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Short communication

THCA → THC conversion and its importance for the stability and quality of the herbal material

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Introduction

Medical cannabis industry requires accurate content determination of the most notable pharmacologically active cannabinoids, i.e. Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD). This parameter is considered critical in the quality control of the cannabis plant and its products. Δ9-tetrahydrocannabinolic acid (THCA) is genuinely synthesized by the plant, while THC does not occur at a significant concentration. Thus, plant material contains very small amount of THC, leading to very high THCA/THC content ratio in plant tissue (Kimura et al., 1970). To date, the pharmacology of acidic and neutral cannabinoids has been found to be very different, but an emerging portion of the cannabis research community still largely and actively explore the pharmacology and medicinal use of acidic cannabinoids (Filer, 2022). Cannabis plant itself is the obvious starting point for potential decarboxylation of THCA into THC. The transformation reaction can occur spontaneously while drying and/or storage of the herbal material, mainly due to exposure at higher temperature, yet it is a process regularly included in the manufacturing of the final cannabis products. The decarboxylation conditions are highly varied among the manufactures due to a lack of agreement that defines the optimal process conditions (Lewis-Bakker et al., 2019). Therefore, monitoring and optimization of the decarboxylation reaction is necessary to achieve satisfactory critical quality attributes of the final product (decarboxylated cannabis flower/extract). This study aims to provide a deeper insight of the THCA → THC transformation and highlight its importance in the stability and the quality of the herbal material by means of HPLC, FTIR spectroscopy and TG analysis.

Materials and methods

THCA powdered analytical standard (98.8 wt%) was supplied from Sigma-Aldrich, USA. Plant material was obtained from *Cannabis sativa* L. ssp. indica, Kerosene Krash®, which belongs to cultivar type 1 that features high THCA and low CBDA content.

Thermogravimetric (TG) analysis of the THCA standard

Netzsch TG 209 F1 Iris analyzer was used in the 25–160°C range, using an open alumina sample pan, under compressed air atmosphere (30 mL/min), at constant heating rate of 2°C/min. After reaching 160°C, the sample was kept for 10 min. The sample leftover was carefully scratched from the pan and stored for HPLC analysis.

Temperature-controlled attenuated total reflectance mid infrared (t-ATR IR) spectroscopy

t-ATR IR spectra were recorded on a Varian 660 FTIR

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spectrometer (4000–400 cm^{-1} region) using a temperature programmable hot-plate from GladiATR module (PIKE technologies) equipped with a diamond crystal and software (TempPro, PIKE technologies).

High-performance liquid chromatography (HPLC)

The assay method from the monograph of cannabis flos of the German Pharmacopoeia, DAB (2018) was employed for quantitative analysis of THCA standard and the cannabinoids in cannabis flower.

Statistical analysis

Principal component analysis (PCA) was carried out for the t-ATR IR spectra by using the Simca14 (Umetrics, Sweden).

Results and discussion

TG analysis revealed that THCA decarboxylation of the standard is one-step continuous process extending from 90°C to 150°C. At the temperature of 130°C decarboxylation step reached the maximum rate. THCA to THC conversion was also confirmed by HPLC analysis.

t-ATR IR was employed in order to evaluate and interpret the IR spectral changes occurring from 25°C to 160°C in both THCA standard and flower sample. A detailed band assignment and spectra-structure correlations were performed, based on the concept of functional groups vibrations. The HPLC results confirmed complete conversion of THCA to THC in the THCA standard and flower sample collected after collection of the t-ATR IR spectra at 160°C.

In order to closely exploit the IR spectral changes due to the THCA decarboxylation in the standard sample and in the cannabis flower, PCA was employed. The results, obtained for the standard, showed practically full complementarity with those obtained from the TG/DTG measurements (133°C). On the other hand, PCA results obtained for the cannabis flower showed that the decarboxylation onset temperature and the peak score corresponding to the decarboxylation maximum rate were determined at significantly lower temperatures (102°C). This finding was considered appropriate because the decarboxylation of THCA in the plant matrix commences in the presence of enzymes and other compounds.

ATR IR experiment at fixed temperature was also conducted to investigate the reaction kinetics for both THCA standard and the cannabis plant at 133°C and at 102°C only for the plant material. The collected spectra at fixed temperatures were PCA analysed. First principal component was further employed for calculation of the reaction kinetics that demonstrates significantly higher values for the decarboxylation of the flower samples at 133°C in comparison to the reaction at same temperature in pure THCA and at 102°C in the flower.

Conclusion

The THCA cannabinoid still attracts a great interest being a precursor to THC, but also due to the potential pharmacological and medicinal use of the acidic form. Hence, its spontaneous decarboxylation and stability as well as the optimization of conditions for conversion to THC, both in herbal material and herbal preparations were extensively studied.

The maximum conversion temperatures both for standard and cannabis flower were outlined at 133°C and 102°C, respectively. TG and ATR IR, combined by conventional HPLC analysis, demonstrated difference in the conversion temperature between pure THCA and cannabis flower.

References

Federal Institute for Drugs and Medical Devices, 2018. revised monograph ‘Cannabis flowers’ BAnz AT 24.04.2018 B5. In: German Pharmacopoeia) 2018th ed., Bonn.

Filer C. N., 2022. Acidic Cannabinoid Decarboxylation. Cannabis Cannabinoid Res. 7(3), 262–273. DOI: 10.1089/can.2021.0072

Kimura, M., Okamoto, K., 1970. Distribution of tetrahydrocannabinolic acid in fresh wild cannabis, Experientia 26 (8) 819–820. DOI: 10.1007/BF02114192

Lewis-Bakker, M.M., Yang, Y.I., Vyawahare, R., Kotra, L.P., 2019. Extractions of medical cannabis cultivars and the role of decarboxylation in optimal receptor responses, Cannabis Cannabinoid Res. 4 (3) 183–194. DOI: 10.1089/can.2018.0067