ ± 1.64 | nd | 90.7 |
| | | none | | | | | 16.5$^{b}$ ± 0.28 | | 41.6 |
| | | With | 20±1 | | | | 1.40$^{c}$ ± 0.06 | | 95.0 |
| | | none | | | | | 19.7$^{a}$ ± 0.05 | | 30.1 |
| 3.b | MCT/ None | With | 5.0±1 | nd | 28.2 ± 0.04 | nd | 0.40$^{d}$ ± 0.04 | nd | 98.5 |
| | | none | | | | | 18.8$^{a}$ ± 0.05 | | 33.5 |
| | | With | 20±1 | | | | 1.70$^{c}$ ± 0.13 | | 93.9 |
| | | none | | | | | 18.0$^{b}$ ± 0.14 | | 36.3 |
| 4.a | EVO/ Vitamin E | With | 5.0±1 | 4.70 ± 0.12 | 9.50 ± 0.00 | 3.20$^{b}$ ± 0.00 | 3.50$^{b}$ ± 0.00 | 32.3 | 63.7 |
| | | none | | | | 2.30$^{c}$ ± 0.40 | 7.10$^{a}$ ± 0.10 | 50.6 | 26.0 |
| | | With | 20±1 | | | 2.50$^{c}$ ± 0.00 | 2.40$^{c}$ ± 0.00 | 46.0 | 74.6 |
| | | none | | | | 3.50$^{a}$ ± 0.15 | 7.10$^{a}$ ± 0.00 | 25.5 | 25.3 |
| 4.b | EVO/ none | With | 5.0±1 | 4.70 ± 0.12 | 9.50 ± 0.00 | 3.50$^{a}$ ± 0.15 | 7.10$^{a}$ ± 0.00 | 41.6 | 64.0 |
| | | None | | | | 2.70$^{b}$ ± 0.33 | 3.40$^{c}$ ± 0.00 | 55.3 | 33.0 |
| | | With | 20±1 | | | 2.10$^{c}$ ± 0.09 | 6.40$^{b}$ ± 0.14 | 44.9 | 77.5 |
| | | none | | | | 2.60$^{b}$ ± 0.00 | 2.10$^{d}$ ± 0.00 | 34.3 | 21.8 |
| 5.a | EVO/ Vitamin E | With | 5.0±1 | 11.6 ± 0.01 | nd | 3.10$^{a}$ ± 0.13 | nd | 37.5 | Nd |
| | | none | | | | 7.30$^{b}$ ± 0.16 | | 22.1 | |
| | | With | 20±1 | | | 9.10$^{a}$ ± 0.09 | | 34.5 | |
| | | none | | | | 7.60$^{b}$ ± 0.12 | | 23.1 | |
| 5.b | EVO/ none | With | 5.0±1 | 11.6 ± 0.01 | nd | 8.90$^{a}$ ± 0.11 | nd | 48.8 | Nd |
| | | none | | | | 5.90$^{d}$ ± 0.02 | | 19.4 | |
| | | With | 20±1 | | | 9.40$^{b}$ ± 0.08 | | 44.7 | |
| | | none | | | | 6.40$^{c}$ ± 0.01 | | 23.3 | |
| 6.a | EVO/ none | With | 5.0±1 | nd | 14.7 ± 0.28 | nd | 6.10$^{c}$ ± 0.20 | nd | 58.5 |
| | | none | | | | | 10.3$^{b}$ ± 0.17 | | 30.2 |
| | | With | 20±1 | | | | 5.00$^{d}$ ± 0.15 | | 65.7 |
| | | none | | | | | 13.4$^{a}$ ± 0.27 | | 9.1 |
| 6.b | EVO/ none | With | 5.0±1 | nd | 14.7 ± 0.28 | nd | 9.20$^{c}$ ± 0.25 | nd | 37.6 |
| | | none | | | | | 12.9$^{a}$ ± 0.05 | | 12.0 |
| | | With | 20±1 | | | | 5.40$^{d}$ ± 0.14 | | 63.6 |
| | | none | | | | | 10.1$^{b}$ ± 0.07 | | 31.1 |

(continued on next page)

**Table II-contd.** CBD and THC (mg mL$^{-1}$) at baseline and after 180 days of storage, with their respective % degradation, in cannabis-based oily products under different oil types and storage conditions

| Sample | Excipient/ additive | Storage condition | | Concentration (mg mL$^{-1}$) Begining (Time 0) | | Concentration (mg mL$^{-1}$) After 180 days | | Degradation (%) | |
|---|---|---|---|---|---|---|---|---|---|
| | | Light | T (°C) | CBD | THC | CBD | THC | CBD | THC |
| 7 | Corn oil/ none | With | | 21.4 ± 0.39 | 19.1 ± 0.16 | 10.0$^{c}$ ± 0.11 | 7.30$^{c}$ ± 0.27 | 53.2 | 61.9 |
| | | none | | | | 11.9$^{b}$ ± 0.17 | 9.90$^{b}$ ± 0.07 | 44.4 | 48.5 |
| | | With | | | | 9.70$^{c}$ ± 0.76 | 4.70$^{d}$ ± 0.07 | 54.8 | 75.4 |
| | | none | | | | 15.5$^{a}$ ± 0.00 | 12.0$^{a}$ ± 0.07 | 27.4 | 37.6 |
| 8 | Corn oil/ none | With | 5.0±1 | 21.4 ± 0.39 | nd | 13.7$^{d}$ ± 0.17 | nd | 35.7 | |
| | | none | | | | 17.2$^{b}$ ± 0.23 | | 19.3 | |
| | | With | 5.0±1 | | | 16.3$^{c}$ ± 0.23 | | 23.8 | |
| | | none | | | | 18.1$^{a}$ ± 0.08 | | 15.1 | |
| 9 | Corn oil/ BHA | With | 20±1 | 49.3 ± 0.74 | 40.5 ± 0.49 | 31.7$^{b}$ ± 0.29 | 23.1$^{c}$ ± 0.04 | 35.8 | 42.9 |
| | | none | | | | 32.7$^{ab}$ ± 0.85 | 26.0$^{b}$ ± 0.47 | 33.6 | 35.9 |
| | | With | 5.0±1 | | | 33.2$^{a}$ ± 0.51 | 20.3$^{d}$ ± 0.12 | 32.7 | 49.9 |
| | | none | | | | 33.5$^{a}$ ± 0.13 | 28.8$^{a}$ ± 0.48 | 32.0 | 29.0 |
| 10 | Corn oil/ none | With | 20±1 | 40.8 ± 0.31 | 34.5 ± 0.49 | 25.4$^{c}$ ± 0.06 | 27.6$^{a}$ ± 0.26 | 37.7 | 20.1 |
| | | none | | | | 30.4$^{b}$ ± 0.58 | 26.9$^{ab}$ ± 0.64 | 25.4 | 21.9 |
| | | With | 5.0±1 | | | 30.3$^{b}$ ± 0.58 | 18.7$^{c}$ ± 0.18 | 25.8 | 45.8 |
| | | none | | | | 34.2$^{a}$ ± 0.12 | 26.1$^{b}$ ± 0.51 | 16.1 | 24.4 |
| 11 | Sesame oil/ BHA | With | 20±1 | 41.9 ± 0.37 | 34.2 ± 0.08 | 20.0$^{b}$ ± 0.78 | 14.4$^{c}$ ± 0.90 | 52.3 | 58.0 |
| | | none | | | | 21.9$^{a}$ ± 0.45 | 17.9$^{a}$ ± 0.32 | 47.8 | 47.7 |
| | | With | 5.0±1 | | | 20.2$^{b}$ ± 0.99 | 9.80$^{d}$ ± 0.09 | 51.8 | 71.3 |
| | | none | | | | 21.2$^{ab}$ ± 0.27 | 15.7$^{b}$ ± 0.28 | 49.5 | 54.2 |
| 12 | Sesame oil/ none | With | 5.0±1 | 42.5 ± 0.28 | 37.0 ± 0.41 | 19.2$^{b}$ ± 0.12 | 13.2$^{c}$ ± 0.07 | 54.8 | 64.3 |
| | | none | | | | 20.5 ± 0.49 | 15.5 ± 1.76 | 51.6 | 58.0 |
| | | With | 20±1 | | | 20.0 ± 1.02 | 11.8 ± 0.20 | 52.9 | 68.1 |
| | | none | | | | 19.2 ± 0.64 | 14.1 ± 0.13 | 54.8 | 62.0 |

Notes: Medium values with similar letters on the same column and sample showed no statistical difference according to the Tukey test at 5% probability; (nd= no detected).

**Table III.** Fatty acid composition of corn oil, olive oil, sesame oil, and MCT used as excipients in the cannabis-based oily products

| Fatty acids | Corn | Sesame | Olive | MCT |
|---|---|---|---|---|
| SFA tot. (%) | 12 – 13 | 14 | 14 – 20 | 100 |
| C8:0 (caprylic) | – | – | – | 50 – 60 |
| C10:0 (capric) | – | – | – | 40 – 50 |
| C12:0 (lauric) | – | – | – | – |

(continued on next page)

**Table III-contd.** Fatty acid composition of corn oil, olive oil, sesame oil, and MCT used as excipients in the cannabis-based oily products

| Fatty acids | Corn | Sesame | Olive | MCT |
|---|---|---|---|---|
| C16:0 (palmitic) | 9 – 14 | 6 – 11 | 7.5 – 20 | – |
| C18:0 (stearic) | 1 – 4 | 2 – 7 | 0.5 – 5 | – |
| C18:1 (oleic) | 24 – 29 | 29 – 45 | 55 – 83 | – |
| C18:2 (linoleic) | 52 – 58 | 38 – 48 | 3.5 – 21 | – |
| C18:3 (linolenic) | 1 – 2 | – | 0 – 1.5 | – |

Adapted from Ref. 30 (licensed under CC BY 4.0) and Ref. 31 (Food and Agriculture Organization, public data).

Regarding the presence of the antioxidant in the samples, we observed that vitamin E (rich in tocopherols and tocotrienols) exerted a more effective preventive effect in some samples (samples 2, 4, and 5) than in others (samples 1, 3, and 6). In general, the degradation percentage was 2 to 11% and 3 to 22% lower than in samples without the vitamin, for CBD and THC, respectively. However, no similar behavior was observed regarding storage conditions (light and temperature) or the presence of one or two analytes. Although discreet in some conditions, the effect of the addition of the antioxidant BHA to sesame oil (sample 11) was also observed, with percentages reaching 5.3 and 10% lower than in samples without antioxidant (sample 12), for CBD and THC, respectively. However, for corn oil, BHA showed no effect (samples 9 and 10).

***Effect of controlled storage variables on cannabis-based oily products***

Both light and temperature influenced analytes degradation ($p < 0.05$). For all oils, the greatest losses, both for CBD and THC, occurred in the presence of light (Figure 5). For THC, this loss is much more prominent (reaching 99.7% at 20 °C, sample 1a, Table I) than for CBD, and can be clearly observed in the excipients MCT, corn, and sesame (Figures 5a, 5b, and 5c). The susceptibility to light of both molecules has been reported in some studies.[11,14,20,26,32,33] Trofin,[14] who also stored oil samples, found THC to be more susceptible than CBD. However, in resins, the results are more conflicting. Some authors report that light influences only THC.[20,32] Lydon,[26] in an accelerated study with ultraviolet irradiation, observed the degradation of CBD but not THC. The rate of photodegradation is also intrinsically associated with the extract composition, as demonstrated by Seccamani,[11] who conducted the study in different solvents. Probably for these reasons, studies are often contradictory.

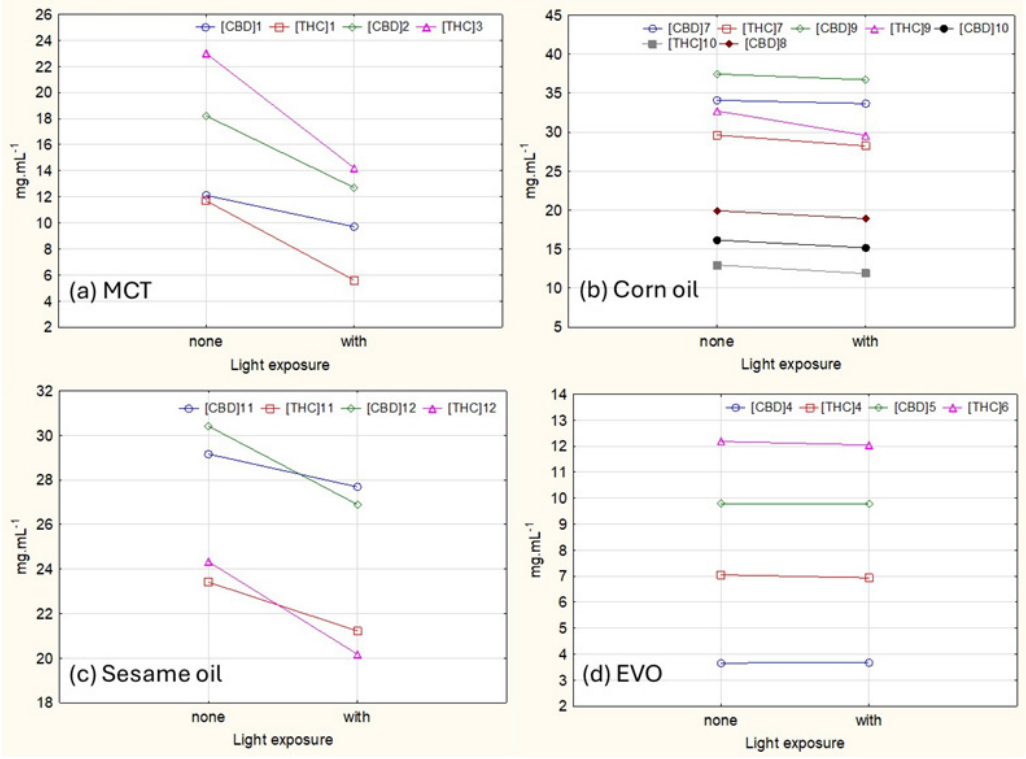



**Figure 5.** Effect of light (Least Squares Means) on CBD and THC in different cannabis-based oily products over 180 days.

Temperature has been shown to be a critical factor in the stability of cannabinoids.[10] When we analyzed the effect of temperature, we noticed that, although it was more discreet compared to light, it also had a significant effect on degradation for both analytes and all excipients ($p \leq 0.05$). Temperature exhibited less uniform behavior compared to light, neither with respect to a specific excipient nor with respect to a specific analyte. In general, it can be observed that for THC, the highest degradation percentages occurred at 20 °C, clearly evident in corn and sesame oils (Figures 6b and 6c). Interestingly, CBD presented, in all excipients, some samples where the greatest degradation occurred at 5 °C (Samples 2, 4, 7, and 12, Figure 6). This behavior could not be explained based on the data available in the present study. The observed variability may be related to subtle differences in sample composition, such as specific interactions between the cannabinoid, the excipient, and minor matrix components, or to combined effects of other storage factors. However, these hypotheses could not be confirmed and require further investigation. Trofin[14] also found greater degradation of THC at 22 °C compared to 4 °C, although this difference was not as pronounced. For CBD, however, temperature made no difference. However, Pacifici *et al*.[12] found similar degradation rates for THC and CBD in olive oil for 14 days at 25 °C and 4 °C, reaching 50% degradation. When analyzing our olive oil samples separately, we also observed the same behavior as the results of Pacifici *et al*.,[12] as the temperature did not show significant differences between CBD and THC (Figure 6d). In resin, Zamengo[32] reported average THC degradation of 11 to 13% at 22 °C in 100 days, and without significant changes in refrigerated samples, albeit in the dark. In the same study, CBD showed no changes. Very similar results were found by Grafström,[34] also in resinous materials.

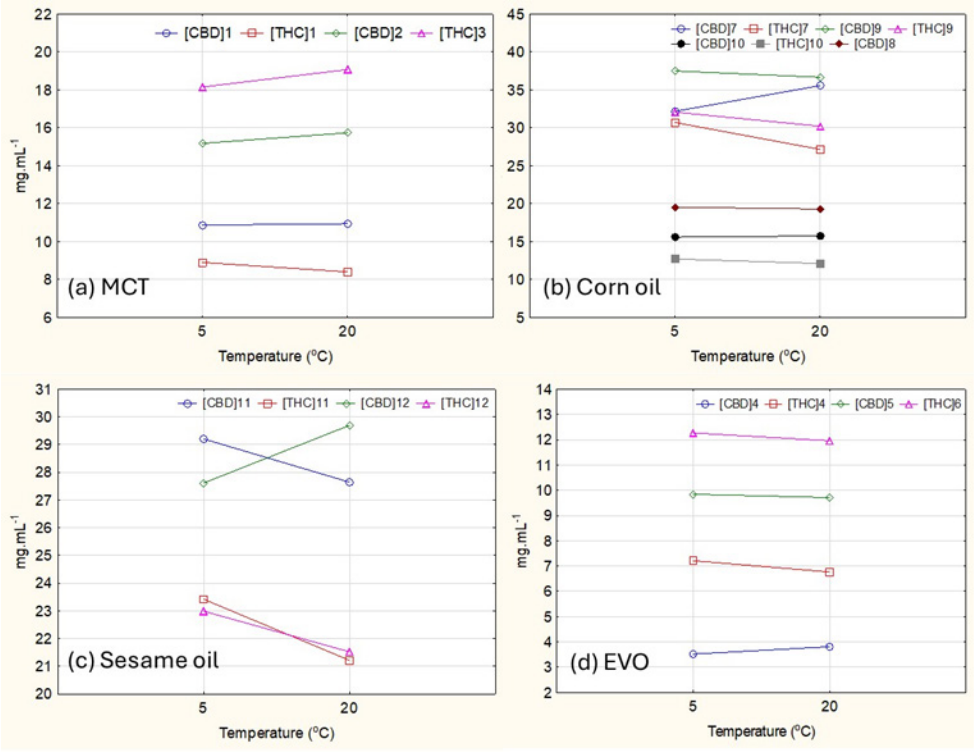



**Figure 6.** Effect of temperature (Least Squares Means) on CBD and THC in different cannabis-based oily products over 180 days.

### *Impact of results for companies and patients*

Due to the potential therapeutic effects of cannabis-based oily products and the increasing number of studies in this field, several associations have emerged in Brazil over recent decades. Currently, more than 259 cannabis associations with active CNPJ registration operate in the country. However, despite this growth, many of these organizations lack adequate infrastructure to conduct analytical studies and perform quantitative analyses with the required accuracy, mainly due to the high costs of equipment and the need for specialized professionals.

Quality control of medicinal extracts, including stability studies, is based on chemical analyses of cannabinoids and the excipient used in the formulation, encompassing both the quantification of active compounds and the assessment of product purity. According to RDC No. 327,[8] cannabis extracts intended for human use must meet pharmaceutical quality standards, and associations are responsible for the technical documentation demonstrating product quality as well as for the operational capacity to perform quality control analyses, which may be outsourced. In this context, outsourcing quality control or establishing partnerships with universities represents viable and strategic alternatives, particularly for small- and medium-sized associations.

The results obtained in this study provide technical support that may assist these associations in improving extract stability and in developing more appropriate guidance for patients regarding the correct storage of medicinal products during treatment.

## CONCLUSIONS

The results demonstrate the high sensitivity of CBD and THC to storage conditions, underscoring the importance of stability studies for cannabis-based products. Both sample composition and storage conditions significantly influenced cannabinoid degradation over a six-month period.

Among the excipients evaluated, corn oil and sesame oil showed the best stability performance, whereas MCT oil exhibited the highest degradation rates. Light exposure was the most critical factor, leading to

the greatest degradation percentages for both cannabinoids, regardless of other variables. Temperature showed a less uniform effect, with higher THC degradation at 20 °C and variable CBD behavior, which in some cases showed greater instability at 5 °C.

The addition of antioxidants had a statistically significant but limited effect. Vitamin E showed greater preventive potential than BHA; however, the results varied depending on the excipient, indicating the need for further studies to better understand these effects.

Overall, the most suitable strategy for cannabinoid preservation involves the use of corn or sesame oil, light-protective containers, the addition of antioxidants, and refrigerated storage. Nevertheless, even under these conditions, high degradation rates were observed, ranging from 19.3% to 51.6% for CBD and from 21.9% to 58% for THC. These values are clinically relevant and require dosage adjustments every two to three months during treatment.

**Conflicts of interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

**Acknowledgements**

This study was financed by the Institutional Program “Agenda Tríplice” of UNILA [Edital No. 205/2021/PRPPG/UNILA] and “Laboratório de Ideias – LABID” [Edital No. 03/2021/IMEA/UNILA]. The authors would also like to thank the financial support granted by “Fundação Araucária” [Public Notice 23/2023 - Program of Scholarships for Productivity in Research and/or Technological Development].

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## SUPPLEMENTARY MATERIAL

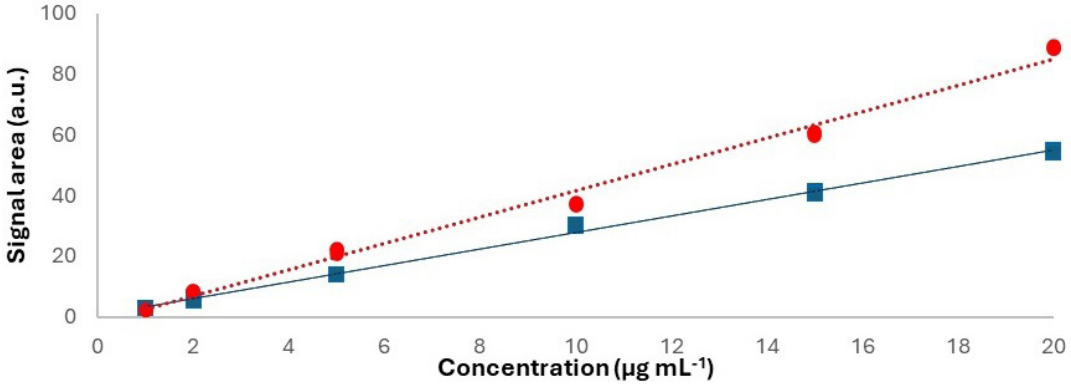


**Figure S1.** Calibration curves of THC obtained in solvent (red) and in matrix (blue).

**Table S2.** Regression parameters of THC calibration curves in solvent and matrix (n = 3)

| Medium | Levels (µg mL$^{-1}$) | Slope (a) | Intercept (b) | Linear regression ($R^2$) |
|---|---|---|---|---|
| Solvent | 1-20 | 4.35 | -1.95 | 0.991 |
| Matrix | 1-20 | 2.75 | 0.53 | 0.997 |

**Table S3.** Statistical analysis of the slopes of calibration curves in solvent and matrix

| Parameters | Student's *t*-test | | | *F*-Snedecor test | |
|---|---|---|---|---|---|
| | ***t* calculated** | ***t* critical (90%)** | ***t* critical (95%)** | ***F* calculated** | ***F* theorical (0.05; 10; 16)** |
| **Results** | 59.7 | 1.74 | 2.11 | 7.58 | 2.70 |
| **Evaluation** | *t* > *t* critical | | | *F* calculated > *F* theorical | |
| **Conclusion** | Slopes are different | | | Variances are different | |

**Table S4.** Linearity range, R, Line equation, LOD and LOQ for the analytes

| Analyte (µg mL$^{-1}$) | Linearity (µg mL$^{-1}$) | R | Line Equation | LOD (µg mL$^{-1}$) | LOQ (µg mL$^{-1}$) |
|---|---|---|---|---|---|
| CBD | 1-20 | 0.9992 | y = 1.6462x - 0.7436 | 0.98 | 3.43 |
| THC | 1-20 | 0.9991 | y = 1.7134x + 0.0724 | 1.34 | 2.42 |

LOD: Limit of detection. LOQ: Limit of quantification.

**Table S5.** Values for Relative Standard Desviation (% RSD)

| Analyte | Level (µg mL$^{-1}$) | %RSD (n=3) | Analyte | Level (µg mL$^{-1}$) | %RSD (n=3) |
|---|---|---|---|---|---|
| CBD | 1 | 4.34 | THC | 1 | 2.45 |
| | 2 | 2.56 | | 2 | 0.73 |
| | 5 | 0.92 | | 5 | 0.65 |
| | 10 | 0.61 | | 10 | 0.62 |
| | 15 | 1.56 | | 15 | 1.23 |