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ADVANCEMENT IN CANNABIS EXTACTION USING DIFFERENT TECHNIQUES

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ABSTRACT

Overview

One of the first oleaginous plants to be cultivated by humans for its non-edible fiber content and potential medical uses is hemp, often known as Cannabis sativa L. (Peters & Nahas, 1999) Carolus Linnaeus, the inventor of modern taxonomy, was the first person to identify the plant as Cannabis sativa. In recognition of his accomplishments, the letter "L" stands for Linnaeus. Linnaeus was the creator of the contemporary classification system (Moroni, Salomón, & O'Leary, 2018). It is commonly recognized that this plant is the primary source of several cannabinoids, such as cannabibigerol (CBG), cannabichromene (CBC), tetrahydrocannabinol (THC), and cannabinol (CBN). Strong potential against inflammation, depression, nausea, epilepsy, and other effects of therapeutic importance has been demonstrated by cannabinoids (Appendino et al., 2008; Atalay, Jarocka-Karpowicz, & Skrzydlewska, 2019; Mechoulam & Parker, 2013). Cannabis has been used for medicinal purposes in China for about 5,000 years (Touw, 1981). As far as the authors are aware, the

first scholarly study on the extraction of hemp's bioactive components was carried out by (Yamauchi, Shoyama, Matsuo, & Nishioka, 1968).

KEYWORDS: Hemp, Extraction, Cannabis, SCFE.

Drug enforcement laws forbade the development and production of hemp products (Johnson, 2014), leaving Pakistan well behind more than thirty other nations that considered the plant an agricultural commodity (Grotenhermen, Karus, & Lohmeyer, 1998). Due to their exceptional medicinal benefits as well as the financial advantages they provided to nearby communities, these products eventually gained international acceptance and were made legal in many nations. In June 2018, the first legal product with a medicinal focus hit the market, opening up a massive market for CBD (Aiello et al., 2016; Koturbash & MacKay, 2020). However, in the majority of US states as well as the EU (Rat, 2000), the top limit of 0.3 wt% (dry biomass weight) still serves as a crucial barrier between cannabis flower and drug due to the psychoactive effects of THC(Dussy, Hamberg, Luginbühl, Schwerzmann, & Briellmann, 2005; Johnson, 2014). The hemp market in the United States was estimated by the Congress to be worth approximately 700 million USD in 2017 (Johnson, 2014). However, According to Arc vision market research (Hong, Sideris, Waldman, Stauffer, & Wu, 2024), with recent openings, this figure is expected to reach 20 billion USD by 2024, boosting global spending to more over 40 billion USD. Yet before standards for industrial-scale manufacturing can be established, there are a number of viable technologies that must be developed that are both legal and profitable. Coping with a live plant whose development is uneven and contentious as a result of varying soil fertility levels (Adesina, Bhowmik, Sharma, & Shahbazi, 2020).

Determining the ideal harvesting circumstances for getting the highest possible THC content is further complicated by local considerations. On the other hand, developing large-scale extraction techniques that are both successful and energy efficient is essential to overcoming the difficulties.

Due to its potential for use in industry (Karche, 2019), decoration(Hesami, Pepe, Baiton, & Jones, 2023), medicine, and recreation (Hesami et al., 2020), cannabis has been grown extensively. Cannabis plants are classified according to the concentration of Δ9-tetrahydrocannabinol (THC), one of the most significant phytocannabinoids, from regulatory and application standpoints (Kovalchuk et al., 2020). If a plant's dried flower contains less than 0.3% THC (the exact percentage varies by nation), it is often categorized and controlled as industrial hemp; if it contains more than this threshold, it is classified and regulated as a drug type (Hesami et al., 2020). Furthermore, considering the widespread use of Cannabis sativa for human consumption and animal feed, research on the plant's phytochemical profile has recently shown to be helpful for traceability purposes in addition to determining the plant's potential toxicity (Amendola et al., 2021; Bengyella, Kuddus, Mukherjee, Fonmboh, & Kaminski, 2022; Nava et al., 2022).

CBD is not euphoric or psychoactive as THC is. Advocates for CBD oil and related products assert that they may be used to treat ailments including anxiety, depression, autoimmune illnesses, migraines, epilepsy, chronic pain, and inflammation.

Cannabis sativa L. has been recognized as a source of major, therapeutically relevant specialized metabolites for at least 2000 years. Several bioactive compounds have been isolated from various chemo-types.

In order to close these gaps, this review article examines several cannabis extraction techniques, weighing the benefits and drawbacks while examining current developments in the area. Furthermore, it reports on the pretreatment methods that increase the extraction yield in addition to evaluating the acceptability of the used technologies in comparison to other options. The post-extraction advancement that has an effect on the composition of the final product is the last thing that is investigated.

However, a number of heterologous production strategies are being investigated concurrently because of the several degrees of complexity involved in both the commercial growth of cannabis and the extraction of its specific metabolites. This review's objective is to give a current overview of innovative extraction methods.

Nomenclature

According to taxonomy, hemp belongs to Cannabinaceae Family (Valizadehderakhshan, Shahbazi, Kazem-Rostami, Scott Todd, et al., 2021), which is made up of the three subspecies Cannabis Indica, Cannabis Sativa, and Cannabis Ruderalis. Their cannabinoid concentrations, uses, and plant morphology set them apart. The two labels designate various types based on the amount of delta 9-tetrahydrocannabinol (Δ 9-THC). If the amount of delta 9-tetrahydrocannabinol in hemp is less than 0.3%, compared to those in marijuana that are higher than 0.3%, then marijuana will cause psychoactive effects (Aiello et al., 2016). Highgrade hemp fiber and edible hemp oil have long been appealing. Following the development of synthetic fiber and the pharmacological restrictions, hemp was classified as a prohibited substance.

Biological Activity

Research has been done on the antibacterial qualities of the plant and its preparations on hemp grown all over the world(Kreji, 1958). The material has strong antibacterial action against acid-fast bacteria, filamentous fungi, yeast-like fungi, Pseudomous aeruginosa, Proteus vulgar, Gram-negative bacteria of the Coli-typhus group, and a dermatophyte (Turner & Elsohly, 1981; Wasim, Haq, & Ashraf, 1995).

The Background of Cannabis Extraction

The main active and potentially medicinal substances found in the cannabis plant are terpenes and cannabinoids, which are primarily generated in those glandular trichomes. Numerous illnesses, including neurological disorders, movement disorders, metabolic disorders, HIV patients who have anorexia, nausea, and pain after chemotherapy in cancer patients, have been demonstrated to benefit from these substances' therapeutic benefits(Namdar et al., 2019; Romano & Hazekamp, 2013).

The focus of the cannabis business is now on product development and extraction techniques as it transform from the illegal to the legal market. Processed cannabis flowers have long been a well-liked product for smoking and vaping. But as market grows, need for cannabis products with more strength and in a variety of forms. Medicinal and recreational goods are now offered as edibles, drinks, topicals, and vaporizer cartridges. Every product type has unique mix of benefits and drawbacks that may be customized to fulfill specific needs (Blake & Nahtigal, 2019). The extraction and separation of the active ingredients and cannabinoid combinations that have been found are important stages that need to be investigated for use in food and medicinal applications(Fathordoobady, Singh, Kitts, & Pratap Singh, 2019).

The food and pharmaceutical sectors have recently shown a strong interest in isolating bioactive substances. This is because our knowledge of the dynamic nature and potential of many biologically active compounds derived from naturally occurring sources has grown (Azmir et al., 2013). The choice of an appropriate extraction method is essential to the advancement of scientific research on the identification, characterization, and selection of biologically active chemicals (Azmir et al., 2013). Neglecting to choose an appropriate sample preparation technique might compromise any analytical process and lead to undesirable results. But unlike other processes, extraction is not given the same attention or research as other fields. This leaves a vacuum in the literature that has to be filled in further (Smith, 2003). The extraction process is widely used to extract target biologically active compounds from plant matter, but it can be modified to serve a variety of purposes. For example, an increase in the concentration of targeted compound, one can increase the sensitivity and selectivity of bioassays and provide a potent and repeatable sample matrix (Smith, 2003). Compared various extraction techniques for Cannabis sativa L. Seeds and trichomes. Additionally, they looked at a number of factors that influence how cannabinoids convert after extraction (Agarwal, Máthé, Hofmann, & Csóka, 2018).

Depending on the process and materials employed, different extraction techniques will produce extracts with differing levels of quality and content (Blake & Nahtigal, 2019). This evaluation compares traditional and modern techniques while concentrating on different drying and extraction techniques. For instance, it takes longer to extract using traditional techniques like Soxhlet and dynamic maceration, and significant volumes of solvent are needed to finish the extraction process (Agarwal et al., 2018). Modern techniques such as pressurized liquid extraction, supercritical fluid, microwave-assisted, ultrasonic-assisted, and pressurized liquid extraction procedures might be viewed as somewhat more environmentally friendly alternatives to traditional techniques. These methods decrease the amount of time spent on operations, generate a higher-quality extract, and need less synthetic and organic solvents (Azmir et al., 2013). Whole trichomes have been found to be extracted using solventless techniques including water extraction and dry sieving. Use of hydrocarbon extraction techniques can help prevent the addition of undesirable water and colors like chlorophyll. Flavonoids may be extracted using ethanol, and depending on the situation, carbon dioxide can be altered to extract various other chemicals (Blake & Nahtigal, 2019).

When selecting a technique, the product's features need to be taken into account. For short time, cannabinoids can be extracted in neutral or acidic form, depending on the application. Extraction must be finished at room temperature in order to preserve acidic cannabinoids (Citti et al., 2016)[. For the purpose of decarboxylating acidic cannabinoids into neutral form, it is recommended that extraction be performed at high temperatures, yet doing so may cause certain terpenes and minor components to be lost(Valizadehderakhshan, Shahbazi, Kazem-Rostami, Todd, et al., 2021). As a result, by reducing the need for modifications, choosing an adequate extraction process will help subsequent phases of development (Blake & Nahtigal, 2019). This review will examine several techniques for drying and extracting the cannabis plant in order to have a deeper understanding of the processes involved and the potential results.

Drying

Cannabis herb needs to be dried for almost all purposes; nevertheless, like many plants, cannabis is mostly composed of water. Drying is therefore regarded as an essential phase in the creation of new products (Hawes & Cohen, 2015). According to ASTM D8196-18, a standard procedure for determining the water activity (aw) in cannabis flowers, drying the plant not only stops the growth of microorganisms like mold and fungus that would otherwise rot plant tissue, but it also makes it possible to store it for an extended period of time without sacrificing its potency, flavor, medicinal qualities, or effectiveness(Hawes & Cohen, 2015). This is accomplished by keeping the water activity level between 0.55 and 0.65 aw, which reduces the possibility of fungal or mold infection while maintaining the flower's quality (ASTM D8196-18). Drying takes place in a dimly lit, shaded area. The temperature is kept between 18 and 23 degrees, while the humidity is kept between 45 and 55%. To preserve the scent and hue of the flowers, a dark environment is utilized.

Hang drying, another name for air drying

The oldest method of drying cannabis plants after harvest that doesn't call for special equipment is hang- or air-drying (Ross & ElSohly, 1996). When drying plants slowly, they are spread out on screens for drying or hung on a rope in a dark, cool room at temperature between 18 and 25 °C and humidity between 45 and 55% (Hawes & Cohen, 2015). (Ross & ElSohly, 1996) Used four different air-drying processes to see how well each worked to produce the most cannabis products. Following flower harvesting at room temperature (0.291% yield, w/v) (A), the treatments were extracted immediately. (B) Following one week of air drying at room temperature (0.201% yield on on the basis wet material, v/w) (C) and air drying for one week, the treatments were stored in bags made by paper for three months at room temperature (0.131% yield on the basis wet material, v/w) (D). The yield from treatments A through D dropped from 29 to 13%, correspondingly, according to the results of this experiment (Ross & ElSohly, 1996). The physical assorting of buds from the stem required a lot of time to finish the procedure are drawbacks of this approach. Because various sections dry at different speeds, the separation is an important step that if skipped might lead to uneven drying. Consequently, the potential for creating a product with a stronger flavor is a drawback of removing buds from stems. The use of gravity in this process is another drawback. The plant's lowest sections will absorb water from the upper sections, causing the drying process to go more slowly and unevenly. Fans, dehumidifiers, and heaters can be utilized to expedite the process. However, moderate drying yields items with a smoother flavor, whereas quick drying may result in a harsher taste. Additionally, it's thought that hastening the process of drying might keep plant from curing to its full potency (Hawes & Cohen, 2015). (Coffman & Gentner, 1974)Assessed how the drying environment affected the profile of cannabinoids. For 1, 4, 16, and 64 hours, the cannabis hang-dried leaves were held at 65°C, 85°C, and 105 °C to compare the average percentage of total cannabinoid content (fig.1). The findings demonstrated that as time and temperature increased, the proportion of total cannabinoids reduced. More specifically, after 1 hour at 65 °C and 64 hours at 105 °C, the percentage average weight loss of total cannabinoids rose from 7.5 to 11%, respectively.

Drying in the oven

The oven-drying procedure is a quicker direct drying method (Mujumdar, 2006). This procedure can be used in a drying oven with air circulation or without air circulation, a vacuum desiccator, or a vacuum chamber (Hawes & Cohen, 2015). Early research compared the final goods under four different oven settings to show the method' results. At 65, 85, and 105 °C, inflorescences were dried for 1, 4, 16, and 64 hours. Gas chromatography revealed that when temperature and drying time rose following ethanol extraction, the quantity of THC and CBD dropped. Additionally, it was noted that the heat breakdown of THC raised the CBN concentration at 105 °C (Coffman & Gentner, 1974). Since CBN is regarded as a moderate analgesic and less strong psychoactive substance, converting THC to CBN will reduce its therapeutic potential (Citti et al., 2016). Important components may also be lost when employing high heat and heavy drying (Coffman & Gentner, 1974). This claim may be the cause of the dearth of knowledge on oven death in the cannabis sector. A research comparing the ratio of cannabis to by-product generated during vaporization brought this to light. The cannabis material was allowed to dry in a desiccator for five days, and rotary evaporator operating at 40 °C was used to dry the vaporized condensate and smoke condensate that had become trapped in the organic solvent. The strong scent that these methods had created is a sign that terpenoids and other volatile components have been lost(Pomahacova, Van der Kooy, & Verpoorte, 2009).

Curing

The last post-harvest step that enables the cannabis plant to mature to its full potential is curing (Vogel, 2018). (Jin, Jin, & Chen, 2019) Said to be the ideal curing conditions, which are 18 °C and 60% relative humidity for 14 days. The ideal way to cure clipped flowers was suggested to be to store them in a container in a dark cabinet for up to 4 weeks, lifting the lid once a day for about 6 hours (Caplan, 2018; Jin et al., 2019). Enzymes and aerobic bacteria will function best at temperatures between 15 and 21 °C and 45 and 55% humidity, breaking down unwanted rbohydrates and degrading minerals. Curing can extend the shelf life by reducing mold development and reducing the unpleasant scent and burning sensation in the throat while smoking or vaping. Curing is also thought to boost the potency of cannabis since it increases the amount of cannabinoids like THC and CBN. Despite the fact that curing is the one of most important step after harvesting for cannabis plants, there aren't enough scholarly studies in this field.

Techniques of extraction

Target components for product development can be concentrated through the use of cannabis extraction. The yield of cannabis extract can be influenced by several critical factors, including temperature, agitation rate, extraction duration, mean particle size, and size dispersion (Blake & Nahtigal, 2019). In relation to cannabis extraction, solvent-based, conventional, and unconventional extraction techniques are investigated.

Extraction Based on Solvents

A solvent is needed to finish the extraction process in solvent-based extraction techniques as Soxhlet, static and dynamic maceration, ultrasonic aided extraction (UAE), and microwave assisted extraction (MAE). Cannabinoids may be extracted using a wide range of solvents, such as carbon dioxide (CO2), ethanol, propane, butane, hexane, methyl tertbutyl ether, petroleum ether, diethyl ether, and olive oil (Dussy et al., 2005; Lehmann & Brenneisen, 1992; Romano & Hazekamp, 2013; Rovetto & Aieta, 2017). For extraction, gaseous solvents like butane and propane can also be utilized(Raber, Elzinga, & Kaplan, 2015). As gas solvent extractions pass through the sample material, they are either cooled or pressed into a liquid condition from their initial gas phase at room temperature (Rovetto & Aieta, 2017). After gathering the extracted sample, the solvent is expelled (Chan et al., 2017). There are safety risks associated with pressurizing these combustible and perhaps explosive gasses(Jensen, Bertelotti, Greenhalgh, Palmieri, & Maguina, 2015). Furthermore, industrial-grade gases are frequently employed in cannabis extraction processes, and these gases include contaminants that find their way into the extracted cannabis. Furthermore, the solvents themselves could end up in the final extract as a residue(Raber et al., 2015). While choosing a solvent, it's believed that the various solubilities of specific phytochemicals, such as cannabinoids, should be taken into account. Cannabis oil binds to solvents due to its stickiness and viscosity, therefore it's critical to take the solvents' toxicity, affinity, and temperature profile into account (Fathordoobady et al., 2019). It is shown that the solvent of choice has a significant impact on the extraction efficiency of traditional techniques. During the solvent selection procedure, key aspects such as solubility, mass transfer, co-solvent, molecular affinity, environmental safety and toxicity should be taken into account (Azmir et al., 2013). Three categories of solvents are frequently employed to extract cannabis: vegetable fats (oils), low molecular mass organic solvents and supercritical fluid (especially supercritical carbon dioxide), (Reichardt & Welton, 2011).

Carbon dioxide that is supercritical as a solvent (CO2)

Similar to other solvents, CO2, although being a polar gas by nature, reaches a condition known as the supercritical state at specific pressure and temperature. There are no separate liquid and gas phases in a supercritical state. The critical density of CO2 is 0.460 g/cm3, the critical pressure is 7.3mpa, and the critical temperature is 31.06 °C (Raventós, Duarte, & Alarcón, 2002). Supercritical CO2 extracts a wide variety of non-polar solutes, including cannabis, since it functions as non-polar solvent. In contrast, at significantly higher temperatures and pressures of 647 K and 22.1 mpa, highly polar water change to supercritical and serves as non-polar solvent. As a result of its low critical temperature and pressure, CO2 is the preferred solvent. In addition, it is plentiful, non-toxic, non-flammable, inert, and quite inexpensive. Take, for instance, the comparison between the extraction of linalyl acetate from lavender oil using supercritical extraction and traditional steam distillation (Reverchon, Porta, & Senatore, 1995). Compared to 12.1% for traditional steam distillation, 34.7% were obtained using supercritical extraction. The explanation put out was that the linalyl acetate underwent unfavorable hydrolysis to produce linalool and acetic acid due to the increased temperature of the steam distillation process. Consequently, supercritical CO_2 low base temperature is most likely an inherent benefit (Reverchon et al., 1995).

Traditional techniques for extracting

Extraction of Soxhlet

German scientist Franz Ritter Von Soxhlet originally created the extraction technique known as Soxhlet extraction, which is mostly used for lipid extraction. But over time, this process has been widely used for variety of extraction needs, most frequently the extraction of biologically active chemicals from plant material. Additionally, Soxhlet is often used as model for contrasting and developing alternative separation techniques (Azmir et al., 2013).

A little quantity of the dehydrated substance is transferred from a thimble to a distillation flask containing a designated solvent. When the solution reaches the overflow level, the extracted analyte is transferred to the bulk liquid using a siphon that aspirates the solute and discharges it into the distillation flask. Until the entire extraction is done, this process is repeated several times(De Castro & Garcıa-Ayuso, 1998). (Lewis-Bakker, Yang, Vyawahare, & Kotra, 2019) Examined many kinds of organic solvents for the process of extracting cannabis using the Soxhlet equipment and it discovered that ethanol produced the best cannabinoid yields. The lengthy running time and high solvent need are drawbacks that not only raise operating costs but also complicate environmental issues, as is frequently observed with other traditional methods (De Castro & Garcıa-Ayuso, 1998). A research by (Wianowska, Dawidowicz, & Kowalczyk, 2015). Comparing the extraction characteristics of THC and THCA using the Soxhlet technique illustrated these limitations. The breakdown route of THC by THCA and ultimately to CBN was evidently enhanced by the prolonged high temperature, leading to high concentrations of both THC and CBN (Wianowska et al., 2015). High sample throughput and yield may be achieved by combining an easy-to-use system optimization process with a straightforward approach. The little need for a skilled workforce to operate the process is also seen as beneficial in comparison to more current extraction techniques. Both manual and mechanized Soxhlet procedures are available; the latter is less risky and enables the simultaneous examination of several treatments to maximize solvent composition, solvent to plant ratio, and process time(De Castro & Garcıa-Ayuso, 1998).

Macerations

The traditional method of extracting solid lipids from a sample involves maceration, which involves immersing the sample in an organic solvent for a certain amount of time and temperature (The polarity of the component that is being targeted determines the solvent that is employed.) and then agitating the sample (Fathordoobady et al., 2019). This is a common and low-cost separation procedure for extracting bioactive chemicals and essential oils

(Azmir et al., 2013). More terpenes can be extracted from maceration using vegetable oils (like olive oil) as solvents compared to alcohol solvents, according to current research, especially when longer heating times are used. Vegetable oils, on the other hand, are difficult to separate from extracted isolates and are not volatile (Romano & Hazekamp, 2013). As an alternative, ethanol is recommended as the ideal solvent for the extraction of cannabinoids. When utilized for neutral cannabinoid recovery, ethanol and other organic solvents (n-hexane, acetone, and methanol) did not significantly vary from one another, according to a research by (Fathordoobady et al., 2019). But ethanol yielded the greatest when acidic cannabinoids were tested for recovery. It was discovered that, when applied twice, the maceration extraction of cannabinoids using ethanol yielded the maximum yield when compared to other extraction techniques, such as supercritical fluid extraction (SFE) or ultrasonic-assisted extraction (UAE) (Fathordoobady et al., 2019). (Romano & Hazekamp, 2013) used maceration to compare five distinct solvents (naphtha, petroleum ether, ethanol, olive oil + water, and olive oil). With the exception of naphtha, the remaining extracts had traces of THCA and THC (between 5 and 10%). The exception was naphtha, which contained both THCA and 33% THC. Unwanted chlorophyll was removed with the cannabinoids using ethanol as a solvent. Removal of the undesirable chlorophyll is deemed vital since it not only gave the final product a disagreeable flavor and a green tint, but it also showed reports of interfering with gas chromatography–mass spectrometry analysis (Fathordoobady et al., 2019). Activated charcoal can be used to treat the ethanol extract in order to remove excess chlorophyll. On the other hand, the cannabis concentration may be reduced by around 50% when activated charcoal is used. As a result, even if ethanol yields are good, THC loss occurs when charcoal is used to remove excess chlorophyll. Regarding toxicity, (Romano & Hazekamp, 2013) discovered considerable levels of petroleum hydrocarbon residues in the extracts made using petroleum ether and naphtha, suggesting that extra care has to be taken to guarantee safe residual concentrations (Romano & Hazekamp, 2013). The olive oil extract was demonstrated to have the highest quantity of terpenes in the same research when compared to other solvents, making it a high-quality extract. Olive oil is an inexpensive, nonflammable solvent that is safe to use topically or internally as long as it doesn't enter the lungs. Additionally, (Citti et al., 2016) found that cannabis extracts based on olive oil retained their cannabinoid content for a longer period of time than extracts based on ethanol. However, the inability of olive oil extracts to be concentrated by evaporation is a drawback. Accordingly, greater amounts of olive oil extracts must be ingested in order for them to have the same medicinal benefits as other extracts (Romano & Hazekamp, 2013). Hexane, the typical petroleum ether, was utilized in a different investigation by (Hazekamp, Fischedick, Díez, Lubbe, & Ruhaak, 2010) as a solvent for the maceration process of cannabis fiber and drug variations. It was found that the cannabinoid yields were 3% and 17%, respectively. Since hexane readily evaporates after extraction and does not extract chlorophyll, it was specifically chosen for this study (Hazekamp et al., 2010). Acetone is typically the preferred solvent for methods that extract chlorophyll from plants; however, since acetone is thought to be carcinogenic, it is not advised to use it for cannabinoid extraction. (Namdar et al., 2019) extracted cannabinoids using a combination of non-polar hexane and partially polar ethanol. The combination produced the maximum yield, although the polar solvent worked best for cannabinoids (Namdar et al., 2019). Similarly, (Brighenti, Pellati, Steinbach, Maran, & Benvenuti, 2017) found that, in comparison to more complex techniques like ultrasonic-assisted extraction (UAE), maceration with ethanol for 45 minutes at 25 ^{o}C was the most effective approach to extract acidic form of non-psychoactive cannabinoids.

Different approaches to extracting

Extraction with ultrasonic assistance (UAE)

Because ultrasound technology may dramatically affect the pace of many operations, it is widely used in food and chemical industries (Chemat, Tomao, & Virot, 2008). The primary characteristic that distinguishes ultrasonic-assisted extraction (UAE) from alternative procedures is the utilization of sound waves, often with frequencies ranging from 20 to 100 khz. This makes it possible for solvents to seep into a sample matrix and extract the desired chemicals. This is carried out when cavitation is occurring. Cavitation is defined as the process by which bubbles in the solution develop, grow, and burst, enabling rapid solvent access into the cell material and intensive mass transfer (Azmir et al., 2013). The UAE's enhanced mixing capacity can be attributed to its decreased extraction temperature, micro-mixing, and quicker energy transfer (Ötles & Kartal, 2016). To get effective extractions, variables like a sample's moisture content, particle size, degree of milling, solvent, temperature, pressure, and sonication duration must be taken into account and adjusted(Azmir et al., 2013). Comparing the results of research using the ultrasonication technique to leach and hydrolyze phenolic compounds to those using subcritical water, microwave assistance, and solid-liquid extractions, the ultrasonication approach demonstrated reduced analyte degradation throughout the extraction process. Following an evaluation of the phenolic compound degradation, it was discovered that the short duration time and low energy type generated by the sonication mechanism were the causes of the reduction in decomposition. But this was only noticeable after fewer than ten minutes of ultrasonic exposure (Herrera & De Castro, 2005). (De Vita, Moskal, Maisto, & Ansell, 2018) Examined the variations in the cannabinoid makeup by contrasting several extraction techniques for hemp and medical cannabis that are sold commercially. The experiment showed that 50 minutes at 60 °C with ethanol as a solvent was the ideal temperature for achieving the maximum yield of cannabis using ultrasonication. Even under ideal circumstances, the total levels of THC and CBD extracted were marginally less than those of the controls, which were extracted in ethanol under reflux for 50 minutes at 90 °C. Despite the limited yield, the ultrasonication process produced extracts at lower temperatures in a safe, effective, and environmentally beneficial manner. According to this investigation, the yield of ethanol extract was three to four times more than that of olive oil extract (De Vita et al., 2018). (Lewis-Bakker et al., 2019) Executed an extraction procedure utilizing the following parameters: Ultrasound-Assisted Extraction (UAE) at 80 W of ultrasonic bath power, 63 W of heating power, at a frequency of 40 kHz for a duration of 5 minutes. In order to further investigate the idea of solvent impact in UAE. As a solvent, a mixture of hexane, ethanol, and hexanes: isopropanol (1:1) was utilized. The yields for ethanol and hexane were almost equal, according to the data, whereas hexanes: isopropanol had the highest extract yield. Because of the co-extracted non-cannabinoid content, the hexanes : isopropanol product had the lowest cannabinoid content, according to an HPLC investigation that revealed a reverse connection between the extract yield and cannabinoids. In addition, the scientists reported that when compared to alternative extraction techniques, the UAE approach preserved the majority of the cannabinoid's acidic forms (Lewis-Bakker et al., 2019). As a conditioning phase before using standard extraction procedures, UAE is recommended to maximize the extraction of desired cannabis components. For instance, it was discovered that adding UAE prior to a Soxhlet extraction increased the yield of crude lipid by almost 24% while maintaining extract quality (Fathordoobady et al., 2019).

Extraction with microwave assistance (MAE)

The microwave-assisted extraction method was developed in 1980 in response to the growing need for sustainable and ecologically friendly industrial operations (Ötles & Kartal, 2016). The quick heating process that occurs after ionic conduction and dipole rotation is facilitated by the electromagnetic energy that is supplied in the form of microwaves, which have frequencies all between 300 mhz and 300 ghz (Azmir et al., 2013). Each molecule acquires the capability to break cell walls and release its contents into a solvent when it is subjected to microwave radiation in a direct manner. Because of its increased surface equilibrium, effective mass transfer, and improved solubility, this environmentally friendly extraction method is superior. A system that swiftly and efficiently generates a high-purity final product while using few solvents also uses less energy, all because of these variables. (Al-Ani, Adhab, & Nawar, 2012). (De Vita et al., 2018) Investigated temperature, solvent, ramping time, and time as factors using MAE. The investigation showed that, in comparison with reference sample, which was made by ethanol reflux at 85 °C for 60 minutes, the extraction of CBD increased by increasing temperature and duration at-least 4 times. Additionally, during an MAE, it was shown that olive oil possessed better qualities than ethanol (De Vita et al., 2018). Because neutral phytocannabinoids have been shown to have therapeutic value, it is imperative to get these substances by extraction methods. By examining phytocannabinoid acid decarboxylation efficiency, extraction techniques for neutral cannabinoids may be investigated. For instance, (Lewis-Bakker et al., 2019) discovered that MAE yielded higher levels of neutral cannabinoids when comparing the procedures of various separation techniques. According to the study, during MAE, high temperatures (over 130 °C) caused more than 99% of acidic cannabinoids to undergo decarboxylation. With extracts from earlier Soxhlet, UAE, and SFE extractions, MAE was utilized for 10 min at 150 °C to further encourage to decarboxylate the acidic phytocannabinoids. But only the isolates obtained using the Soxhlet technique have fully decarboxylated. Even after increasing the period to 30 minutes in Microwave assisted Extraction (MAE), the extract produced 0.6% of CBN. Given that THC undergoes oxidation modifications to create CBN, this may be the result of radical-mediated oxidation or oxidation during MAE (Lewis-Bakker et al., 2019).

Supercritical fluid extraction

Organic solvent extraction and traditional pressing techniques are being replaced by environmentally friendly techniques like supercritical fluid extraction (SFE). Using supercritical fluids, these processes lessen their negative effects on the environment and the amount of harmful residue left on products (Aladić et al., 2015). SFE may be boiled down to two steps: (1) solubilizing the target plant material in a preferred supercritical solvent (usually CO2) in order to extract the desired chemical. (2) The final product is then created by recovering those components from the solvent. Because supercritical fluids are gaseous at ordinary temperature and may be recovered by straightforward evaporation, their usage is desirable (Santos & MEIRELES, 2015). Selective extraction is made possible by the varied solubility's of the various solvents, as slight changes in temperature or pressure may also provide selectivity (Perrotin-Brunel, 2011). Utilizing low temperatures is also seen favorably as it uses less energy and permits the preservation of substances that are sensitive to heat, such THC(Santos & MEIRELES, 2015). Except in supercritical situations, CO2 functions as a polar molecule. Polarity modifiers, like acids, water, and alcohols, can be utilized as co-solvents when supercritical CO2 is insufficiently polar to function as a solvent (Rovetto & Aieta, 2017). Nonetheless, because to their overwhelming no polarity, CBD and THC are soluble in supercritical CO2, which makes it a suitable solvent (Grijó, Osorio, & Cardozo-Filho, 2018). (Rovetto & Aieta, 2017)The effect of pressure and use of ethanol as a co-solvent on cannabinoids can be studied. Pressures of 17, 24, and 34 Mpa were used for the extractions. At 34 Mpa, cannabis at this pressure, the yields rose almost linearly as compared to conventional ethanol extraction. A greater pressure may not be the best situation because it might boost solvation power but reduce the extraction's selectivity. It was shown that ethanol was beneficial as a co-solvent: adding it in pulses can speed up the supercritical CO2 extraction process of cannabis (Rovetto & Aieta, 2017). It has also been shown (Grijó et al., 2018) that the yield may be raised by employing a co-solvent. At 55 °C and 34 mpa, the ideal yield of these cannabinoids was obtained by employing ethanol as a co-solvent (Fathordoobady et al., 2019). However, (Brighenti et al., 2017) found that the least quantity of CBDA, CBD, and CBG was recovered when comparing SFE with other extraction techniques. Makes the process of supercritical fluid extraction visible.

CONCLUSION

In this review, a comprehensive overview of advancement in Cannabis extraction using different techniques are given. Based on the outcomes of this review, it was found that around 4 techniques have been widely used for the extraction of CBD and other bioactive components in the versatile Cannabis plant. The best methods based on the final products reviewed and suggested is supercritical fluid extraction as it is yield and cost efficient. The extraction technique in Cannabis needs more investigations in the future studies to find more reliable technique with more efficiency.

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