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Review

Extraction of Cannabinoids from *Cannabis sativa* L. (Hemp)—Review

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Abstract: Cannabis plant has long been execrated by law in different nations due to the psychoactive properties of only a few cannabinoids. Recent scientific advances coupled with growing public awareness of cannabinoids as a medical commodity drove legislation change and brought about a historic transition where the demand rose over ten-fold in less than five years. On the other hand, the technology required for cannabis processing and the extraction of the most valuable chemical compounds from the cannabis flower remains the bottleneck of processing technology. This paper sheds light on the downstream processing steps and principles involved in producing cannabinoids from *Cannabis sativa* L. (Hemp) biomass. By categorizing the extraction technology into seed and trichome, we examined and critiqued different pretreatment methods and technological options available for large-scale extraction in both categories. Solvent extraction methods being the main focus, the critical decision-making parameters in each stage, and the applicable current technologies in the field, were discussed. We further examined the factors affecting the cannabinoid transformation that changes the medical functionality of the final cannabinoid products. Based on the current trends, the extraction technologies are continuously being revised and enhanced, yet they still fail to keep up with market demands.

Keywords: cannabinoids; organic solvent extraction (OSE); supercritical fluid extraction (SFE); CBD purification; cannabinoid transformation

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1. Introduction

Hemp, or *Cannabis sativa* L., is an oleaginous plant known as one of the oldest plants cultivated by humankind, specifically for medicinal properties and non-edible fiber content [1]. The letter "L" stands for Linnaeus in recognition of the contributions of the father of modern taxonomy, Carolus Linnaeus, who first named the species as *Cannabis sativa* [2]. This plant is widely known to be the major source of cannabinoids, including cannabidiol (CBD), tetrahydrocannabinol (THC), cannabichromene (CBC), cannabigerol (CBG), and cannabinol (CBN). Cannabinoids have shown strong remedial potential against inflammation, depression [3], nausea, epilepsy, and other effects of clinical relevance [4,5]. Initial uses of cannabis date back to almost 5000 years in China [6]. Since then, hemp consumption has been spurred on by its wide range of properties and uses from one civilization to another through consecutive millennia. The first academic research on the extraction of bioactive ingredients of hemp, to the best of these authors' knowledge, was conducted by Yamauchi et al. in 1968 [7].

From the taxonomical point of view, hemp belongs to the family of Cannabinaceae [8] that includes three subspecies, namely *Sativa*, *Indica*, and *Ruderalis*. The differences between these three subspecies mainly lie in the overall shape of the plant, the applications, and the most suitable climate for its growth. The division of the cannabis strains into hemp and marijuana is simply a wrong nomenclature that is wholly misconceived with a broader classification of cannabis [9]. The two names differentiate varieties with Δ9-tetrahydrocannabinol (Δ9-THC) contents of less than 0.3 wt.% (hemp) from those having more than 0.3 wt.% (marijuana) that induces psychoactive effects [10]. Occasionally, these terms are falsely adapted and interchangeably applied in the literature [11,12]. The cannabis with a THC content of over 0.3 wt.% (marijuana) is outside of the scope of this review paper.

Hemp has historically been attractive for its top-quality fiber and edible oil; however, with the advancement of synthetic fibers, as well as mounting public anti-drug movements, it was categorized as a controlled substance by the 1968s prohibition legislation. This prohibition, under drug enforcement laws [13], banned the production and research on hemp products, putting the United States far behind more than 30 other nations that considered the plant to be an agricultural commodity [14]. In the early 1990s, commercial hemp cultivation and its research and development were promoted in the U.S. Ever since, a growing number of states have enacted the legislation and have expanded state-level research and production. The status of legality, decriminalization, permission for medical use, and the specific state laws can be found in continuously updating marijuana maps [15].

The outstanding therapeutic effects along with the economic benefits to local communities resulted in increasing public support and the eventual legalization of these products in many countries around the world and recently in several states in the U.S. Beginning with the 2014 Farm Bill, the growth and production of hemp experienced a partial relief in the U.S. [13], and the first medically-oriented legal product came to the market in June 2018, creating a huge market for CBD [16,17]. Nevertheless, due to the psychoactive properties of the THC, the upper limit of 0.3 wt.% (dry biomass weight) still remains a key barrier between the cannabis flower and the drug [13,18] in most U.S. states and the European Union [19]. Based on the 2017 congressional research, the total hemp market was about 700 million USD in the U.S. [13], while in light of the recent openings, this number will hit 20 billion USD by 2024, pushing the global spending to go beyond 40 billion USD worldwide, according to Arcview market research [20].

Yet, developing various feasible technologies that are both legitimate and economic are important steps that need to be taken before industrial-scale production standards can be set. Dealing with a living plant that is controversial and inhomogeneous in growth due to different soil fertility levels [21], as well as other local factors, poses challenges on the determination of optimum harvesting conditions to obtain a maximum cannabinoid content. On the other hand, establishing effective and energetically efficient large-scale extraction protocols are keys for the successful resolution of the challenges. Despite the routine lab-scale extraction methods, the variables affecting the choice of extraction method, as well as the final extraction yields, are not well understood. Further, the growth and processing of this plant are going through a transition phase that requires closing the knowledge gap in the extraction field to set a complete processing system up. This review article aims to fill these gaps by looking at different methods of cannabinoid extraction, their pros and cons by reviewing the recent advances in the field. In addition, it reports the suitability of the employed technologies by comparing them with other alternatives as well as the pretreatment protocols that boost the extraction yield. Finally, it looks at the post-extraction transformation that affects the final product composition.

2. Categories and Procedure

2.1. Discretion of Two Categories

Throughout the hemp industry, the term "extraction" is used in two different contexts and categories: (1) the trichome category, in which the extraction of cannabinoids and terpenes from trichomes takes place with the aim of producing medical or recreational

grade supplements; and (2) the seed category, in which the extraction of fatty acids or lipids from hemp seeds takes place. Triglycerides make up to over 30% of hempseed weight [22,23], which is the suitable form of lipid for trans-esterification into fatty-acid methyl esters (FAME) or biodiesel [24]. In addition to biodiesel production, the extracted lipid has a wide spectrum of applications in the cosmetics [25] and food industries [26]. The extraction of lipids from seed (seed category) is outside of the scope of this review. We will focus mainly on the trichome category, discussing the processes involved in cannabinoid and terpene extraction.

Assuming that a typical farm produces male and female plants in equal numbers, the females appear shorter with many flowers, while the males are taller and exude pollens only (Figure 1). If harvested and dried on time, the female flowers contain a significant amount of cannabinoid, whereas the pollens from males pollinate the flower buds to produce seeds [27]. That is why the growers of cannabinoids usually root the male plants out prior the pollination.

Figure 1. Hemp flower. Cannabinoid-rich female flower buds before pollination (**a**) and a microscopic image of the trichomes in the buds (**b**). The adult seeded flower is the result of pollination (**c**), and the hempseeds are produced by pollinated buds (**d**).

2.2. Downstream Process in Cannabinoid/Terpene Extraction

Figure 2 shows the processing steps required to produce cannabinoids and terpenes from the hemp flowers. Depending on the final analytes of interest or the chosen extraction method, some of these steps might be modified. Once harvested, the hemp flowers should be trimmed manually or with the help of bucking machines. The flowers then need to be dried (in the absence of sunlight to prevent the photochemical transformation) and milled to reduce particle size. The shredded biomass is transferred to extraction tanks and immersed in the solvent(s) of choice for a known period of time to let the extraction take place.

While being exposed to the solvent, in addition to the extraction of cannabinoid and terpene, usually volatiles, moisture, and heavy residues also leave the plant matrix as co-extracts. The latter includes pigments, phospholipids, fatty acids, heavy metals, etc., and resembles a highly viscous, gooey black gum that forms an inhomogeneous tar when exposed to increased temperatures. This black mixture is called wax and needs to be removed before further processing, as it spoils the thermodynamics of separation. Winterization involves the separation/sedimentation of the waxy fractions by the deep freezing of the crude for over 24 h [28,29] and subsequent filtration of the solution. The separated wax is used in electronics, candles, machinery lubricants, as well as other applications. Once winterized, the solvent is removed using a rotary evaporator and

recycled back to the extraction process. The obtained material can then be distilled to fractions that can be marketed as vapes, edibles, topicals, food supplements, or additives.

Medical or therapeutic applications require the products to be ultra-pure (beyond 99% purity), which can be attained via chromatographic methods, crystallization, or distillation techniques [29,30]. One major downside of distillation is the involvement of thermal energy. Neutral cannabinoids (THC, etc.) do not occur at significant concentrations in the plants [31–33] and are usually produced by thermal transformations during extraction. Therefore, some extra caution should be exercised during the process to maintain the THC contents controlled, especially in the production of medical products. This will be further discussed within the following sections.

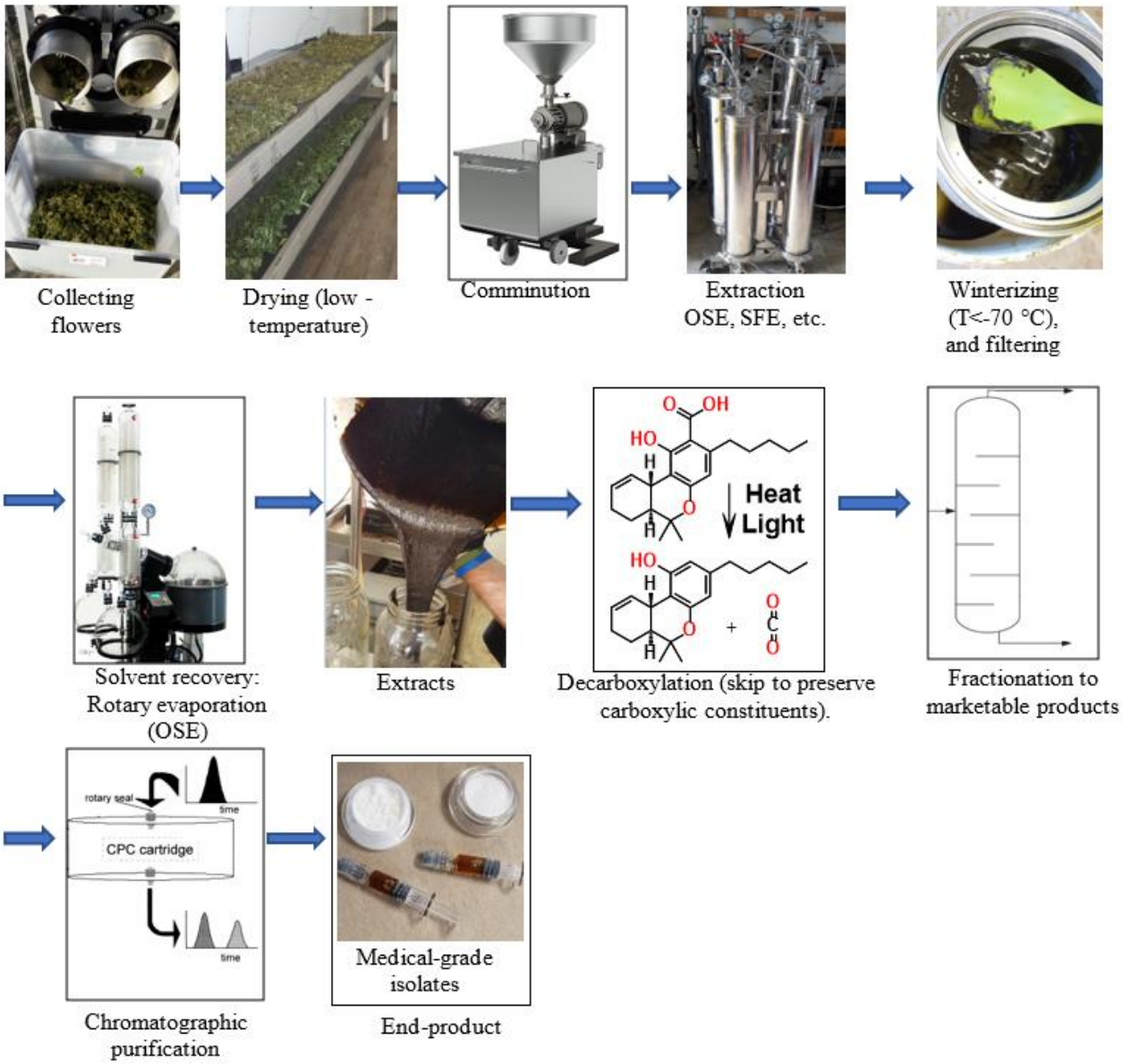


Figure 2. Process flow diagram showing the downstream processing steps needed to produce cannabinoids from *Cannabis sativa* L. OSE: organic solvent extraction; SFE: supercritical fluid extraction.

3. Extraction

3.1. Basics

Of the four main processing stages in the hemp industry (variety selection, cultivation, harvesting, and extraction), the latter plays a key role in the overall economy and demands the highest technology scrutiny. *Cannabis sativa* L. possesses well over 500 natural chemical

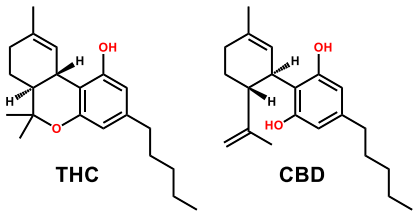
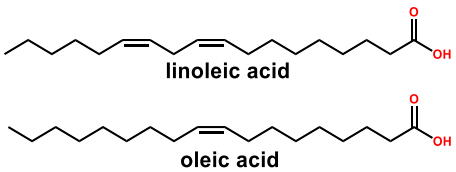
compounds [34,35]. Estimates show that between 30–60% of the total cannabinoid in hemp flowers are lost somewhere during the extraction or purification process [29]. With CBD alone possessing over half of the entire cannabis market [13,36,37], the selection of proper extraction and processing method results in a significant impact on the overall process economy.

Table 1 summarizes the two extraction categories. In the trichome (cannabinoid-terpene) category, a broad spectrum of polar solvents such as methanol, ethanol, isopropanol, dimethyl ether, etc., can be used to extract the semi-polar cannabinoids and terpenes from the flower trichomes. In both categories, dealing with real-time hemp biomass incorporates a significant number of inconsistencies in the extraction process; for instance, Deferne et al. (1996) reported an inhomogeneous feed of ripe and unripe seeds for the procedure. This resulted in increased moisture content and lower oil yield and modified product taste [38]. Moisture content and the overall health of the plant affect the cannabinoid composition in the buds [39]. Cannabinoids are housed in trichomes outside the buds, which makes the concentration gradient between the solvent media and trichome surface the main barrier to chemical transfer. Intense and aggressive grinding or crushing of herb is not required as it enhances the dissolution of undesirable substances [40].

With hemp seeds, the target is the fatty acids inside the seeds. Extraction is achieved using nonpolar solvents, sometimes coupled with prior pressing by screw expellers to squeeze these chemicals out of the plant's fibrous structure and overcome the mass transfer barriers. In this category, the extraction kinetics are governed by the complex and multi-step transfer of the molecules from the seed's interior structure all the way out to the solvent media.

As Table 1 displays, there are multiple techniques for the extraction of chemicals from the hemp depending on the target chemical of interest, e.g., mechanical extraction, Soxhlet method, hot water extraction (hydrolysis) [41], DME liquid-liquid extraction [42], supercritical CO_2 extraction (SC-CO_2) [43], enzyme-assisted extraction (EAE) [44], microwave-assisted extraction [45], etc. The following section elaborates on extraction methods widely employed in both laboratory and industrial scales.

Table 1. Two categories where extraction takes place in the hemp industry.

	Trichome Category	**Hempseed Category**
Target chemicals	Cannabinoids and terpenes	Fatty acids
Occurrence in plant	Female flower buds before pollination	Hempseed
Solvent used	Mainly polar solvents	nonpolar and polar solvents
Mass transfer driving force	~($\Delta C_{trichome\text{-}media}$) = Concentration gradient between the solvent in contact with the trichome and that of the media	~ ($C^* - C$) = Concentration gradient between the saturated solution in contact with the seed particles and that of the media. [46]
Extraction method	OSE, SFE, and Soxhlet (small scale only)	Cold press, screw expeller followed by OSE, SFE, or Soxhlet (small scale only)
Co-extracts	Waxes, pigments, etc.	Defatted oil, oil sludges, etc.
Other application	pharmaceutical, recreational supplements, Electronics	Bioenergy production, abrasive fluids, food supplements, and cosmetics
Typical structures of chemicals of interest	 THC CBD	 linoleic acid oleic acid
Pre-extraction treatment	Mild comminution is sufficient; intense grinding leads to the co-extraction of undesirable substances [40]	Crushing and grinding the seed to smaller pieces contribute to an enhanced mass transfer

3.2. Solubility Parameters

Several thermodynamic models have been proposed to predict the solubility of solutes in different extraction candidates, of which the Hansen solubility parameter (HSP) is widely accepted [33]. The HSP works based on the solubility parameter theory (SPT) by offering a mathematic tool that quantifies the effectiveness of the solute-solvent interaction in the form of (Equation (1)):

$$R_a{}^2 = 4(\Delta\delta)_D{}^2 + (\Delta\delta)_M{}^2 + (\Delta\delta)_H{}^2 \quad (1)$$

where $\Delta\delta$ ($= \delta_{solvent} - \delta_{solute}$) is the difference between the solubility parameters, and the subscripts D, M and H signify the bonding parameters associated with dispersion (van der Waals), molecular dipolar and hydrogen bonding parameters, respectively. Equation (1) can be visualized as a solubility sphere with the radius R_a (distance of the solvent from the center of the solubility sphere), where the closer solubility parameters of the analyte to those of the solvents ($\Delta\delta$~0), the solvent lies closer to the center of the solubility sphere and is, therefore, a suitable solvent. These values are found in the literature [33,47] and are often functions of temperature and/or pressure, rendering varying solubility. This method will be employed later in this paper to study the effectiveness of each solvent system.

3.3. Chemically Assisted Extraction

3.3.1. Soxhlet Extraction Method

Soxhlet extraction is an old yet effective method for plant oil extraction [48]. It has been used to extract organics from over a hundred types of biomass, including Sunn hempseeds [49], marijuana cigarette [50], hashish [51], coffee [52], vanillin [53], rice bran [54], walnut kernel [55], fungal biomass [56], algal oil [57,58], orange juice [59], etc. It operates based on a continuous cycle of solvent and leaving the extracts in the extract chamber and contacting the biomass in the batch process. Because this apparatus exposes the biomass to a fresh stream of the organic solvent all along the operation, it accommodates the strongest extraction driving force among all extraction methods, i.e., the reference method [40,57,60–62].

Several research experiments have been carried out to examine Soxhlet processing of *Cannabis* sp. for bio-oil extraction. However, cannabis sativa L. (hemp) has rarely been studied in the literature for the purpose of cannabinoid extraction. Matthäus et al. [63] conducted research focusing on the fatty-acid composition of virgin hemp seed oil using a different method and found that depending on the variety of species, climate and geographical factors, as well as the year of cultivation, hemp seeds may contain 28–35 wt.% oil. Using the Soxhlet method, the maximum of 35 wt.% was easily met by Aladic et al. [40], additional evidence for the outstanding capability of this method.

Table 2 provides a brief summary of the recent research on the extraction of various compounds using the Soxhlet apparatus. Molina et al. [61] used Soxhlet in a step-wise manner to collect the total THC content of the hemp oil under relatively low pressure in a 6-h period. Increasing the solvent's polarity by switching from hexane to ethyl acetate and then to ethanol extraction batches (polarity gradient), they tried to extract the entire THC spectrum. Using solvents with different polarity indices, they removed THC molecules bound to different cell structures and obtained total THC content as the baseline for comparison with other methods.

Chasing ω-type acids, Da Porto et al. [64] found that *Cannabis sativa* L. seeds contain 81% polyunsaturated fatty acids (PUFA), mainly comprised of linoleic acid (ω-6). Unlike most other researchers, they noticed that the highest oil yield from hemp seeds was obtained by SC-CO_2, accounting for 22%, corresponding to 72% of the total recovery. This result is slightly lower than 28–35% oil content obtained by Aladic et al. [65], using Soxhlet extraction.

The extraction of other cannabinoids has also been investigated. Wianowska et al. [66] conducted a thorough study on extracting Δ^9-THC, THCA, and cannabinol (CBN) from *Cannabis sativa* L., using Soxhlet and pressurized liquid extraction (PLE) method and proved

that during different time intervals from 1 to 3 h, THCA quantity dropped by nearly half while the amount of THC content increased significantly, confirming the transformation of THC from one form to another during the extraction process. A similar result was observed by Crescente et al. [67] in which higher yields of Δ^9-THC were obtained while comparing Soxhlet extraction (with n-hexane) with ultrasonication, microwave irradiation, and supercritical fluid extraction (SFE). They attributed the THC increase to heating involved during the prolonged solvent cycling in Soxhlet. Unlike most other earlier studies, Crescente et al. claimed that there is no significant difference in the total extractable oil obtained by various methods [67].

To maintain Soxhlet's efficiency relatively high, prior treatment of the feed might be required, such as milling operation depending on particle size and other properties of the feed [68]. Despite all the advantages, Soxhlet's apparatus demands a significant amount of energy to keep the distillation-evaporation cycles running [69,70], which poses severe problems for upscaling (Table 1). Therefore, Soxhlet's apparatus fails to be the ideal method of choice due to its wastefulness of energy, tedious reloading, fire risks, and inevitable side reactions such as the transformation of THCA to less desirable THC.

Table 2. Recent research on the extraction of various compounds from *Cannabis sativa* L. using the Soxhlet method.

Biomass sp.	Dry Weight	Pretreatment	Solvent (s)	Extract	Target Analytes	Ref
Industrial-grade hemp (cannabis)	0.5 g	Ground and sifted 368 µm	Consecutive batches of ethyl acetate 2 × 300 mL	batch 1, 1.5 h at 78 °C batch 2, 1 h at 78 °C	Cannabinoids	[68]
Seized *Cannabis sativa* L. plants	2 g	Ground	*n*-hexane or methanol 75 mL	1–3 h	Δ^9-THC, THCA, CBN	[66]
Hemp (*Cannabis sativa*) seed oil	10 g	Desiccated seeds	*n*-hexane 100 mL	24 h at 70 °C	ω-6 and ω-3 fatty acids	[60]
Cannabis sativa L. seeds	30 g	Ground hempseed	*n*-hexane 240 mL	8 h at 70 °C	Fatty acids, e.g., ω-3 fatty acids	[64,71]
Hemp seed	15 g	Extraction	Methanol 300 mL	8 h at 90 °C	Cannabinoids	[72]
Industrial hemp dust residue	11 g	Finely powdered hemp	Heptane 200 mL	4 h	Waxes and cannabidiol (CBD) C16 was predominating	[73]
Hemp raw material and hemp cellulose pulps	-	-	Acetone	8 h	Lipophilic extractives	[74]
Hemp seed oil	5 g	Ground hemp seeds	*n*-hexane 120 mL	2 h, 45 min at 180 °C	Tocopherols, fatty acids, and pigments	[65]
Cannabis sativa L. plant	4 g	NA	Solvent polarity gradient:hexanes, ethyl acetate, and ethanol	Reduced pressure, 6 h	Total THC content	[61]

3.3.2. Maceration (Immersion) Method

As the name indicates, this method involves immersion of the biomass in the solvent media to provide effective mass transfer for a given period. This generic term essentially involves all methods conventionally used today for extraction purposes, which includes the use of different machines in batch, semi-batch or continuous form to provide the required contact between solvent and solute in any scale. In practice, however, organic solvent

extraction (OSE) methods other than Soxhlet are termed immersion/dipping extraction methods. More often, the extraction method is named based on the employed solvent, e.g., ethanol extraction, in which the biomass is immersed in ethanol. The latter method is particularly the choice of interest for large-scale cannabinoid extraction due to its polar properties even though nonpolar solvents such as hexane have also been used for extraction [66]. Depending on the target analyte of the interest (fatty-acid, cannabinoid, or terpenoid), the involved solvent might differ; however, considering their solvent capabilities, relative price, and more importantly, their boiling point (for recovery purposes), ethanol and methanol have been found to be interesting choices compared to propanol, butanol, and isopropanol. For medical or dietary applications, ethanol is preferred owing to its lower toxicity. Although alcohols have been an attractive choice for maceration, Tagen et al. (2020) disclosed the details of successful hexane maceration. With 24 h maceration at room temperature and solvent recovery, they obtained an extract of 40 wt.% CBD after decarboxylation [75]. This technique is still the basis for several new inventions; for instance, several recent patents used modified maceration for the extraction of cannabinoids from hemp [75–77].

3.3.3. Extraction by Supercritical Fluids

There has always been extensive criticism against the traditional organic solvents for extraction due to environmental concerns and safety hazards as well as the high production costs [78]. The emerging "green" technology, supercritical fluid extraction (SFE), uses safe and capable solvents in their critical state to efficiently extract chemicals. As the temperature and pressure rise to the critical state (T_c and P_c), where the fluid can no longer be liquified by a further increase in the pressure, the solvent density increases drastically. This is the most important parameter associated with the solvent power [78]. Since the manipulation of pressure and temperature tunes density and solvent power, SFE conveniently enables selective extractions [79]. Additionally, because of their unique properties (transitional between gas and liquid), supercritical fluids exhibit superior mass transfer diffusion rates. These unique physical properties are summarized in Table 3.

Table 3. Typical physical properties of the gas, liquid, and supercritical fluids. Adapted from Hong G.T. [80], reprint permission had been obtained from the American Chemical Society (Copyright 1996).

State of the Material	Density (kg m^{-3})	Diffusion (mm^2 s^{-1})	Viscosity (μPa s)
Liquid phase	~1000	~0.001	~(500–1000)
Supercritical state	~100 to 1000	~0.01 to 0.1	~(50–100)
Gas state	~1	~(1–10)	~10

Various fluids have been employed in the SFE process, including ethene, water, methanol, carbon dioxide, nitrous oxide, sulfur hexafluoride, *n*-butene, and *n*-pentane [81]. Among these candidates, supercritical carbon dioxide (SC-CO_2) stands out and has been widely used since it is abundant, inexpensive, non-toxic, non-flammable, relatively chemically inert, and forms at almost room temperature T_c (31 °C) that is proper for thermolabile bioactive compounds [74,78,82]. Additionally, unlike the organic solvents, SC-CO_2 leaves the biomass completely and effortlessly, with zero energy consumption at the end of cycles with a facile tune of temperature and/or pressure [64,65]. Figure 3 schematically shows a typical SC-CO_2 extraction process along with the required pieces of equipment. Since the recovered CO_2 remains pure, it is fully recycled back into the chamber for reuse.

The addition of modifiers (cosolvents) was shown to assist the solubility of the target compound by providing a specific chemical interaction with the desired solute. This can be justified by the relative solubility parameters (δ) of the additives that fall in between the co-solvent and that of the target analytes. A number of cosolvents have been reported for SC-CO_2 extraction, including acids, water [83], low molecular-weight alcohols, aldehydes, esters, and ketones [84]. Of these, ethanol has been mostly used [83]. The co-solvent mediates between the solute and solvent, paving the way for increased extraction; however, it may also enhance the co-extraction of unwanted constituents and lower the product purity.

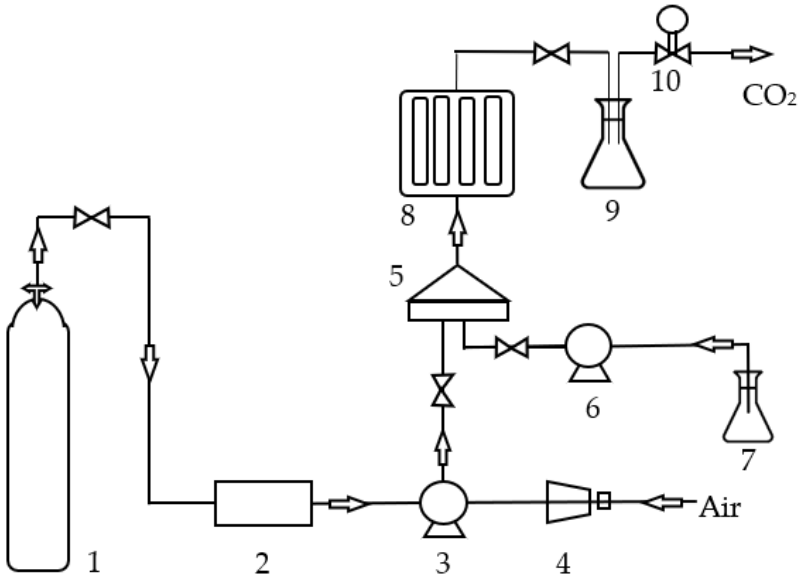


Figure 3. Schematic view of SC-CO_2 extraction unit. CO_2 cylinder (1); CO_2 cooler (2); booster (CO_2 pump-3 and compressor-4); mixer (5); co-solvent pump (6); co-solvent source (7); extraction unit (8); separation vessel (9); flow meter (10).

To design an SFE processor, several parameters need to be determined, including the operating pressure and temperature, solvent flow (scale), solvent-to-feed ratio, recovery conditions (precipitation), pretreatment of the solid matrix, initial moisture content, and other mass transfer parameters [85,86]. Because there are multiple parameters affecting the process efficiency and that different researchers have different interests and perceptions, there is an obvious lack of quality research for formulating the SC-CO_2 extraction parameters. However, a number of trends have been found experimentally through trial-and-error processes, including the optimal temperature for each set of extraction parameters. Due to high capital costs, safety issues, and other technical considerations, different companies offer diverse SC-CO_2 extraction technologies [87–90]. Table 4 summarizes a number of widely used, large-scale SC-CO_2 extraction systems, along with their technical details.

As Table 4 shows, the supercritical extraction machines are usually automated, allowing savings on labor costs and fewer safety concerns. Yet, the equipment is still expensive enough to deter startups lacking sufficient funding, which serves as another reason for the choice of OSE over the SC-CO_2 extraction method. The processing capacity, and thus yield, depends on the density of the inlet materials. The operation parameters can be adjusted based on the inlet material properties as well as the desired product compositions of interest.

Despite its high capital costs, myriads of biomass species have been processed with SFE for extraction of different chemicals [79,94]. Working on anti-inflammatory compounds, Arranz et al. employed supercritical carbon dioxide extracting terpenolic camphor accounting for more than 33% of the overall extract, showing the selective capability of SC-CO_2s toward terpenes [95].

Table 5 summarizes a number of recently published studies on SC-CO_2 processing of medical cannabinoids. SC-CO_2 also exhibits great potential in fatty-acid extraction (Table 6). In an effort to correlate the parameters with the results, Perrotin-Brunel et al. (2010) proposed thermodynamic models to exhibit the mutual behavior of cannabinoid blends [96]. However, from what appears in literature and industry, it is evident that SC-CO_2 is an established method for extraction of higher-value chemicals, with insufficient formulation and protocols for scaling purposes, so much so that trial-and-error procedures are still considered the sole way of process optimization. In addition to the application of supercritical CO_2, subcritical CO_2 has also shown to be a suitable choice for cannabinoid extraction. For instance, B. A. Whittle et al. (2020) disclosed the details of an invention employing CO_2 at

10 ± 5 °C under the pressure of 60 ± 10 bar (subcritical CO_2), indicating efficient extraction of the main cannabinoids [28,97].

Table 4. Different SC-CO_2 extraction pieces of equipment used in cannabinoid extraction and their technical details. Adapted from Terasvalli H. [91], reprint permission had been obtained from the LUT university (Copyright 2020).

Product Name	The Force®	The Bambino®	E-180	Hi-Flo™ FX2
Manufacturer	Apeks Supercritical (Columbus, OH, USA)	Apeks Supercritical (Columbus, OH, USA)	ExtraktLAB (St Croix Falls, WI, USA)	Eden Labs (Seattle, WA, USA)
Production scale	Large-scale commercial, industrial	Small scale commercial, R&D	Large-scale commercial, industrial	Commercial
Extraction vessel volume	80 L	5 L	80 L	20 L
Per run dry biomass capacity	18 kg	1.4 kg	10–16 kg	4.5 kg
Max vessel pressure	344 bars	137 bars	344 bars	344 bars
Extraction temperature	Max 71 °C	Max 71 °C	25–100 °C	−60 °C–60 °C
Flow rate of CO_2	3.5–4.2 kg.min^{-1}	0.4–0.8 kg.min^{-1}	Not disclosed	2.2 L.min^{-1}
CO_2 recovery	95%	95%	Not disclosed	Up to 95%
Run time	Not disclosed	Not disclosed	Not disclosed	3–7 h
Remarks	Fully automated, subcritical extraction possible	Fully automated, subcritical extraction possible	Automated process control, possible subcritical extraction	Extensive automation
Ref.	[88]	[92]	[93]	[89,90]

Table 5. Published studies about cannabinoid extraction using SC-CO_2.

Biomass Form	Pretreatment	Operating Temperature and Pressure	Objective of Study	Ref
Hemp flower	NA	42, 54, 61, and 72 °C; 13.2–25.1 MPa	Solubility of cannabinoids using analytical methods	[98]
Hemp flower	NA	42, 53, and 61 °C; 11.3–20.6 MPa	Comparing the solubility of psychoactive and non-psychoactive compounds	[96]
Hemp	N.A	110–140 bar, 40–60 °C	Comparison of the molar solubility of the different cannabinoids in SC-CO_2	[99]
Hemp inflorescence	Ground	10 and 14 MPa, 40 °C	Recovery volatile compounds from the inflorescences and comparison with the hydro-distillation performance	[25]
Hemp	Ground	60 MPa, 35 °C	Method of preparing an herbal drug extract from medicinal cannabis	[28]
Leaves and buds	Ground	17, 24, and 34 MPa at 55 °C CO_2 flow rate of 200 g min^{-1}	Exploring the effects of pressure, initial cannabinoid plant composition, time, and the use of ethanol as a co-solvent	[83]
Hemp inflorescence	Ground	25 MPa, 60 °C	Proposing a method for extraction of CBD-rich and THC-rich product from cannabis plant materials	[87]

Table 6. Published studies on fatty-acids extraction using SC-CO_2.

Biomass	Pretreatment	Parameters	Objective of study	Ref.
Hempseed	Desiccated ground hempseed sieved (24-mesh tray)	40–80 °C pressures of 20–40 MPa CO_2 flow rate 3 mL min^{-1}	Determine fatty acids, tocopherols, and pigment content (chlorophyll a and b and total carotene)	[100]
Hempseed	Ground for 10, 30, and 60 s	Temperature (40, 50, and 60 °C), pressure (250, 300, and 350 bar) and particle diameter (0.59, 0.71, and 0.83 mm)	Total extraction and oxidation stability	[71]
Hempseed	Finely ground	Temperatures of 40, 60, and 80 °C and pressures of 300 and 40 MPa	Extraction yields, fatty-acid composition of the oil, and oxidation stability	[64]
51 different genotypes of hemp	Finely ground	Optimized extraction temperature, 40 °C restricted heating, and a total volume of parameters were: 51.7 MPa, 100 °C extraction temp 120 mL carbon dioxide for each extraction	Fatty-acid composition and tocopherol content	[101]
Hempseed	Pressed	Pressure of 20 MPa and temperature of 40 °C with a CO_2 mass flow rate of 4.9 kg h^{-1}	Evaluate the influence of extraction conditions on concentration of tocopherols, fatty acids, and pigments	[65]
Hemp stem fiber	Fine powder	35 MPa and 50 °C (40 MPa and 65 °C, highest yield of crude wax extraction)	Extraction of fatty acids, policosanols (fatty alcohols), fatty aldehydes, triterpenoids, hydrocarbons, sterols, and cannabinoids	[73]

3.3.4. Comparison between Organic Solvent and SC-CO_2 Extraction Methods

The SPT theory shows a medium to low extraction potential of SC-CO_2 in the solubility of the cannabinoids and terpenes. On the other hand, ethanol possesses a larger solubility sphere (Equation (1)), hence a greater solubility range. On the downside, ethanol extraction is followed by winterization, in which the solubility of cannabinoids and terpenes subsides with the decrease in temperature, resulting in partial sedimentation of cannabinoids and terpenes along with the extraneous compounds. Figure 4 shows the approximate solubility parameter values of cannabinoids, terpenes, the co-extracted waxes, as well as those for ethanol and SC-CO_2 [33]. It needs to be mentioned that the solubility parameter (δ-values) is a known constant value for a given pure substance in a given physical state. For instance, the liquid CO_2 has a δ-value of about 17.5 at −10 °C, but this number varies in the form of f (temperature, pressure) for SC-CO_2 and f (temperature) for organic solvents. During winterization, the δ-value of ethanol swings toward 29, thereby the resulting Δδ puts the solubility status outside the solubility sphere, meaning that the wax no longer becomes dissolved in the media. Conversely, the addition of alcohols to SC-CO_2 (co-solvent) increases the cannabinoid solubility capacity, reducing the SC-CO_2 flow required to conduct the extraction [33,83]. King J.W. (2019) has conducted a thorough study on the solubility parameters in cannabinoid extraction [33].

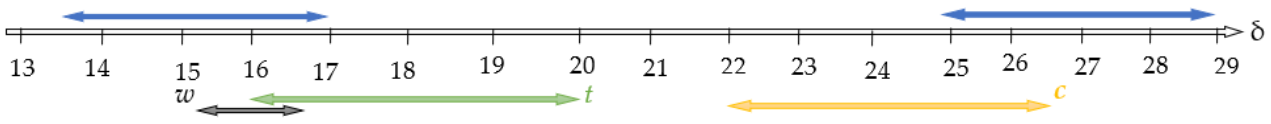


Figure 4. Approximate δ-values ($MPa^{0.5}$) of SC-CO_2 (top-left), ethanol (top-right), cannabinoids (c), terpenes (t), and waxes (w). Adapted from King J.W. [33], reprint permission had been obtained from Elsevier (Copyright 2019).

The predictions by SPT theory are also backed by experiment results [87]. Whittle B. et al. (2008) proposed a method for the precipitation of a significant portion of undesirable waxy materials from cannabis extracts dissolved in C1–C5 alcohols kept

in chilled environments for prolonged periods [28]. A similar study by Rosenthal (2014) describes the details of the dewaxing process by programming the temperature change [29].

In their comparison of heptane's Soxhlet and SC-CO_2, Attard et al. [73] reported that SC-CO_2 was superior in the extractions of hemp dust; samples yielded significant quantities of high-value lipophilic molecules including fatty acids, policosanols (fatty alcohols), fatty aldehydes, hydrocarbons, sterols, triterpenoids, and cannabinoids (CBD: 5832 µg/g of dust). They found that 35 MPa and 50 °C was the optimum condition to reach the highest extraction yield for the majority of compounds.

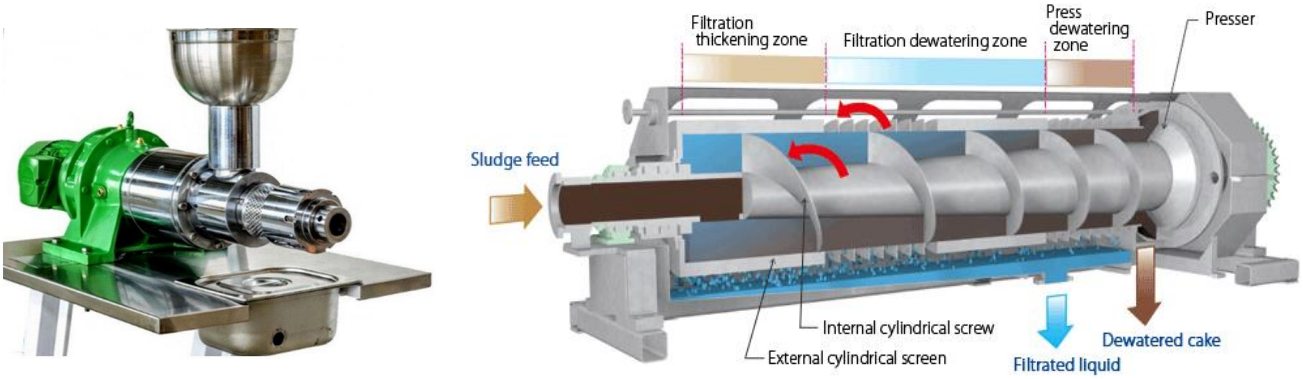
3.4. Effect of Pretreatment on Oil Extraction

Pretreatment methods are classified based on the manner in which they contribute to effective mass transfer. These methods include high-pressure homogenization, press, ultrasonication, microwave, acids lysing, enzymes, and osmotic shocks. We will briefly look at two of the main methods that have been studied for hemp processing.

3.4.1. Mechanical (Press) Extraction

Mechanical extraction mainly serves as a preliminary step for oil extraction from the hempseed. To prevent sprouting, hempseeds undergo a drying process that reduces their moisture content to 10% or less. Dry seeds are then fed into the screw expellers or pressing instruments to remove the physically extractable fatty acids. Afterward, the solvent is introduced to the pressed biomass to dissolve and remove the remaining oil.

Pressing with a screw extruder or pressurized liquid extractor (PLE) has been found to be low-cost methods for the extraction of hempseed oil, proteins, and other nutritional byproducts [24,102]. This process can take place at room temperature (cold press) or elevated temperatures. Cold pressing is slow and low-cost and protects the quality of chemical compounds that are heat sensitive. Screw expellers (Figure 5) are generally faster and cheaper because they do not require prior preparation [40,71,103]. However, this method leaves a significant quantity of waste: peels, seeds, defatted oilseed meals, and oil sludge [104], requiring further processing [105].



(**a**) (**b**)

Figure 5. Two common types of screw expellers used for the cold pressing of hemp, (**a**) feed from top and (**b**) feed from front.

Because the majority of cannabinoids accumulate at the surface of flower trichomes, the screw-expelling or pressing method does not serve as the proper way to extract cannabinoids and terpenes. An extreme grind of the biomass down to powder, in fact, contributes to the extraction of undesirable constituents of the inner tissue matrix, leading to complex downstream purification [106]. Nevertheless, mild shredding or crushing of the flowers prior to extraction helps reduce solvent consumption [40,64,66,71].

3.4.2. Microwave-Assisted Extraction

Microwave-assisted extraction (MAE) can be described as a mechanical pretreatment at the molecular level in which the waves penetrate the plant tissue, are absorbed, generate heat, expand it and disintegrate the biomass matrix, thereby facilitating the mass transfer [107]. This method is faster and has been found to be a powerful alternative for traditional OSE or SC-CO_2 methods [45] and skips the necessity of drying the biomass [108]. The key parameters to be adjusted are solvent polarity, extraction time, irradiation power, temperature, and contact surface area [109], and most of the lab-scale research has focused on optimization of parameters. For example, Rezvankhah A. et al. (2019) conducted an optimization study on the extraction of fatty acids from hemp seed oil and were able to reach nearly 34 wt.% at the optimum point of 450 W and 7 min. Comparing their results with Soxhlet performance, the authors noticed a relatively higher oil extraction yield (37.93% w/w) by Soxhlet but lower oil oxidation stability [110].

Table 7 briefly shows the classification of different pretreatment methods used in the extraction of cannabinoids, terpenes, and fatty acids. Essentially all mechanical pretreatment methods, either in macro-scale (grinding) or micro-scale (ultrasonic), improve the extraction yield and reduce the operation time by facilitating the mass transfer rate [111]. However, the mechanical energy exerted to the system eventually ends up converting into thermal energy that might lead to transformation; therefore, care must be taken in the extraction of cannabinoids from hemp seeds, [72] as the generated heat can decarboxylate the natural cannabinoids.

Table 7. Classification of pretreatment methods.

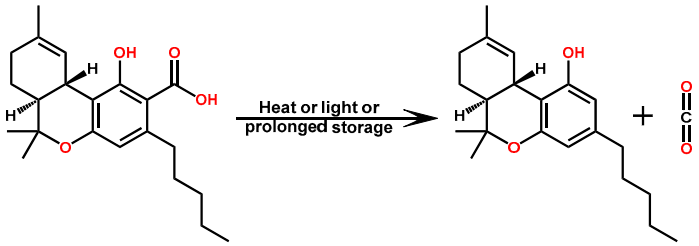
Pretreatment Method	Flower vs. Seed (Cannabinoids vs. Lipids)	Proper Scale	Remark	Selected Publications
Press and screw expeller	Fatty-acid	Small and large	Slow, cheap	[40,55,65,82,112]
Grind	Both	Small and large	Fast, cheap	[40,64,66,71,106]
Microwave	Fatty-acid	Small and large	Fast, cheap	[45,110,113,114]
High-pressure homogenization	Both	Small	Fast	[65]
Ultrasonication	Both	Small	Fast, expensive	[65,72,115]

3.5. Supercritical Hot Water Extraction

In addition to the conventional OSE and SFE methods, newer "green" approaches have also been developed and employed to extract different products from hemp. Pressurized hot water in its supercritical form as a solvent has been tried on different biomass samples and was found to have similar solvability properties as methanol and ethanol [116]. In a recent optimization study, Nuapia Y. et al. (2020) applied the pressurized hot water extraction (PHWE) technique to extract THC, CBN, CBD, CBG, and CBC components from hempseed [117]. Comparing their extraction results with those of traditional methods, they claimed that this method is faster and more selective toward less-psychoactive component extraction. On the downside, comparing the critical temperature and pressure of CO_2 (31 °C, 73 bars) with that of the water (374 °C, 217 bars) clearly shows that taking water to its supercritical condition is costly and might pose safety concerns. Further, as it exerts a significant energy load on the system, the method is not a proper choice for thermolabile component extraction [118], as was mentioned before.

4. Transformation of Constituents

The THC content has always been an issue of controversy due to the negative psychoactive effects in the U.S. and different parts of the world. This quantity undergoes changes while processing the plant or extracts [14]. As was mentioned above, the neutral cannabinoids (THC, etc.) do not occur at significant concentrations in the plants; rather, they are present in the form of their carboxylic acidic precursor [31]. This transformation takes place during the decomposition of THC-acid (THCA) into neutral THC and release of CO_2 in a reaction called decarboxylation (reaction scheme 1) in which it loses 12% of the mass. Several studies confirmed that the decarboxylation obeys a first-order kinetic model [119,120] where the rate constant depends on the dominant driving force.



(Reaction Scheme 1)

Various factors affecting THC quantity have been investigated including the desiccation conditions [121], including the temperature [119,121], electron-beam irradiation [41,122,123], length of processing [66,124,125], storage conditions [121,125], extraction procedure [66], and other applications involving the chemical evolution [18]. The decarboxylation reaction (reaction scheme 1) proceeds with the decrease in pressure and increase in temperature due to the well-known Le Chatelier's principle. Therefore, the THC quantity rises significantly during extraction and low-pressure distillation (purification).

Most producers in the food and drug industry use a conservative formula: "Total THC = THCA + THC" to calculate total THC content. However, this kinetic model is not realistic [50] and is another controversial gauge among legislators in the U.S. In a simulation study, Dussy F.E. et al. (2004) investigated the increase in THC content while smoking and found that only 30% of THCA transforms into psychoactive THC during smoking [18]. According to Iffland et al. (2016), the conversion of THCA to THC is often overestimated by as much as 50% above the actual THC amount because the decarboxylation reaction hardly proceeds to completion. They concluded that the amount is miscalculated and does not reflect the real amount of the psychoactive portion [119].

Effect of Light on Transformation

The effects of light on the photobiology of cannabis have been the focus of many researchers [126]; however, there are only a few published papers looking at the post-harvest cannabis profile change induced by light. Cannabinoids carry various functional groups, including carbon-carbon double bonds and aromatic moieties, namely chromophores, that interact with light. This interaction involves the absorption of light, which photo-excites the molecules. The absorption of light by the molecules elevates their overall energy level placing them in their photoexcited state, having greater vibrational and rotational motions that facilitate photophysical and chemical changes. Although the absorption of light can trigger reversible photophysical transformations such as photoisomerization [127,128], here, we mainly discuss the irreversible chemical changes that occur in the presence of light, such as decarboxylation. In a four-year-long study, Zamengo et al. (2019) remarkably noticed that the CBD content remained constant over time at different storage conditions, even though CBDA dropped significantly [129]. They realized that the presence of light has a significant positive effect on the kinetic and stoichiometry of the decomposition. Another four-year-long study by Trofin et al. [130] compared darkness with natural light exposure at 4 and 22 °C and proved that light caused significant THC degradation. Both studies demonstrated that the CBN and THC values follow an exponential trend in opposite directions, plateauing between 800 and 1200 days,

where CBN forms as THC degrades. Ramirez et al. (2018) conducted a thorough review and proposed the potential routes for natural, thermal, and photochemical transformation of carboxylic cannabinoids during inflorescence (Figure 6) [106]. As evidenced Figure 6, higher temperatures neutralize all acid cannabinoids to decarboxylated products, which can be further decomposed into degradation products, as was proved by earlier researchers.

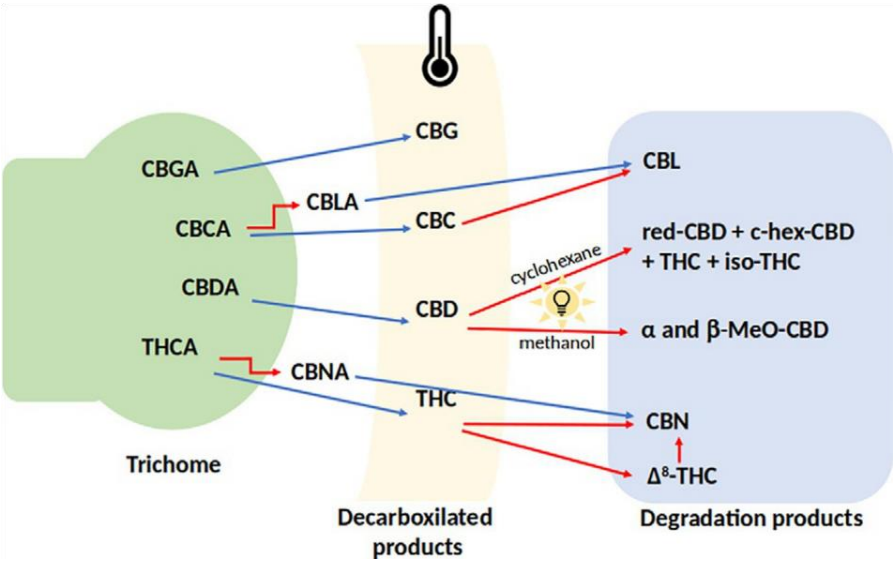


Figure 6. Hemp's key components interconnected by decarboxylation. Adapted from Ramirez et al. [106], reprint permission had been obtained from Elsevier (Copyright 2019).

Fairbrain et al., on the other hand, did not observe any CBN transformation accompanied by light-induced THC degradation, even though they found lighting induces the most significant effect on the THC contents comparing to air-oxidation and changes of the temperature [131]. Working on direct UV photolysis or UV/H_2O_2 photobleaching processes on the photodegradation/oxidation of THCA, Park et al. (2018) used a medium-pressure polychromatic UV lamp (200–300 nm) and found out that both the direct UV photolysis, as well as the UV/H_2O_2 (increased acidity) followed pseudo-first-order kinetics [132]. In this research, even though lowering pH solely did not contribute to THCA degradation, the incorporation of acidic agents under UV light showed a noticeable effect [132]. This can be attributed to the radical-scavenging properties of hydroxyl groups by the absorption of UV during a process called advanced oxidation processes (AOP) [133].

Nevertheless, the fact that the low-temperature operations prevent THC production and UV light degrades it raises the possibility of THCA removal by irradiation of the hemp crude extracts. A critical issue about which the authors did not address. If proved to be feasible, based on the cannabinoid evolution cycle (Figure 6) [106,134], new research directions could be opened for the most efficient extraction of cannabis products in low-cost and low-risk.

5. Conclusions

Fueled by the recent opportunities provided by changing legislation, as well as the recent scientific advances, hemp's product market capacity shows a historic jump off as high as 10 times in less than a decade. The tried extraction protocols are borrowed from those used traditionally for other biomasses, and the obtained results are, in some cases, contradictive for hemp, indicating that this step remains the bottleneck of hemp downstream processing technology.

Among hemp products, CBD now has the greatest market potential and is highly attractive for its recreational and medical potentials. During CBD purification, the co-extraction of its psychoactive cousin, THC, poses a significant challenge. Therefore, ideal extraction technology is expected to be not only cannabinoid-specific but also selective

toward the extraction of CBD. Additionally, the chosen method needs to be safe, efficient (both in terms of economy and time), and capable of maximizing the yield (minimum CBD loss). Recent studies have demonstrated the successful application of supercritical fluids and organic solvents in the extraction of cannabinoids, terpenes, and fatty acids. Despite the effectiveness of organic solvents in extraction, the SC-CO_2 seems to be superior in terms of operation economy, environmental concerns as well as large-scale purification technicalities.

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