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Extraction and purification of major phytocannabinoids (Δ^9-THC and CBD) in *Cannabis sativa* grown in northeastern Brazil

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Abstract. Chemical profile and stability of cannabinoids in *Cannabis sativa* are influenced by environmental conditions and extraction procedures. Selective and mild extraction methods are essential to preserve cannabinoid integrity and ensure reproducibility and quality of medicinal *Cannabis* products. This study investigated the occurrence of the major cannabinoids Δ^9-tetrahydrocannabinol (Δ^9-THC) and cannabidiol (CBD) in *Cannabis sativa* cultivated in the semi-arid Agreste region of Northeast Brazil and evaluated a novel, low-stress method for their simultaneous extraction and purification. An experimental comparative study was conducted using cultivated *Cannabis sativa* inflorescences and two distinct extraction–purification approaches. Inflorescences of *Cannabis sativa* L. (var. Charlotte's Web) cultivated in Sairé, Pernambuco, Brazil, were subjected to Soxhlet extraction and to the Góes method, a milder extraction procedure with reduced thermal exposure. Cannabinoid profiles and degradation products were analyzed by gas chromatography-mass spectrometry (GC-MS). Soxhlet extraction using ethanol and cyclohexane resulted in higher total cannabinoid yield but promoted partial thermal degradation of Δ^9-THC, evidenced by the formation of cannabinol (CBN). The Góes method selectively yielded purified Δ^9-THC without detectable degradation products. CBD was not detected in the analyzed samples, which may be related to solvent polarity constraints and cultivation under high temperature and intense solar radiation typical of the Agreste region. Extraction conditions, particularly temperature and solvent polarity, critically affect cannabinoid yield and chemical stability. The Góes method emerges as a selective, low-cost alternative for obtaining high-purity Δ^9-THC, supporting improved standardization and quality control of medicinal and artisanal *Cannabis* preparations.
Keywords: Analytical chemistry, Chromatography, Continuous processing, High concentration, Mass Spectrometry.

Introduction

Cannabis sativa is a plant with millennia-old uses described by ancient civilizations that already demonstrated its significant therapeutic value (Pierro Neto, 2023). It is considered a chemically complex plant due to the presence of a variety of chemical substances from different classes, with phytocannabinoids being the most prominent. These are responsible for the psychoactive effects and pharmacological activities (Blebea et al., 2024). These compounds have been used in the treatment of chronic diseases and various neurological/psychiatric disorders, such as Alzheimer's, cancer, fibromyalgia, autism, multiple sclerosis, depression, anxiety, epilepsy, rheumatoid arthritis, among many other conditions, serving as a therapeutic alternative in the management of serious illnesses (Fernandes et al., 2023).

In Brazil, medical *Cannabis sativa* has been mainly used for chronic pain and neurological disorders, although the most prevalent and proven therapeutic use in studies is in controlling seizure

episodes in patients with refractory epilepsy. In this case, the plant is primarily used in the form of a phytotherapeutic extract containing cannabidiol (CBD) and Δ⁹-tetrahydrocannabinol (Δ⁹-THC), two of the major phytocannabinoids found in the plant (Figure 1) (Moreira et al., 2023; Motta and Rodrigues, 2023).

CBD and Δ⁹-THC are the main molecules responsible for the therapeutic properties of *Cannabis* due to their interaction with CB1 receptors distributed in the Central Nervous System (CNS) and CB2 receptors in the Peripheral Nervous System (PNS). Endocannabinoid receptors recognize phytocannabinoids, thus providing therapeutic benefits (Ibsen et al., 2017). The pharmacological effects depend on the dosage and the interaction between Δ⁹-THC, CBD, and other components of the plant (such as other phytocannabinoids, terpenes, and flavonoids), which can be present in different proportions in the extracts (Cavalli and Dutra, 2021).

Basically, there are three classes of products available on Brazilian market in the form of medicinal *Cannabis* phytotherapeutic oils based on the formulation of the medications: full spectrum (oil made from the whole plant extract containing Δ⁹-THC); broad spectrum (oil made from the whole plant extract without Δ⁹-THC); and CBD isolate (Motta and Rodrigues, 2023).

In Brazil, the regulatory body responsible for this regulation is the National Health Surveillance Agency (ANVISA), entity linked to the Brazilian Ministry of Health, with some relevant resolutions, including RDC 327/2019 and RDC 660/2022, which allow the manufacture, handling, and commercialization of *Cannabis* products in the country. ANVISA also participates in the supervision and regulation of patient associations, such as ABRACE, which operates under a court order from the Federal Court of the state of Paraíba (JFPB) and in accordance with RDC 16/2014, as well as companies within the national medicinal Cannabis market (Martins and Posso, 2023).

Currently, access to medicinal *Cannabis* in Brazil occurs in different ways: (i) Pharmacy-Available Medications – these are primarily isolated and quantified cannabinoids, available at a high cost, ranging from R$ 2,000.00 to R$ 3,000.00 (US$ 370.00 to US$ 550.00 approximately); (ii) Medication Importation – in more than 40 countries, the use of medicinal *Cannabis* is authorized. Imported medications come with a certificate of analysis detailing the components present in the oil, available as isolated cannabinoids or full spectrum oil, with prices around R$ 1,000 (US$ 180.00 approximately); (iii) *Cannabis* Associations – some associations have collective Habeas corpus, allowing them to cultivate Cannabis sativa and produce the extract, typically in an artisanal manner and without component titration. Prices for these products range from R$ 200 to R$ 500 (US$ 35.00 to US$ 90.00 approximately); and (iv) Individual, Artisanal Production – patients may cultivate *Cannabis sativa* themselves, either with or without an impetrated *Habeas corpus*, and produce their own artisanal oil. This method incurs lower or similar costs compared to the products provided by associations (Souza et al., 2022).

Despite the lower costs associated with phytotherapeutic medications obtained through associations or self-cultivation, there remains a significant lack of studies addressing the quality and robustness of phytocannabinoid extraction and purification processes. This gap makes it difficult to determine whether the administered concentrations of active compounds are accurate and whether the final products meet basic safety and quality requirements. In this context, the determination of the major cannabinoids, particularly Δ⁹-THC and CBD, in extracts obtained from *Cannabis* plants cultivated in the Northeast of Brazil is of critical importance. The semi-arid climate of this region, characterized by high temperatures, intense solar radiation, and irregular water availability, may substantially influence cannabinoid biosynthesis, leading to variations in Δ⁹-THC and CBD content and in their relative proportions. Without precise determination of these major cannabinoids, it is not possible to ensure therapeutic predictability, appropriate dosing, or compliance with safety and regulatory parameters. Therefore, the establishment of reliable analytical methods for Δ⁹-THC and CBD determination, in parallel with efficient extraction and purification processes, is essential to preserve the identity, quality, and consistency of the resulting extracts (Hall et al., 2022).

Investing in low-cost and efficient extraction strategies, combined with rigorous determination of Δ⁹-THC and CBD levels, is essential to guarantee both patient safety and product efficacy, particularly in contexts where artisanal production predominates. Currently, such scientifically validated practices are not widely adopted by many producers of artisanal oils in Brazil. Within this framework, the central objective of this study is to contribute to the expansion of knowledge regarding the quality of phytocannabinoid extraction processes used in the production of artisanal extracts and oils by associations and/or patients, with a specific focus on plant material cultivated in the semi-arid regions of Northeastern Brazil. This work involves the investigation and development of efficient extraction and purification methods capable of ensuring consistency, reproducibility, and accurate quantification of the major cannabinoids Δ⁹-THC and CBD. By providing a robust scientific basis for production practices, this study aims to improve dosing precision, reduce variability associated with regional cultivation conditions, and ensure the safety and effectiveness of Cannabis-derived herbal medicinal products

Material and methods

Plant material

Samples of inflorescences of the *Cannabis sativa* plant variety Charlotte's Web were used,

cultivated through outdoor organomineral cultivation in the municipality of Saíre, state of Pernambuco, Brazil (-8.222623, -35.686300). Mineral fertilizer was used with a mixture of 50% organic soil (*humus* + carolina soil). The harvest was carried out between the months of June and August 2023 and occurred after 60 days of flowering, in which pre-defoliation was carried out before harvesting. The planting site also had a mini-garden with other herbs that worked as natural pest repellents, in order to avoid the use of agricultural pesticides. A 50% shade screen was used to reduce the intensity of sunlight. Side protection was also provided on the plantation with tiles to avoid the effects of stronger winds. The plants were grown in jars until the end of the growing season, and then placed in the soil.

Phytocannabinoid extraction methods

To obtain the extracts from *Cannabis sativa* inflorescences, two extraction methods were applied. The Soxhlet method was used, initially with ethyl alcohol (boiling range 76-78 °C) and then with cyclohexane (boiling range 78-80 °C). The extraction rate was set at 6 to 8 siphonations per hour at a constant temperature, with a dripping flow between 150 and 200 drops per second (Gallo-Molina et al., 2019). A 10 g sample was weighed, and 120 mL of solvent was used. The extractions were carried out over an 8-hour period. After extraction, the extract was vacuum-concentrated in a Fisatom rotary evaporator (model 803) at 40–45 °C, and the solvent was recovered.

In addition to the Soxhlet methodology, the Góes method (Silva et al., 2019) was employed. The column was partially filled with 10 g of Merck silica gel 60 (230-400 mesh, Flash) and then with 10 g of powdered *Cannabis sativa* inflorescences. The concentration gradient system used consisted of pure cyclohexane, cyclohexane/acetate (9/1), and ethanol. The cyclohexane fractions were combined (F. 1-4), yielding 1.80 g (18%). The cyclohexane/acetate (9/1) fraction (F. 5) yielded 0.995 g (9.95%), and the ethanol fraction (F. 6) yielded 0.903 g (9.03%). The system was heated to a temperature sufficient to feed the column (78-80 °C), using 120 mL of pure cyclohexane for 8 h. After this period, the cyclohexane/acetate (9/1) system was prepared by adding 13.3 mL of ethyl acetate to the flask containing cyclohexane, and the process was continued for 6 h with 100 mL of ethanol (Figure 2)

During the process, the fractions were collected and concentrated under reduced pressure.

Extracts characterization

The *Cannabis sativa* extracts were analyzed by Gas Chromatography coupled to Mass Spectrometry (GC-MS). The analyses were performed using an Agilent GC 7890A system coupled to an Agilent MSD 5975C detector, equipped with an HP-5MS capillary column (30 m × 0.25 mm × 0.25 µm). Helium was used as the carrier gas at a constant flow rate of 1.0 mL/min. The oven temperature program was as follows: initial temperature of 80 °C (held for 1 min), followed by an increase to 250 °C at a rate of 30 °C/min, and then to 300 °C at 10 °C/min. The injector temperature was maintained at 260 °C, and injections were performed in splitless mode. A CombiPal CTC autosampler was used for sample injection.

Data acquisition was carried out in full-scan mode. The obtained mass spectra were compared with those contained in the 2023 NIST/EPA/NIH Mass Spectral Library for compound identification.

The analytical procedure was adapted from the Recommended Methods for the Identification and Analysis of *Cannabis* and *Cannabis* Products published by the United Nations Office on Drugs and Crime (UNODC, 2022).

Results and discussion

The chromatogram of the extract prepared using the Soxhlet method can be observed in Figure 3. Figure 3a corresponds to the chromatogram of the fraction with pure cyclohexane. A major peak can be seen at 3.11 min corresponding to Δ^9-THC, and a smaller peak at 3.303 min corresponding to cannabinol (CBN). Figure 3b corresponds to the chromatogram of the fraction with ethanol. Only baseline noise can be observed.

In Figure 4, the chromatograms of the extracts prepared using the Góes method can be observed. Figure 4a corresponds to the chromatogram of the pure cyclohexane fraction (F. 1-4), Figure 4b corresponds to the chromatogram of the cyclohexane/acetate fraction (F. 5), and Figure 4c corresponds to the chromatogram of the ethanol fraction (F. 6). In the chromatograms shown in Figures 4a and 4b, a single peak at 3.087 min corresponding to Δ^9-THC can be observed. In Figure 4c, only baseline noise is observed.

Figure 5 shows the mass spectra obtained by the Soxhlet method (5a and 5b) and by the Góes method (5c and 5d). The red mass spectra correspond to the sample spectra, while the blue ones correspond to the mass spectra from the 2023 NIST/EPA/NIH Mass Spectral Library, which was used for compound comparison and identification. Using the Soxhlet method with the pure cyclohexane fraction, two phytocannabinoids were obtained, Δ^9-THC and CBN, respectively. In contrast, with the Góes method, only one phytocannabinoid, Δ^9-THC, was obtained, both in the pure cyclohexane and in the cyclohexane/acetate fractions.

Medicinal *Cannabis* extracts are produced from the inflorescences of pistillate (female) specimens. Essentially, the extraction is classified as solid-liquid extraction, as the inflorescences are the solid part and the extract consists of the extraction solvent (Lazarjani et al., 2021). Before extraction, the samples undergo a drying process, which can take place in natural circulation ovens, vacuum ovens, or lyophilizers, which perform the process without heating. The dried samples are then ground, and extraction follows (Martinez et al., 2023).

Regarding extraction, there are various methods, ranging from classical ones such as hydrodistillation, steam distillation, maceration, cold fat extraction (enfleurage), and Soxhlet extraction, to more modern ones like ultrasound-assisted extraction, supercritical fluid extraction, pressurized liquid extraction, and microwave-assisted extraction. The sophistication of the methods involves more elaborate apparatus, leading to higher costs, but also greater extraction efficiency. Thus, choosing an extraction method should be a decision that considers various factors, such as the quantity of extract to be produced, the purity level of the extract, the stability of phytocannabinoids during extraction, cost, and environmental impact (Ubeed et al., 2022).

The results obtained demonstrated that both extraction methods evaluated, Soxhlet and Góes, were effective in extracting cannabinoids from the analyzed plant matrix, though they exhibited distinct chromatographic profiles and selectivities. The chromatogram of the apolar fraction obtained by Soxhlet revealed a major peak at approximately 3.11 minutes, corresponding to Δ⁹-THC, and a secondary peak at 3.303 minutes, identified as CBN. In the Góes method, only the Δ⁹-THC peak was observed, with no detection of CBN, and no relevant signals were found in the ethanolic fractions for either method. Mass spectra were obtained corresponding to Δ⁹-THC, with a base peak at *m/z* 299, a molecular ion peak at *m/z* 314, and other relevant peaks at *m/z* 271, *m/z* 258, *m/z* 243, and *m/z* 231, as well as to CBN, with a base peak at *m/z* 295, a molecular ion peak at *m/z* 310, and another relevant peak at *m/z* 238 (Hassan et al., 2023). These findings indicate that, although the Soxhlet extraction is efficient, it promotes partial degradation of Δ⁹-THC, while the Góes method better preserves the integrity of the compound.

Among these selection parameters, some variables are of great relevance because they influence more than one of these factors. For instance, the extraction temperature affects both the cost of extraction and the stability of the phytocannabinoids, as certain interconversions caused by temperature are known. The type of solvent used also impacts the extraction efficiency of specific phytocannabinoids due to chemical affinity and the environmental impact. The most commonly used solvent for CBD-rich extracts is ethanol, and the extraction temperatures are below 100°C. Labels on imported products and products produced by patient associations describe that the most commonly used vehicle is medium-chain triglyceride (MCT), while in artisanal preparation, *Cannabis* resin is generally dissolved in olive oil, coconut oil, or sunflower oil (Nahar et al., 2020).

The exclusive presence of CBN in the Soxhlet extract is consistent with literature reports that associate the increase of this oxidized cannabinoid with the thermal and oxidative degradation of Δ⁹-THC and/or THCA during prolonged heating (Garcia-Valverde et al., 2022; Jaidee et al., 2022). The Soxhlet apparatus operates under continuous reflux at temperatures near the solvent's boiling point (80-90 °C), subjecting bioactive compounds to thermal stress that favors oxidation and dehydrogenation reactions converting Δ⁹-THC into CBN. Conversely, the Góes method, which employs sequential extraction at milder temperatures and shorter times, minimizes these degradative reactions, resulting in cleaner and more selective chromatograms for Δ⁹-THC. This behavior corroborates comparative cannabinoid extraction studies that indicate cold methods as more suitable for preserving thermolabile compounds (López-Olmos et al., 2022; Garcia-Castaño et al., 2025).

The absence of a CBD signal in both methodologies can be explained by multiple physicochemical and biological factors. Firstly, CBD has slightly higher polarity than Δ⁹-THC and is therefore less soluble in apolar solvents such as cyclohexane – the main solvent used in the extraction steps. Consequently, the partition favors Δ⁹-THC, resulting in selective extraction and reduced CBD recovery. Moreover, the predominant form of the compound in the plant may be cannabidiolic acid (CBDA), which is more polar and thermally unstable. This form is not efficiently extracted in apolar solvents and may undergo incomplete decarboxylation or degradation during GC-MS injection. It is also relevant that CBD is thermally less stable than Δ⁹-THC and may undergo partial isomerization to Δ⁹-THC at high injection temperatures, leading to underestimation of its actual content (Tsujikawa et al., 2022; Lazarjani et al., 2021). It is possible that the analyzed sample derives from a naturally THC-rich chemotype, with low CBDA-synthase expression and trace CBD concentrations below instrumental detection limits.

An additional aspect that may have contributed to the predominance of Δ⁹-THC in the samples is the set of environmental conditions at the cultivation site. Regions of the Agreste region of Pernambuco, such as the municipality of Sairé, are characterized by high solar radiation, average daytime temperatures above 30 °C, low relative humidity, and irregular rainfall – all factors known to affect gene expression and secondary metabolism in *Cannabis sativa*. Several authors have reported that thermal stress, intense UV-B radiation, and water deficit promote the activation of the biosynthetic pathway of tetrahydrocannabinolic acid (THCA) to the detriment of CBDA, due to differential regulation of THCA-synthase and CBDA-synthase enzymes (Tahir, 2021; Payment and Cvetkovska, 2023; Dimopoulos et al., 2025). Under such conditions, even cultivars originally rich in CBD, such as Charlotte's Web, may express chemotypes with higher Δ⁹-THC levels – a behavior already observed in plants grown under strong sunlight and water stress (Lydon et al., 1987; Fusaro et al., 2025). This adaptive response has a photoprotective function, since Δ⁹-THC acts as an antioxidant and UV-absorbing molecule, contributing to the plant's defense against environmental stress.

Therefore, the results obtained reflect not only intrinsic differences between the extraction methodologies but also environmental influences on the chemical composition of the source plant. While the Soxhlet method yielded a higher total amount of cannabinoids at the cost of partial degradation, the Góes method proved to be more selective and conservative, extracting predominantly Δ^9-THC under mild conditions. The absence of CBD and the presence of CBN in the former method reinforce the need to tailor solvent choice and thermal conditions to the desired chemical profile, especially when the goal is the simultaneous extraction and purification of both neutral and acidic cannabinoids.

Additionally, the findings highlight the importance of considering terroir and agronomic management as determining factors for the Δ^9-THC /CBD ratio, even in stable genotypes. Semi-arid tropical environments may favor a "metabolic shift" toward the Δ^9-THC pathway, compromising the standardization of CBD-rich medicinal cultivars. Thus, it is recommended that future extractions include quantitative recovery analyses, precise control of time and temperature, and environmental monitoring of chemotype expression to ensure greater reproducibility and selectivity of the process.

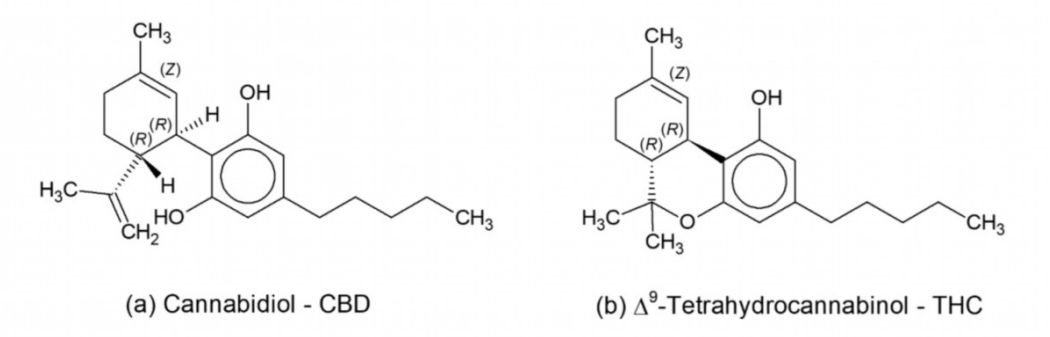

Figure 1. Molecular structure of (a) CBD and (a) Δ^9-THC.

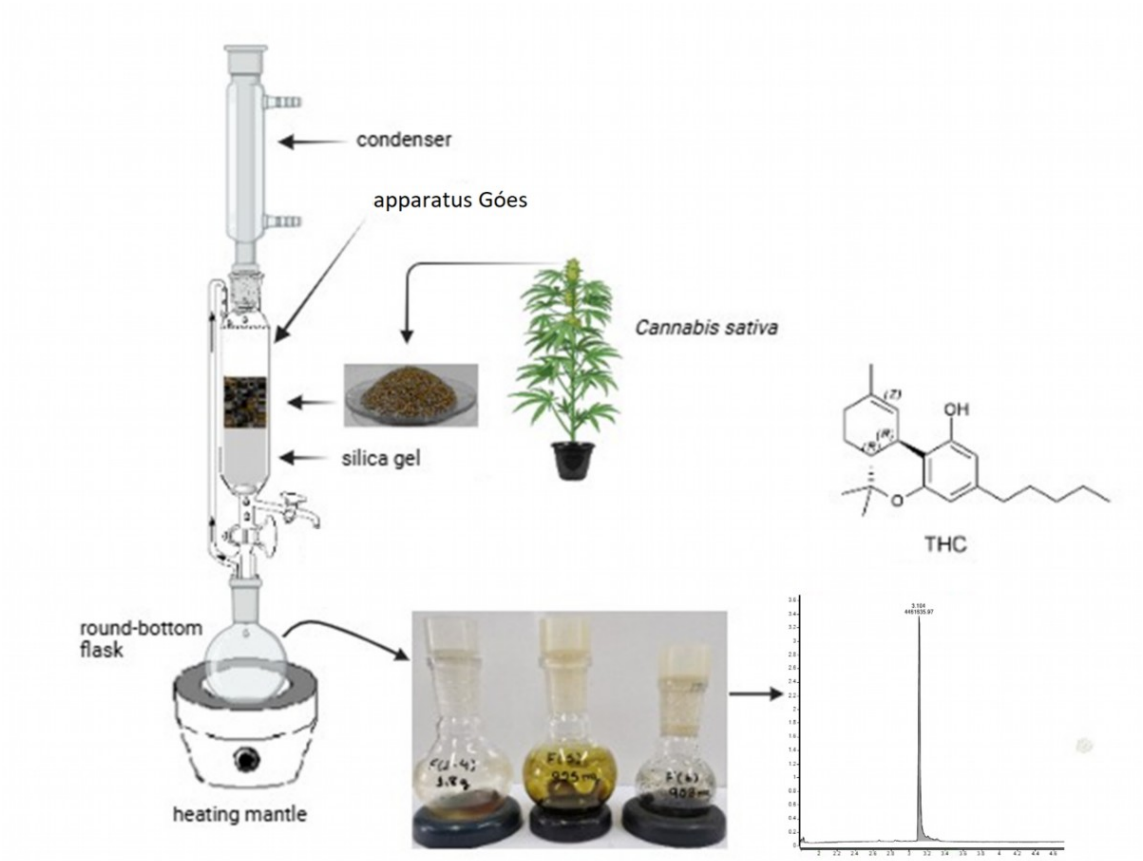

Figure 2. Process for extraction and simultaneous purification *Cannabis sativa* inflorescences.

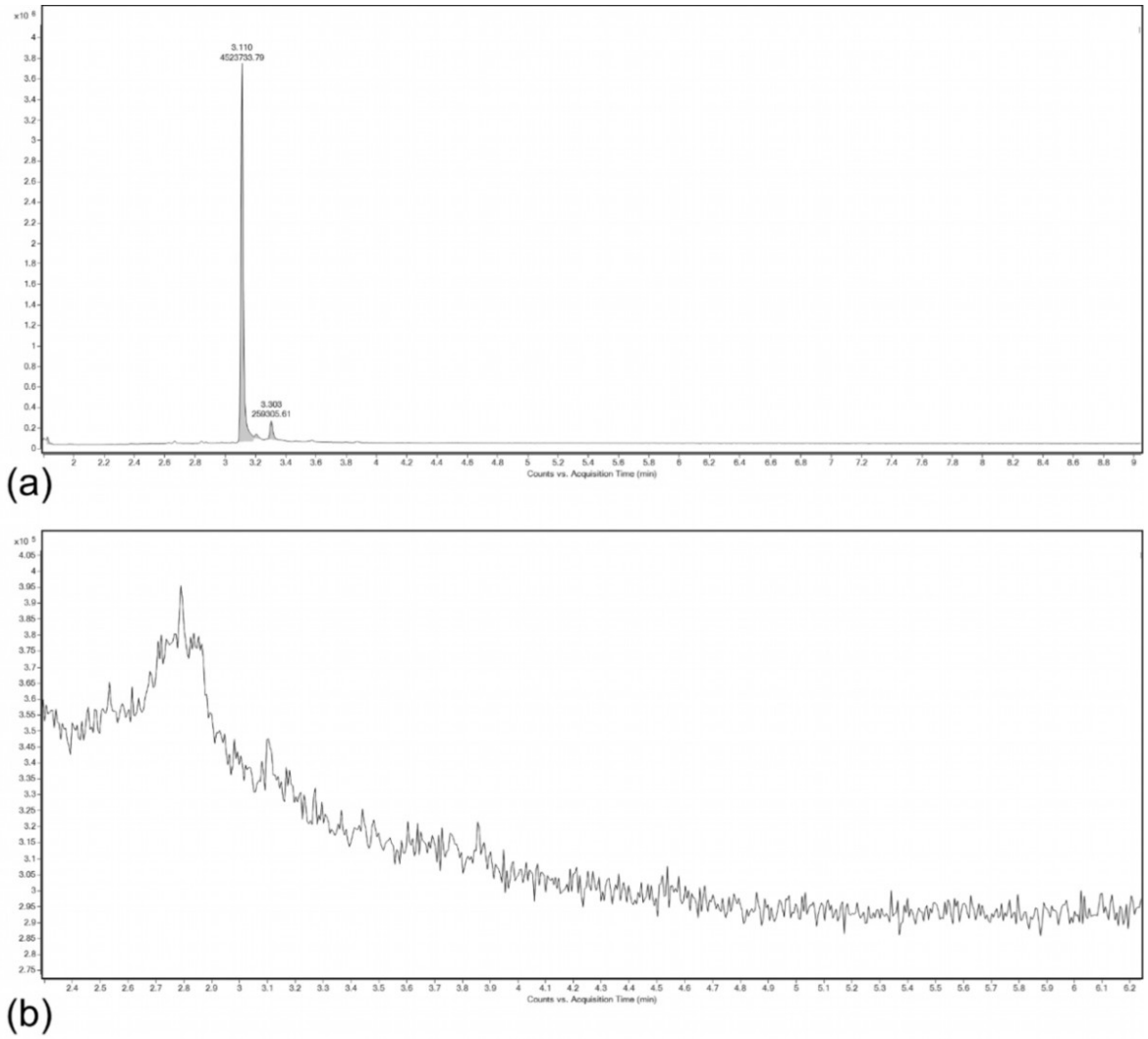

Figure 3. Process for extraction and simultaneous purification *Cannabis sativa* inflorescences.

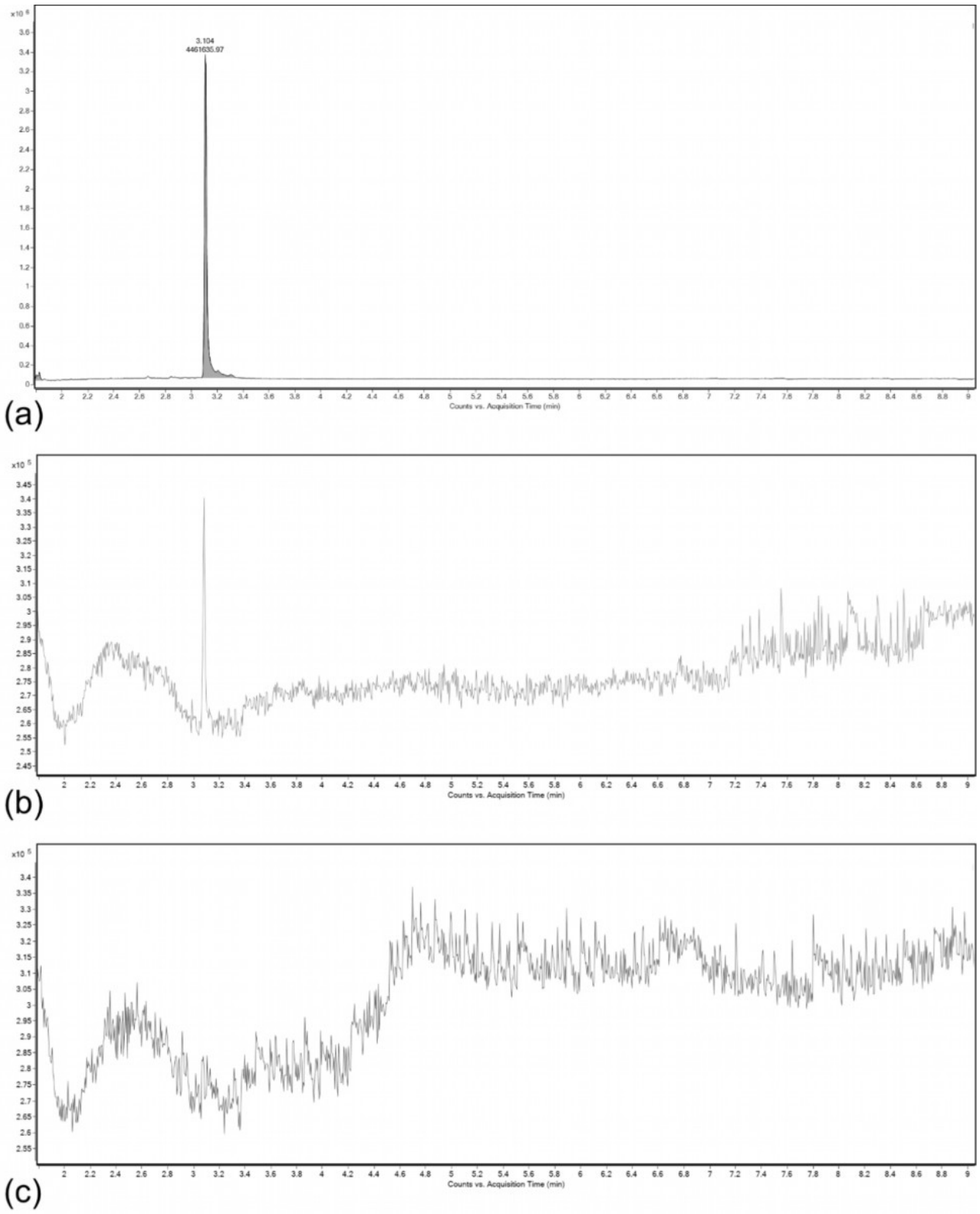

Figure 4. Process for extraction and simultaneous purification *Cannabis sativa* inflorescences.

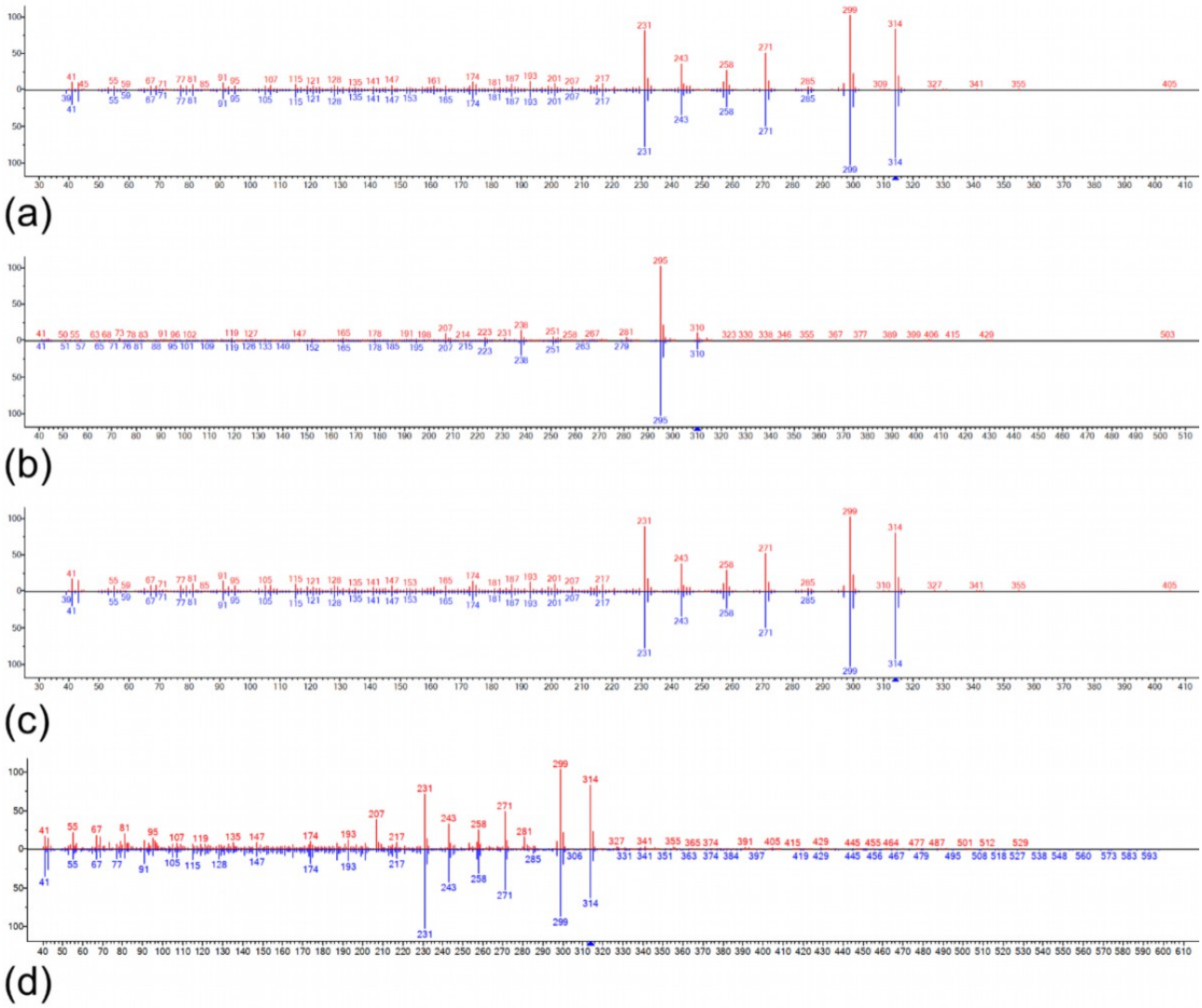

Figure 5. Process for extraction and simultaneous purification *Cannabis sativa* inflorescences.

Conclusion

The results of this study demonstrate that the proposed methodology enables the simultaneous extraction and purification of cannabinoids, with significant differences in selectivity and compound integrity between the evaluated methods. The Soxhlet method exhibited a higher total yield of cannabinoids but showed evidence of thermal degradation, resulting in the formation of CBN. In contrast, the Góes method, conducted under milder conditions, proved to be more selective, preserving the integrity of Δ⁹-THC and preventing the formation of degradation products. These results indicate that the cold extraction methodology represents a promising alternative for obtaining purer extracts that are more representative of the plant's original composition.

The absence of CBD in the analyzed samples can be attributed to a combination of physicochemical and environmental factors. From an analytical perspective, the use of apolar solvents may have compromised the extraction and detection of the compound, either due to its low solubility, CBDA decarboxylation, or thermal isomerization of CBD into Δ⁹-THC. From a biological standpoint, it is possible that the source plant exhibits a high level of Δ⁹-THC, whose expression may have been intensified by the environmental conditions of the Agreste region of Pernambuco. Factors such as high UV radiation, elevated temperatures, and water deficit favor the activation of the THCA biosynthetic pathway to the detriment of CBDA, which would explain the predominance of THC even in cultivars genetically rich in CBD.

Future perspectives include the improvement of the extraction and purification methodology, with particular attention to the use of solvents of intermediate polarity, the reduction of heating time, and the application of an inert atmosphere to minimize oxidative processes. Comparative extraction assays under different climatic conditions and *Cannabis sativa* genotypes could clarify the environmental impact on the Δ⁹-THC /CBD ratio, consolidating the understanding of the "cannabinoid terroir." Additionally, the application of chemometric approaches may contribute to assessing compositional variability of extracts and

optimizing experimental parameters. Thus, the proposed methodology represents an advance in the development of selective and sustainable extraction protocols, with potential applications in both pharmacological research and quality control of medicinal *Cannabis*-derived products.

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