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Aplicaciones terapeúticas y técnicas de extracción de canabinoides

Therapeutic applications and extraction techniques of cannabinoids

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Resumen

El cáñamo (*Cannabis sativa* L.) es una planta compuesta por sustancias bioactivas denominadas cannabinoides. De acuerdo con reportes científicos, se han identificado más de cien cannabinoides, entre los que destacan el cannabidiol (CBD), el cannabigerol (CBG), el cannabinol (CBN) y el cannabicromeno (CBC), como los más representativos.

En la actualidad, la investigación sobre cannabinoides ha cobrado una importancia creciente, dado que se ha demostrado que estos compuestos bioactivos poseen propiedades que pueden aprovecharse en el desarrollo de productos medicinales y terapéuticos. Dichos productos buscan satisfacer la demanda de tratamientos alternativos para enfermedades crónico-degenerativas, genéticas y neuropsiquiátricas.

El proceso de extracción de cannabinoides puede llevarse a cabo de diversas formas. En el presente documento se discuten algunas de las técnicas de extracción más ampliamente reportadas, analizando sus principios de operación, los parámetros clave del proceso, y una evaluación comparativa de sus ventajas y limitaciones.

Palabras clave: Cannabinoides, Cannabidiol, Aplicaciones terapéuticas, Extracción, Cáñamo.

Abstract

Hemp (Cannabis sativa L.) is a plant that is composed of bioactive substances called cannabinoids. According to cientific reports, more than a hundred cannabinoids have been identified, including cannabidiol (CBD), cannabigerol (CBG), cannabinol (CBN) and cannabichromene (CBC), as the most representative of them.

Currently, cannabinoid research has become increasingly important, as these bioactive compounds have been shown to possess properties that can be harnessed in the development of medicinal and therapeutic products. These products aim to meet the demand for alternative treatments for chronic- degenerative, genetic, and neuropsychiatric conditions.

The cannabinoid extraction process can be carried out in diverse ways. This document discusses some of the most used techniques, describing the methodology, the equipment required, and finally, their advantages and disadvantages.

Keywords: Cannabinoids, Cannabidiol, Therapeutic Applications, Extraction, Hemp.

INTRODUCTION

The hemp plant (*Cannabis sativa* L.), or simply Hemp, is widely known for its bioactive compounds. These substances, called cannabinoids, are responsible for the various effects the plant may offer. Among them, cannabindiol (CBD), cannabigerol (CBG), cannabinol (CBN), and cannabichromene (CBC) are the most representative cannabinoids (Zekič & Križman, 2020). Hemp is usually referred to as the cannabis plant that does not contain psychoactive compounds. In contrast, "marijuana" refers to cannabis that does contain these types of substances (Sandiego-Villaverde, 2020), such as tetrahydrocannabinol (THC), which is the psychotropic compound with the highest presence in the plant responsible for its narcotic effects (Protti, 2019) and properties for recreational use (Fiorito et al., 2024; Tiago et al., 2022; Valizadehderakhshan, 2021).

To quantitatively determine whether a plant is Hemp or marijuana, its characterization is required (Sandiego-Villaverde, P., 2020). According to the General Health Law in Mexico, the percentage of tetrahydrocannabinol (THC) allowed in dry weight is 1 %. A difference from the laws of several European countries, which indicate that the use of cannabis with 0.2 % THC by weight is legal for industrial use (Correia, Ahmad, & Quintas, 2023; Baldino, Scognamiglio & Reverchón, 2020; Hartsel et al., 2016).

To classify cannabis, researchers categorize the plant into distinct chemotypes. There are several types of cannabis; type I and type II refer to the plant that contains more than 5 % THC, which is called drug-type, and type III is the plant that contains a maximum of 0.3 %. THC and higher levels of CBD, which is called fiber-type (Fiorito et al., 2022). Typically, drug-type plants have THC and its carboxylated form (THCA) as their most abundant cannabinoids. Thus, fiber-type plants contain CBD and CBG, as well as their carboxylated forms (CBDA and CBGA), which are their most abundant cannabinoids (Brighenti et al., 2017). The cannabis plant has been gaining significant importance due to the pharmacological potential displayed by some of the main cannabinoids present in the plant. For this reason, it is of great interest to delve deeper into the different analytical techniques used for both the extraction and identification of the most important constituents present (Sandiego-Villaverde, 2020).

The legality of the cannabis market has been in transition in recent years, with the trade of some of the substances that make up the cannabis plant becoming legal. Thanks to this, cannabinoid extraction methods and the development of new products have become focal points (Lazarjani et al., 2021). For pharmaceutical and food applications, the extraction and separation of the active components, along with the combination of identified cannabinoids, are critical steps that must be explored (Fathordoobady et al., 2019). This legal landscape has been a key driver of interest in the plant's therapeutic potential. Consequently, research into these properties is essential, as it will provide the scientific evidence needed to establish the necessary regulatory frameworks.

Cannabinoids present diverse bioactive profiles with applications from analgesia in arthritis and chronic pain (Protti et al., 2019) to therapies for clinical depression, anxiety, and oncology care. In particular, the growing interest in non-psychoactive cannabinoids has increased the need for efficient, direct extraction methodologies (Lago-Fernandez et al., 2017; Pisanti et al., 2017; Moreno et al., 2020) to leverage the properties of cannabinoids. These methodologies involve extracting cannabinoids, which are done in various ways. There are, for example, innovative methodologies, such as supercritical fluid extraction, as well as classic methodologies, such as dynamic maceration. These methodologies have recently been studied, yielding various results. The objective of this article is to analyze and evaluate different extraction methods, comparing their strengths and areas for improvement when implemented.

CANNABINOIDS

The *Cannabis sativa* L. plant contains bioactive compounds, including terpenes, alkaloids (Sánchez Guevara, 2023), esters, pigments, flavonoids (Sandiego-Villaverde, 2020), polyphenols, phytosterols, tocopherols, fatty acids, and specifically, cannabinoids, defined as an atypical category of secondary terpene-phenolic metabolites (Kornpointner et al., 2021; Lu et al., 2023).

Cannabinoids are the hallmark of the cannabis plant (Sandiego-Villaverde, 2020) and the most valuable compounds in terms of biological activity (Sainz Martinez et al., 2023). Cannabinoids are the most important constituents found in the plant, specifically in the glandular trichomes of unfertilized female inflorescences (Russo, Plumb, & Whiteley, 2021). Their content within the plant depends on biotic factors, including genotype and environmental factors such as light, temperature, photoperiod, and nutrient availability. It is important to mention that cannabinoids are not evenly distributed throughout the plant. Cannabinoids are found mainly in trichomes and, to a lesser extent, in leaves (Kornpointner et al., 2021).

Among the cannabinoids, Δ9-THC stands out as the most important psychoactive compound (González et al., 2002; Monsalve-Maestro & Gomar-Sancho, 2000), and CBD, which has diverse properties devoid of

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psychoactive properties (Leyva-Gutierrez, Munafo & Wang, 2020), which presents a great advantage for clinical applications and recurrent treatments (Sánchez Guevara, 2023). These cannabinoids, CBD and THC, are the most abundant in the cannabis plant (Fernández-Ruiz et al., 2013; Pandopulos et al., 2020; Martinez et al., 2022), and of them, CBD is the dominant cannabinoid in industrial Hemp (Drinić, 2021).

An important characteristic for identifying cannabinoids lies in the number of atoms in their main chain. Cannabinoids in their neutral form have a skeleton of 21 carbon atoms. The type or subcategory to which they belong depends on their constituents. In the living cannabis plant, cannabinoids are found in their carboxylated form (Meehan-Atrash et al., 2021; Ramirez, Fanovich & Churio, 2019), that is, they have an easily removable carboxyl group. Decarboxylation occurs naturally (Meija et al., 2022) and can be induced by exposure to light, air, and/or temperature (Perrotin-Brunel, 2011). These factors have also been shown to influence the production of secondary metabolites in the cannabis plant (Lazarjani et al., 2021).

Types of cannabinoids

Until 2020, 500 natural compounds had been identified within the cannabis plant (Lu et al., 2023), of which more than 100 are cannabinoids (Teräsvalli, 2020), 42 phenolic compounds, 34 flavonoids, 120 terpenes (Hartsel et al., 2016), and 2 alkaloids (Sainz Martinez et al., 2023).

Cannabinoids have been classified into ten different subcategories, namely: cannabidiol (CBD), cannabigerol (CBG), cannabichromene (CBC), cannabicyclol (CBL), cannabielsoin (CBE), cannabinol (CBN), cannabinodiol (CBND), cannabitriol (CBT), Δ8-THC, Δ9-THC, and others (Leyva-Gutierrez et al., 2020). In terms of cannabinoid biosynthesis, cannabigerolic acid (CBGA) is the main precursor of tetrahydrocannabinolic acid (THCA) and cannabidiolic acid (CBDA), which, under high temperatures, both degrade to their decarboxylated forms, THC and CBD, respectively (De Vita et al., 2020; Maayah et. al., 2020; Takahara, Ferdaoussi, & Dyck, 2020).

Physicochemical properties of cannabinoids

Cannabinoids are thermolabile, meaning they are affected by temperature. Cannabinoids are sensitive to oxygen and ultraviolet radiation, which can lead to oxidative degradation (Sandiego-Villaverde, 2020), and they also have hydrophobic properties, making them lipid-soluble (González et al., 2002). CBD has relatively low toxicity (Attard et al., 2018), making it suitable for medical applications; it is used in isolation or in combination with other cannabinoids (Sainz Martinez et al., 2023).

The UV absorption and luminescence properties of cannabinoids were evaluated in ethanol, despite the inherent difficulties in assessing photochemical changes in these molecules. The absorption bands of Δ9-THC, Δ8-THC, CBD, CBG, CBC, and CBN span 272-285 nm (Ramirez et al., 2019).

The structured phosphorescence bands range from 450 to 550 nm and can be detected at 77 K in 100 % ethanol solutions. These emissions have a lifetime of 1.5–2.0 s (Ramirez et al., 2019).

Medicinal and therapeutic applications of cannabinoids

Despite its long-standing controversy, the hemp plant is now recognized for its medicinal and therapeutic uses, including the treatment of various human diseases. The medicinal properties of cannabis-based products have long been known in medicine (Azmir et al., 2013). However, the potential use of these products and substances is limited by their narcotic nature (Szalata et al., 2022).

CBD and its carboxylated form, cannabidiolic acid (CBDA), have been shown to exert modulating effects on the human endocannabinoid system; because its sedative properties (Sánchez Guevara, 2023), analgesic (Leza & Lorenzo, 2000), antiepileptics, anti-inflammatories, anti-proliferative, antipsychotics (Vági et al., 2020), antispasmodics (Sainz Martinez et al., 2023), anxiolytics (Duminy et al., 2024), antibiotics (Brighenti et al., 2017), neuroprotectors (Drinić et al., 2021) and anticonvulsants (Leza & Lorenzo, 2000).

The most investigated cannabinoids within the cannabis plant, for their therapeutic properties, are CBD and THC (Teräsvalli, 2020). Cannabinoids have shown excellent therapeutic potential, as they can alleviate nausea (Duminy et al., 2024) in patients undergoing chemotherapy (Lorenzo & Leza, 2000). Cannabinoids can stimulate appetite in patients diagnosed with HIV (Perrotin-Brunel, 2011). The diseases treated with cannabinoids are Alzheimer's (Attard et al., 2018), Parkinson's, have also shown potential in the control of Tourette syndrome, migraine, neurosis (Hardisson et al., 2002), epilepsy (Namdar et al., 2018), glaucoma (Berrendero, 2002), schizophrenia (Sainz Martinez et al., 2023) depression (Vági et al., 2020), bipolarity and general pain (Duminy et al., 2024), as well as chronic pain (Sainz Martinez et al., 2023). They have also demonstrated beneficial effects as antitumor agents (Berrendero, 2002) in the treatment of diseases.

Beyond CBD, other cannabinoids present in *Cannabis sativa* L. also have relevant therapeutic properties. Cannabigerol (CBG) is a non-psychoactive cannabinoid and a biosynthetic precursor to both THC and CBD. It is considered a potential therapeutic agent due to its interactions with the CB1, CB2, and TRP receptors (which help regulate vital functions such as pain perception, inflammation, appetite, and mood), as well as with α2-adrenoceptors (Nachnani et al., 2021). Cannabichromene (CBC), the third most abundant cannabinoid in the plant, has demonstrated anti-inflammatory, antifungal, and antiviral properties, and has shown neuroprotective potential by promoting neurogenesis in preclinical models (Ferber et al., 2020). Cannabinol (CBN), a mild CB1 and CB2 agonist formed by the oxidative degradation of THC, has been associated with sedative, antibiotic, and appetite-stimulating effects and has shown potential to delay the progression of neurodegenerative diseases such as amyotrophic lateral sclerosis (Correia et al., 2023).

The antioxidant properties are also of interest; cannabinoids have demonstrated the capacity to neutralize reactive oxygen species (ROS). In particular, CBD has been shown to exhibit antioxidant capacity comparable to that of vitamins C and E, acting through mechanisms including inhibition of lipid peroxidation and modulation of the NRF2 pathway (Atalay et al., 2019). Likewise, it has been reported that CBG reduces NOX-mediated ROS production in cells exposed to oxidative stress, while CBC decreases nitric oxide production, contributing to its anti-inflammatory and cytoprotective effects (Nachnani et al., 2021). These antioxidant properties are particularly relevant in neurodegenerative and inflammatory diseases, where oxidative stress plays a central role

It is worth noting that the therapeutic effects of cannabinoids are not solely due to individual compounds in isolation, but also to their interactions with terpenes and other plant components. This can be seen in the therapeutic benefits of full-spectrum cannabis extracts (Ferber et al., 2020). To effectively harness these synergistic benefits, it is crucial to employ extraction methods that offer high selectivity and yield. The following sections provide a comparative analysis of current methodologies, discussing their physicochemical principles and the operational variables.

CANNABINOID EXTRACTION

The extraction of cannabinoids from plant inflorescences has increased in popularity due to their therapeutic effects, medicinal benefits, and potential for pain management (Qamar et al., 2022). However, not all extraction methods are equally suitable for every application: the choice of methodology directly determines the purity, yield, and integrity of the final extract. Furthermore, there is an urgent need for green technologies; the production of energy and resources has led to a new trend toward the valorization of Hemp and its derived products for different applications (Mastellone et al., 2024).

Cannabis extractions can be used to concentrate compounds for product development. The most important parameters to consider in cannabis extraction are particle size, size distribution, temperature, agitation, and extraction time. Extraction types include solvent-based, solvent-free, and alternative methods (Lazarjani et al., 2021).

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Cannabinoid extraction techniques

The extraction of products of interest from plant matter has been carried out using various techniques to preserve their biological and pharmaceutical properties while achieving high extraction yields (Baldino et al., 2020).

The development of feasible, legitimate, and cost-effective technologies is an important step that must be considered before industrial-scale cannabinoid production. The growing interest in non-psychoactive compounds, such as CBD (Moreno et al., 2020) and CBG, and their therapeutic potential (Monsalve-Maestro & Gomar-Sancho, 2000), along with their pharmacological potential, has allowed the development of efficient extraction methods for cannabinoids (Szalata et al., 2022). For the development of pharmacological potential, the quantities of pure CBD and CBG must be abundant. To achieve this, it is necessary to develop efficient extraction methods (Perrotin-Brunel, 2011). There are different methods for extracting CBD-rich cannabis resins from the plant (Teräsvalli, 2020). These include novel methodologies such as supercritical fluid extraction and pressurized liquid extraction; there are also more conventional and safer methodologies such as organic solvent extraction, deep eutectic solvent extraction, Soxhlet extraction, dynamic maceration extraction, water extraction, and even alternative extractions such as microwave- or ultrasound-assisted extractions (Nuapia et al., 2020).

The choice of extraction method must preserve the aroma, flavor, and purity of the active ingredient, while ensuring the safety of the solvents and reagents used. Clearly, the safety of the reagents will ensure an optimal product for consumption. Extraction efficiency also depends on parameters such as extraction temperature and time, as well as the solvent ratio (Sánchez Guevara, 2023). In general, the most appropriate methodology for obtaining certain medicinal preparations should be selected based on the characteristics of the desired product (Ramirez et al., 2019).

Each of the methods described has its advantages and disadvantages, which must be analyzed and considered, as each will extract different compounds. Choosing the right method for extracting cannabinoids can be complicated by the many variables to consider, such as solvent properties, temperature, pressure, and time. Other factors to consider when choosing a solvent include environmental safety, toxicity, and cost (Teräsvalli, 2020).

The following subsections describe the most reported extraction methods, discussing their operating principles, critical process variables, and the advantages or limitations observed.

Supercritical Fluid Extraction

Recently, supercritical fluid extraction (SFE) has emerged as one of the most widely adopted methods for obtaining high-purity cannabinoid extracts (Baldino et al., 2020). SFE is based on the extraction of analytes from a solid sample using a fluid under supercritical conditions, where the distinction between liquid and gas does not exist (Duarte et al., 2014). SFE is a fast, efficient, and clean methodology that allows for high yields, productivity, and selectivity in the extraction of bioactive compounds (Duarte et al., 2014). This methodology is one of the most popular, using supercritical carbon dioxide ($scCO_2$) and other solvents (Teräsvalli, 2020). SFE has been used to extract bioactive compounds and essential oils on a pilot scale (Qamar et al., 2022).

Supercritical carbon dioxide is the most widely used solvent for this type of extraction (Ramirez et al., 2019), as under supercritical conditions CO_2 behaves as a non-polar solvent, which is necessary for extraction. CO_2 is used for several reasons, one of the most important being that its supercritical conditions are relatively easy to achieve (31.06 °C and 73.83 bar) (Lazarjani et al., 2021), although this solvent is also chosen for its characteristics: it is non-flammable, non-toxic, relatively inert, renewable, easy to remove, abundant, and relatively low-cost (Attard et al., 2018). Compared to water, its supercritical conditions are 374 °C and 221 bar. At this temperature, the cannabinoids of interest are degraded. Therefore, water is ruled out as a solvent.

Designing a supercritical fluid extraction (SFE) system requires a comprehensive evaluation of key factors, including processing time, cost-effectiveness, experimental feasibility, and selectivity for target compounds such as terpenes, flavonoids, and cannabinoids (Qamar et al., 2022). Although supercritical fluid extraction (SFE) achieves higher yields, its industrial

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implementation is limited due to high investment costs and the need for specialized operational expertise (Sánchez Guevara, 2023). For this reason, process optimization must focus on operating parameters such as temperature, extraction time, and the addition of co-solvents, which determine the balance between yield and selectivity. For example, when $scCO_2$ is used at a temperature of 328 °K, an increase in pressure from 17 to 34 MPa results in a nearly linear increase in extraction yield, reaching up to 0.185 g of extract per gram of cannabis—a value 40 % higher than the 0.132 g/g obtained through conventional ethanol extraction (Lazarjani et al., 2021). However, very high pressures can also promote the undesirable co-extraction of waxes and pigments, thereby affecting the technique's selectivity (Moreno et al., 2020). However, pressure is not an isolated parameter, as it typically interacts non-linearly with temperature; at high pressures—above 20 MPa—an increase in temperature improves the solubility of THC in $scCO_2$, whereas at low pressures the opposite effect is observed (Perrotin-Brunel, 2011). Therefore, it is necessary to perform simultaneous parametric optimizations rather than isolated ones.

Pressurized Liquid Extraction (PLE)

Pressurized liquid extraction (PLE) represents a technically refined alternative to SFE, sharing some of its operating principles while offering greater flexibility in solvent selection (Duarte et al., 2014). This method, also known as accelerated solvent extraction, is documented as an efficient and rapid method for extracting compounds.

This process is highly comparable to supercritical fluid extraction (SFE), as both use high temperatures and pressures to perform the extraction. However, the main difference between the methods is that the solvent remains in a liquid state throughout the process (Baldino et al., 2020). Pressurized liquid extraction (PLE) is one of the most promising techniques for extracting bioactive compounds, in which solvents are used near the supercritical region. In this approach, high temperatures promote mass transfer by increasing solute solubility while reducing viscosity and surface tension, while high pressure keeps the solvent below its boiling point, allowing for greater solvent penetration into the sample (Amador-Luna et al., 2023). Typically, the temperatures at which this process works range from 50 to 200 ℃ (Amador-Luna et al., 2023) with a pressure range of 50 to 300 psi (Duarte et al., 2014), for a time of 5 to 10 minutes in solid or semi-solid matrices (Duarte et al., 2014). However, other methodologies suggest operating at pressures of 1600 psi, with temperatures of 80 to 160 ℃ for 3 minutes (Lewis-Bakker, 2019).

In addition to temperature, time, and pressure, another factor that significantly affects extraction selectivity is the solvent. Currently, the solvents used are those considered environmentally friendly, such as water and ethanol, or a mixture of both, to reduce the negative impact that organic solvents have on the environment (Amador-Luna et al., 2023).

Extraction with pressurized liquids using water as the solvent is an alternative technique that is considered green. At high pressures, water exhibits the same solvation properties as methanol and ethanol. Extraction with this solvent has been used to obtain phenolic compounds (Nuapia et al., 2020).

Water Extraction

There are several ways to extract cannabinoids with water as a solvent, either by dynamic maceration or by pressurized liquids. For example, dynamic water maceration is a solvent-free extraction method that involves immersing the sample in cold water. The plant is then shaken to separate the trichomes and then filtered. The resulting product is a 50–70 % cannabinoid concentrate. Subsequently, the decarboxylation process is carried out with pressurized hot water to obtain the extract with a high CBD content while simultaneously reducing the THC and CBN content (Szalata et al., 2022). This methodology is usually suitable for most active components of herbal species, but alternative methods are necessary for cannabis components due to their very low solubility in polar solvents (Ramirez et al., 2019).

Extraction Using Organic Solvents

Organic solvent extraction is one of the most widely used approaches for obtaining cannabinoids at both laboratory and industrial scale, owing to its technical simplicity and relatively low equipment cost (Szalata et al., 2022). The method is based on the principle of like dissolves like: since cannabinoids are lipophilic compounds, non-polar or moderately polar solvents such as ethanol, hexane,

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acetone, and methanol are required for efficient extraction (Ramirez et al., 2019). Among these solvents, ethanol is among the most commonly used due to its favorable solubility for certain cannabinoids, including cannabidiol, its relatively low toxicity, and its safety for use in food and pharmaceutical applications (Teräsvalli, 2020).

Some of the main advantages of this technique are its accessibility, ease of scaling, and the wide availability of equipment. However, this technique also has certain significant limitations, as non-polar solvents tend to co-extract undesirable compounds, such as chlorophyll, waxes, and lipids, which requires additional purification steps (Baldino et al., 2020). Furthermore, many organic solvents are considered hazardous materials due to their flammability and toxicity (Sainz Martinez et al., 2023). Furthermore, most organic solvents are classified as hazardous materials due to their flammability and toxicity, which necessitates safety and environmental measures (Sainz Martinez et al., 2023). Additionally, the presence of residual solvents in the final extract may pose a risk in products intended for human consumption.

Extraction with Deep Eutectic Solvents

Over the last decade, a new class of solvents, deep eutectic solvents (DES), has emerged. When these solvents are mixed in the appropriate molar ratio, they have much lower melting points than any of the individual components, resulting in a eutectic solvent (Sandiego-Villaverde, 2020). DESs are a new class of environmentally friendly solvents that have received significant attention as extraction media. For this reason, DES are attractive candidates as solvents due to their properties, such as storage, low cost, nonflammability, and high solvation capacity.

Soxhlet Extraction

Soxhlet extraction is an effective method for extracting oils from plants and has been used to extract organic compounds from more than 100 different types of biomass.

The method operates in continuous solvent cycles, leaving the extract in a chamber and contacting the biomass in the batch process. To maintain a relatively high extraction efficiency, pretreatment of the material, such as grinding, may be required, depending on the sample size.

The Soxhlet apparatus requires significant energy to maintain the distillation and evaporation cycle, which poses severe problems for industrial-scale-up. Aside from this, equipment preparation, fire risk, and inevitable side reactions are reasons why the Soxhlet apparatus fails as the ideal method for cannabis extraction (Lazarjani et al., 2021).

Lewis-Bakker et al. (2019) confirmed that the cannabis extract obtained using this methodology favored the decarboxylation of cannabinoids, thanks to the heating process inherent in the methodology.

Dynamic Maceration Extraction

Dynamic maceration is the most accessible extraction method from a cost and infrastructure standpoint, making it a common choice in small-scale and early-stage research settings (Lazarjani et al., 2021). It is a conventional solid-liquid extraction method that involves immersing the sample in an organic solvent for a specified time and temperature, then agitating. This process is inexpensive and widely used for the production of essential oils and bioactive compounds (Lazarjani et al., 2021). Recently, vegetable oils have been found to be more effective than alcohol for terpene extraction; however, they are difficult to remove.

A study conducted by Fathordoobady et al. (2019) demonstrated no significant difference between organic solvents (n-hexane, acetone, methanol) and ethanol when used for the extraction of neutral cannabinoids.

Brighenti et al. (2017) found that dynamic maceration with ethanol as the solvent for 45 minutes at room temperature was a more suitable technique for cannabinoid extraction than UAE and MAE.

Microwave-Assisted Extraction

Microwave-assisted extraction (MAE) has gained attention as an energy-efficient alternative to conventional heating methods, offering significantly reduced extraction times while maintaining competitive yields (Azmir et al., 2013). The technique uses electromagnetic energy at frequencies between 300 MHz and 300 GHz to generate rapid, localized heating through ionic conduction and dipolar rotation, which disrupts cell walls and releases their contents into the liquid phase (Lazarjani et al., 2021). This mechanism facilitates the decarboxylation of cannabinoid acids—especially the conversion of CBDA to CBD—because high temperatures are achieved during treatment (Sánchez Guevara, 2023). Temperature is one of the variables that most significantly affects cannabinoid extraction yields; studies using response surface methodology have identified optimal extraction temperatures in the range of 100 to 109 °C, depending on the matrix and the type of cannabinoid to be obtained (Shi et al., 2017). Other variables that must be controlled and optimized include microwave power and extraction time. In a comparative study, it was observed that a power of 375 W, at a temperature of 109°C, with an extraction time of 30 minutes, and using methanol produced a higher total cannabinoid content (6.09 µg/g) compared to Soxhlet extraction (5.81 µg/g), SFE (3.61 µg/g), and UAE (3.73 µg/g) (Shi et al., 2017). Another important factor is the sample-to-solvent ratio, where it has been determined that a 1:14 ratio maximizes cannabinoid recovery (Wiredu Addo et al., 2022). The solvent also influences yield, as it must efficiently absorb microwave energy and dissolve the compounds of interest; the most commonly used solvents are methanol and ethanol (Shi et al., 2017).

Compared to other techniques, MAE is efficient, fast, and cost-effective; however, high temperatures can cause partial degradation of thermolabile terpenes and cannabinoids (Lazarjani et al., 2021).

Ultrasound-Assisted Extraction

Ultrasound-assisted extraction (UAE) exploits acoustic cavitation to enhance mass transfer between the solvent and plant matrix, resulting in improved extraction kinetics compared to static maceration methods (Duarte et al., 2014). The range of sound waves ranges from 20 to 100 kHz. This allows solvent penetration into the sample to extract products of interest.

Factors such as sample moisture, particle size, grinding degree, solvent, temperature, pressure, and sonication time must be considered and manipulated to achieve efficient extraction (Azmir et al., 2013).

The main disadvantage of this methodology is related to the scale-up process and the use of organic solvents (Baldino et al., 2020).

Ultrasound-assisted extraction is a very rapid and inexpensive technique compared to other techniques; however, its efficiency depends on the nature of the analytes to be extracted. De Vita et al. (2020) found the conditions for optimal extraction yield using this methodology, using ethanol as a solvent for 50 minutes at 60 °C.

Table 1 summarizes the main extraction methods discussed in this review, comparing their key operating conditions, reported cannabinoid yields, and principal advantages and limitations.

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Table 1. Comparison of cannabinoid extraction methods

Method	Key conditions	Reported yield	Advantages	Limitations
Supercritical Fluid Extraction (SFE)	17–34 MPa, 40–60°C, CO_2 ± ethanol co-solvent	Up to 0.185 g/g plant material	Solvent-free product; mild temperatures; selective; environmentally favorable	High equipment cost; requires technical expertise; lower yield for polar cannabinoids without co-solvent
Pressurized Liquid Extraction (PLE)	50–300 psi, 50–200°C, 3–10 min	Comparable to SFE	Fast; flexible solvent selection; high penetration into matrix	High energy consumption; solvent residues possible
Organic Solvent Extraction	Room temperature, ethanol or hexane, variable time	Moderate–high	Simple; low equipment cost; scalable	Co-extracts chlorophyll and waxes; residual solvent risk; additional purification required
Deep Eutectic Solvent Extraction (DES)	Variable, ambient to moderate temperatures	Limited data available	Green chemistry approach; low toxicity; zero flammability	Limited data for cannabinoids; not yet scalable
Soxhlet Extraction	Solvent boiling point, continuous cycles	Moderate	Widely available equipment; promotes decarboxylation	High energy use; long extraction time; fire risk; poor scale-up
Dynamic Maceration	Room temperature, organic solvent, 45 min	Moderate	Very low cost; simple equipment; accessible	Low efficiency; requires long contact times; co-extraction of undesirables
Water Extraction	Cold water (maceration) or pressurized hot water	50–70% cannabinoid concentrate	Solvent-free; green approach	Very low solubility of cannabinoids in water; limited applicability
Microwave-Assisted Extraction (MAE)	375 W, 109°C, 30 min, methanol	6.09 µg/g (highest among compared methods)	Fast; low solvent consumption; promotes decarboxylation	Scale-up limitations; risk of terpene degradation at high temperatures
Ultrasound-Assisted Extraction (UAE)	20–100 kHz, ethanol, 50 min, 60°C	Competitive with MAE	Rapid; inexpensive; improves mass transfer	Difficult to scale; requires organic solvents

Sources: Lazarjani et al. (2021); Shi et al. (2017); Wiredu Addo et al. (2022); Baldino et al. (2020); Teräsvalli (2020); Sainz Martinez et al. (2023).

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CANNABINOID ANALYSIS

The growing regulatory and commercial interest associated with *Cannabis sativa* L. has increased the need for reliable analytical methodologies capable of determining the chemical composition of products derived from this species. These analyses are essential for verifying that cannabinoid concentrations fall within the limits established by current regulations, as well as for ensuring the quality, safety, and consistency of products intended for therapeutic, food, or industrial applications (Aubin et al., 2018).

Among the available analytical techniques, high-performance liquid chromatography (HPLC) is one of the most widely used for the identification and quantification of cannabinoids present in both plant material and *Cannabis* extracts. Its main advantage lies in the fact that it allows cannabinoids to be analyzed without requiring a volatilization step, thereby avoiding thermal transformation of the compounds. This makes it possible to simultaneously determine acidic forms together with their corresponding decarboxylated neutral forms (Meija et al., 2022). This characteristic is particularly relevant when a complete cannabinoid profile is required.

The most commonly used detection systems in HPLC are ultraviolet (UV) and diode-array detectors (DAD), due to their availability, ease of operation, and adequate sensitivity for analysis. The recent incorporation of HPLC-UV-based methods into regulatory documents evidences the consolidation of this technique as a reference method for cannabinoid analysis (Mochi et al., 2024). However, one of its main limitations is that UV detection depends on the spectroscopic properties of the analyzed compounds, which can pose difficulties for identifying cannabinoids at very low concentrations or distinguishing compounds with similar absorption spectra.

Another widely used technique is gas chromatography (GC), particularly when combined with mass spectrometry (GC-MS). Unlike HPLC, this methodology requires sample vaporization prior to chromatographic separation. Due to the high temperatures involved, acidic cannabinoids may undergo decarboxylation during the analytical process, rendering acidic and neutral forms indistinguishable (Meija et al., 2022). Additionally, due to the low volatility and thermal stability of some cannabinoids, chemical derivatization is often required prior to analysis, which increases experimental complexity, sample preparation time, and associated costs.

Despite these limitations, GC-MS remains a technique of interest for specific applications, primarily in the characterization of volatile compounds associated with the plant's terpene profile. Its main strength relates to its ability to provide structural information through mass spectral comparison, although its application for cannabinoid quantification is more limited compared to liquid chromatography-based techniques (Zekič & Križman, 2020).

Mass spectrometry as a detection system coupled to liquid chromatography (LC-MS) has expanded the analytical capabilities available for cannabinoid research, enabling the detection of trace-level compounds and the analysis of complex matrices (Mochi et al., 2024). In particular, liquid chromatography coupled to tandem mass spectrometry (LC-MS/MS) improves analytical reliability, making this technique widely used for confirmatory analysis, quantification of minor cannabinoids, and determination of metabolites in biological samples (Rosendo et al., 2023).

Additionally, high-resolution mass spectrometry platforms, such as LC-TOF-MS, have further expanded analytical possibilities by enabling non-targeted chemical profiling and tentative identification of unknown cannabinoid-related compounds. However, their higher acquisition costs, the need for specialized personnel, and the complexity of data processing are among their main limitations.

Taken together, chromatographic techniques offer different advantages depending on the analytical objective. While HPLC-UV stands out for its simplicity, accessibility, and utility for routine potency control, LC-MS-based methods offer greater identification and quantification capabilities when more detailed characterization is required. Therefore, the selection of the analytical technique must consider factors such as sample nature, required sensitivity level, analytical purpose, and available resources.

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CONCLUSIONS

Cannabinoids are terpene-phenolic secondary metabolites produced by *Cannabis sativa* L. that have attracted considerable scientific and clinical interest due to their broad therapeutic potential. Beyond the extensively studied CBD and Δ9-THC, minor cannabinoids such as CBG, CBC, and CBN have demonstrated pharmacological activities, including anti-inflammatory, antioxidant, neuroprotective, and antibiotic effects, mediated by interactions with the endocannabinoid system and related signaling pathways. The growing body of evidence supporting the therapeutic value of these compounds, particularly in the context of neurodegenerative diseases, epilepsy, chronic pain, and oxidative stress-related conditions, reinforces the need for reliable and efficient methods to obtain them from plant material.

The extraction of cannabinoids from *Cannabis sativa* L. can be accomplished through a wide range of methodologies, each with distinct operating principles, performance characteristics, and practical constraints. Among the techniques reviewed, supercritical fluid extraction with CO_2 stands out for producing solvent-free extracts of high purity, though its high equipment cost and operational complexity limit its accessibility. Microwave-assisted extraction has shown the highest cannabinoid yields in comparative studies, with the added advantage of promoting in-process decarboxylation, while organic solvent extraction, particularly with ethanol, remains the most widely adopted approach due to its simplicity and scalability, though it requires additional purification steps to remove co-extracted impurities. Emerging approaches such as deep eutectic solvents offer promising green chemistry alternatives, though their application to cannabinoid extraction remains insufficiently characterized.

The selection of an appropriate analytical method is equally critical to the integrity of cannabinoid research and quality control. HPLC-UV has established itself as the standard platform for routine potency testing, given its ability to quantify both acidic and neutral cannabinoid forms without derivatization. However, LC-MS and LC-MS/MS methods provide superior sensitivity and selectivity for the characterization of minor cannabinoids and metabolites in complex matrices, and are increasingly regarded as the gold standard for pharmaceutical-grade analysis.

Future research should focus on the systematic optimization of extraction parameters, particularly pressure, co-solvent concentration, and plant material selection, across methods, as well as on the comparative evaluation of full-spectrum versus isolated cannabinoid preparations in clinical settings. The integration of green extraction technologies with high-resolution analytical platforms represents a promising approach to advancing both scientific understanding and the sustainable production of therapeutically relevant cannabinoids.

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