UDC: 633.88:547.94]:543.956.4
Review article

THE ROLE AND IMPORTANCE OF THE DECARBOXYLATION PROCESS IN THE PRODUCTION OF QUALITY FULL-SPECTRUM CANNABIS EXTRACT FOR MEDICINAL PURPOSES

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Abstract

Cannabis is now one of the most thoroughly studied and analyzed plant materials. More than 100 cannabinoids have been isolated and identified in cannabis along with the primary psychoactive component, Δ9-tetrahydrocannabinol (Δ9-THC). In addition to Δ9-THC, there are other components of cannabis that are medically beneficial. For example, cannabidiol (CBD) and cannabigerol (CBG) can moderate or influence the psychoactive effects of Δ9-THC. The raw cannabis plant consists of cannabinoids in their acidic form. When someone states that cannabinoids are in their "acidic form", they are referring to the chemical structure of the compound itself. A cannabinoid in its acidic form has a carboxyl group (-COOH) attached. While tetrahydrocannabinolic acid (THCA) is the non-psychoactive precursor to THC, it does not bind to the CB1 and CB2 receptors. Instead, it binds with other cannabinoids receptors in the endocannabinoid system. When THC is not decarboxylated, it is THCA. Although THCA possesses therapeutic effects, like anti-inflammatory and neuroprotective qualities, it is not in its most beneficial or psychoactive form. Decarboxylation is a chemical reaction that removes a carboxyl group (-COOH) and releases carbon dioxide (CO2). The two main catalysts for decarboxylation to occur are heat and time. High CBD strains tend to decarboxylate a bit slower than those with high THC content. Decarboxylate high CBD strains by baking them for 15-20 minutes at 149°C and decarboxylate high THC strains by baking them for 10-18 minutes at the same temperature (149°C) in the oven. Full decarboxylation may require more time to occur. It is important to keep tight temperature control applying cannabis to various technological applications. While heat is needed to decarboxylate the acids into the active form of cannabinoids our bodies can use, extreme temperatures can destroy many of the important plant materials that contribute to positive health outcomes, like terpenes.

Keywords: cannabinoids, carboxyl group, chemical reaction, decarboxylation, temperature.

1. Introduction

Cannabis is an annual, biennial, pollinating plant, from the genus of flowering plants that belongs to the family Cannabinaceae. There are three types of cannabis: *Cannabis sativa* L., *Cannabis indica* L., and *Cannabis ruderalis* L. (Abuhasira *et al.*, 2018). These three species are also considered subspecies of the species *Cannabis sativa*. The plant is also known as hemp, although this term is often used for certain varieties of cannabis, which are cultivated for making medicines (Ammerman *et al.,* 2015). The plant *Cannabis sativa* L., in the form of crude drugs, marijuana, hashish, or hash oil, is the most widely consumed and popular recreational/medicinal botanical drug product in the world. At present, there is a growing interest in cannabis and its medicinal uses (Bar-Lev Schleider *et al.*, 2018).

The *Cannabis* spp. contains more than 400 different ingredients, including at least 60 cannabinoids. Cannabinoids are divided into several subclasses: cannabigerol (CBG), cannabichromene type (CBC), cannabidiol (CBD), cannabinol (CBN), cannabitriol (CBT), Δ9-tetrahydrocannabinol (THC) – a heterogeneous group of cannabinoids (Fischedick *et al.,* 2009). Of all these types, the most proven are the effects of: CBD (cannabidiol) – a non-psychoactive cannabinoid, which is not intoxicating and euphoric. It is often used to help reduce inflammation and pain (Hazekamp *et al.*, 2007). Also, THC, a psychoactive cannabinoid, which is considered to be the main psychoactive compound in cannabis, as well as the presence of secondary metabolites – terpenes, which are thought to contribute to the therapeutic effect (Zivovinovic *et al.*, 2018). The secondary metabolites (terpenes) are mixed to provide a ratio to the major cannabinoids (THC and CBD), whereby the cannabinoids are then isolated, purified, and formulated as pharmaceutical drugs. The other main compounds in cannabis are terpenes. These are aromatic compounds which give cannabis varieties distinctive smells and tastes (Russo, 2011). Terpenes may have additive therapeutic action, meaning they may work together with cannabinoids to modify or enhance medicinal effects (Booth and Bohlmann, 2019). To date, more than 120 different terpenes have been identified in cannabis. Unlike cannabinoids, all major terpenes present in cannabis (e.g., limonene, humulene, α-bisabol, myrcene, α-pinene, and β-caryophyllene) can be found abundantly in nature. It is thought that the terpenes work together with cannabinoids to modify or enhance their effects. This is known as the 'entourage effect' (Baron, 2018).

The cannabinoids and terpenes are produced in the plant's resin glands. These are called glandular trichomes. The trichomes are located on the surface of the entire plant. The largest concentration of the glands are found in the flowering heads of the female plant (Mahlberg et al., 1980).

The cannabinoids exist mainly in an inactive acid form. The pharmacologically active cannabinoids (e.g., THC/CBD) are formed when cannabis is heated to a temperature of at least 180°C resulting in 'decarboxylation'. With the use of a vaporizer, the active cannabinoids are released from the glandular trichomes in a vapour at 230°C which can then be inhaled into the lungs (Mahlberg and Kim, 2004).

In Cannabis sativa, cannabinoids are biosynthesized as phytoprotectants; in fresh biomass, 95% of the THC, CBD, and CBC exist as their acidic parents: tetrahydrocannabinolic acid (THCA), cannabidiolic acid (CBDA), and cannabichromenic acid (CBCA). The cannabinoids are biosynthesized in the glandular trichomes, or "marijuana bud" of female flowers. Trichome-poor male flowers are typically very low in cannabinoids. Trichomes are also present on bracts, leaves, and on the underside of the anther lobes of male flowers (Fischedick et al., 2010).

During the biosynthesis of various phytocannabinoids, cannabigerolic acid (CBGA) serves as the key branching point for a number of cannabinoids such as Δ9-THC, CBD, cannabielsoin (CBE), cannabichromene (CBC) and cannabicyclol (CBL) families of phytocannabinoids. Δ9-Tetrahydrocannabinol is transformed into CBN through an oxidative aromatization, and CBN can in turn be photochemically rearranged into the catechol, cannabinodiol (CBND) (Burdick *et al.*, 2010).

Preparations obtained by the processing of cannabis can be used for medical purposes for the following indications: states of stress, nervousness, anxiety, depression, etc. Helps maintain the intestinal flora, and is used against nausea and vomiting, especially during chemo- or radiation therapy for malignant diseases. Relieves pain of various origins and can be used for muscle spasms and the prevention of cardiovascular disease (Dryburgh *et al.,* 2018).

In our country, the production, use and sale of cannabis are regulated by the amendments to the Law on Use of Narcotic Drugs and Psychotropic Substances. This law allows the cultivation of hemp intended for the production of narcotic drugs for medical or scientific purposes, and is allowed only to legal entities that have an Authorization for the cultivation of hemp issued by the Ministry of Health, with the prior consent of the Government of the Republic of North Macedonia (Sluzben Vesnik na R.M. br. 103 od 2008.).

Over the last decade the number of patients exposed to medicinal cannabis (THC- and CBD-extracts) has increased alongside a variety of conditions where patients have reported symptomatic benefit. These include, but are not limited to: chronic pain; multiple sclerosis; nausea, vomiting and appetite stimulation; epilepsy; and anxiety (Devinsky et al., 2016). Others include: sleep disorders, fibromyalgia, Gilles de la tourette syndrome, therapy-resistant glaucoma, Crohn's disease and ulcerative colitis, Parkinson's disease, rheumatoid arthritis, attention-deficit disorder (ADD), and posttraumatic stress disorder (PTSD). Each has shown varying degrees of response, and many still require being confirmed by good clinical science (MacCalluma and Russo, 2018).

Medicinal cannabis is a novel class of medicine. It is not a panacea or a cure for the disease. Currently, in most parts of the world, it is also not a first-line treatment. Rather, eligible patients have not responded well to other medicines, or experience unacceptable side effects (Russo, 2017). While only a few are officially registered medicines, cannabis products for medical use are still required to meet certain quality standards. As a result, government medicine regulators often are managing a patient's and doctor's demand for medicinal cannabis alongside the requirements of product safety, quality, and efficacy (Chandra *et al.*, 2017). So, as much as there is a need for clinical data and prescribing guidance, robust information to support policy development and decision-making by government officials is just as essential.

1.1 What is decarboxylation and why does cannabis need it?

All cannabinoids contained within the trichomes of raw cannabis flowers have an extra carboxyl ring or group (-COOH) attached to their chain. For example, tetrahydrocannabinolic acid (THCA) is synthesized in prevalence within the trichome heads of freshly harvested cannabis flowers. In most regulated markets, cannabis distributed in dispensaries contains labels detailing the product's cannabinoid contents. THCA, in many cases, prevails as the highest cannabinoid present in items that have not been decarboxylated (e.g., cannabis flowers and concentrates) (Moreno et al., 2020).

Tetrahydrocannabinolic acid has several known benefits when consumed, including anti-inflammatory and neuroprotective qualities. But THCA is not intoxicating and must be converted into THC through decarboxylation before any effects can be felt (Kenneth and Chad, 2021).

The two main catalysts for decarboxylation to occur are heat and time. Drying and curing cannabis over time will cause partial decarboxylation to occur. This is why some cannabis flowers also test for the presence of small amounts of THC along with THCA. Smoking and vaporizing will instantaneously decarboxylate cannabinoids due to the extremely high temperatures present, making them instantly available for absorption through inhalation.

While decarboxylated cannabinoids in vapor form can be easily absorbed in our lungs, edibles require these cannabinoids present in what we consume for our bodies to absorb them throughout digestion. Heating cannabinoids at a lower temperature over time allows us to decarboxylate the cannabinoids while preserving the integrity of the material we use so that we may infuse it into what we consume (Veress et al., 1990).

The THCA in cannabis begins to decarboxylate at approximately 105°C after around 30-45 minutes of exposure. Full decarboxylation may require more time to occur. Many people choose to decarboxylate their cannabis at slightly lower temperatures for a much longer period of time in attempts to preserve terpenes. Many mono- and sesquiterpenes are volatile and will evaporate at higher temperatures, leaving potentially undesirable flavors and aromas behind. The integrity of both cannabinoids and terpenoids are compromised by using temperatures that exceed 300°F (149°C), which is why temperatures in the 200's are recommended (Gigopulu et al., 2022).

Heat and time can also cause other forms of cannabinoid degradation to occur. For example, CBN (cannabinol) is formed through the degradation and oxidization of THC, a process that can occur alongside decarboxylation. CBN accounts for a much more sedative and less directly psychoactive experience (Chang and Zhongli, 2021).

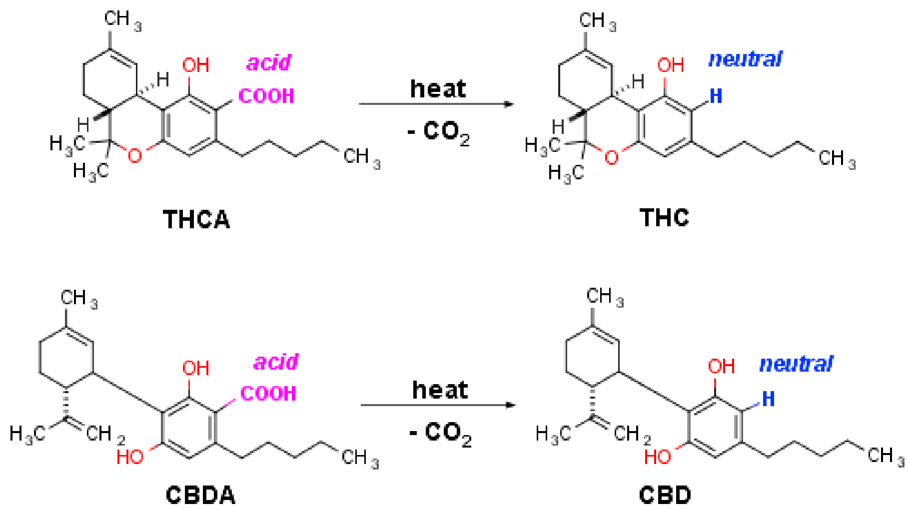

Figure 1. Chemical reactions of decarboxylation of THCA and CBDA (https://ascensionsciences.com/newsroom/technical-articles/effects-of-storage-conditions-on-cannabinoid-conditions/)

2. The importance of decarboxylation process in a pre- and post-extraction phases in production of cannabis crude oil

What makes THC different from THCA, and CBD different from CBDA? Hinges on a process known as "decarboxylation," or "decarbing," whereby raw cannabis is heated so that the chemical structure of the acid cannabinoids changes to a neutral (non-acid) form. THC and CBD are the neutral forms of THCA and CBDA. The major difference, chemically, between acid cannabinoids and their neutral counterparts is an extra -COOH bond, known as a "carboxyl" group, which consists of a carbon-oxygen-oxygen-hydrogen molecular cluster (Solowij et al., 2014). In order to transform cannabinoids acids into their neutral forms, they need to go through a process that removes the carboxyl group. This process is referred to as decarboxylation. As it turns out, the bond holding the carboxyl group in place is pretty weak and easily broken by a combination of heat and time. Decarboxylation is what happens when the carboxyl group is shed due to high temperature or combustion (Wang et al., 2016).

The raw cannabis plant consists of cannabinoids in their acidic form. When one states that cannabinoids are in their "acidic form", they are referring to the chemical structure of the compound itself. A cannabinoid in its acidic form has a carboxyl group (-COOH) attached. While THCA is the non-psychoactive precursor to THC, it does not bind to the CB1 and CB2 receptors. Instead, it binds with other cannabinoids receptors in the endocannabinoid system. When tetrahydrocannabinol (THC) is not decarboxylated, it is THCA. Although THCA possesses therapeutic effects, like anti-inflammatory and neuroprotective qualities, it is not in its most beneficial or psychoactive form (Dussy et al., 2005).

The two main catalysts for decarboxylation to occur are heat and time. Drying and curing cannabis over time will cause partial decarboxylation to occur. Therefore, some cannabis flowers also test for the presence of small amounts of THC along with THCA. Heating cannabinoids to a lower temperature over time allows the cannabinoids to be decarboxylated while preserving the integrity of the material used so that it can be incorporated into what is consumed (Roggen *et al.*, 2018).

The therapeutic potentials of acid cannabinoids are:

- THCA: Anti-nausea, anti-inflammatory, neuroprotective, anti-convulsant, fat-storage reducing, metabolic regulator and stress reducing.
- CBDA: Anti-anxiety, anti-inflammatory, painkilling, anti-nausea and anti-convulsant.

The therapeutic potential of neutral cannabinoids are:

- THC: Anti-nausea, weight gain in anorexia and AIDS, anti-inflammatory, painkilling, neuroprotective, muscle relaxing, and more.
- CBD: Anti-epileptic, anti-anxiety, anti-depressive, anti-inflammatory, antipsychotic, antispasmodic, reduces insulin resistance, and more (Nair et al., 2015).

Efficient production of Δ9-THC, CBD, and CBG from cannabis is important for the development of dosage formulations to facilitate the successful medical use of cannabis. These neutral cannabinoids do not occur at significant concentrations in plants. Cannabis synthesizes primarily the carboxylic acid forms of Δ9-THC, CBD, and CBG, namely, Δ9-tetrahydrocannabinolic acid A (THCA-A), cannabidiolic acid (CBDA), and cannabigerolic acid (CBGA). These acidic cannabinoids are thermally unstable and can be decarboxylated when exposed to light or heat via baking or refluxing. As a result, the requisite forensic analyses are usually expressed as the sum of the acidic and neutral forms of the cannabinoids. Reports also show that Δ9-THC itself readily oxidizes to cannabinol (CBN) with oxygen and light during the decarboxylation process (Lewis-Bakker *et al.,* 2019).

2.1 Temperature and time – the most important parameters for decarboxylation of CBD and THC

There is a dispute over the exact decarboxylation temperature of CBD. According to studies, however, it appears to be approximately 230°F (110°C). As for the timeframe, neither THC nor CBD will decarboxylate instantaneously at their precise "decarb" temperatures. A longer period – typically between 40 and 60 minutes – will be required for the -COOH group to break down into water and carbon dioxide. Also, be advised that the boiling points of cannabinoids, terpenes, and flavonoids are much different than their decarboxylation points (Nuapia et al., 2021).

Boiling points for these compounds have been much more thoroughly studied than decarboxylation temperatures:

- Cannabinoids: CBD = 356°F / 180°C; CBC = 428°F / 220°C; THC = 314.6°F / 157°C; CBN = 365°F /185° C; THCV = 428°F / 220°C (HATCH A Breakthrough Experience. Boil Points of Cannabis & Terpenes).
- Terpenes: Myrcene = 330°F–334°F / 165°C–168°C; Limonene = 350.6°F / 177°C; Linalool = 388.4°F / 198°C; α-pinene = 312.8°F / 156°C (Steven Cargyle, 2021).

It is advisable to keep the decarboxylation temperatures at a low point to preserve the terpenes. There are also compounds that are volatile and evaporate at higher temperatures. The result is an unpleasant odor and unpleasant taste. If terpenes are to be stored, temperatures in the range of 200-300°F should be maintained.

Now that the key to faster decarboxylation is known to be greater heat (in common sense), this should be a clear process. Unfortunately, this is not easy. The existence of another mechanism means that decarboxylation temperatures must be controlled very carefully (Philpott, 2021).

Table 1. Decarboxylation temperature and times chart (Alex Trpkovich, 2021. Green Camp. https://greencamp.com/decarboxylation/)

Temperature ± 5°F	Heating mode	Plant material time		Kief* / Hash time		Cannabis Oil time
		High THC	High CBD	High THC	High CBD	
300	Oven	10-18 min	15-25 min	5-10 min	10-15 min	n/a
250	Hot oil bath / reactor for decarboxylation	n/a	n/a	n/a	n/a	Until bubbles taper off
245	Oven	50-60 min	60-90 min	30-40 min	40-50 min	n/a
212	Boiling water bath	90-120 min	2-4 h	90-120 min	2-4 h	n/a

**Kief is the name given to the crystallized structures that stick to the surface of pure weed. In other words, it is essentially cannabis pollen that acts as a defense mechanism to keep pests away. Kief is a popular "by-product" of weed consumption that is often used for edible creation.*

To decarboxylate Kief or Hash in an oven, bake it for 10 minutes at 300°F (149°C). Need to have in mind that, at higher temperatures, Kief and Hash tend to decarboxylate faster than dried flowers. High CBD strains tend to decarboxylate a bit slower than those with high THC content (Olejar and Kinney, 2021).

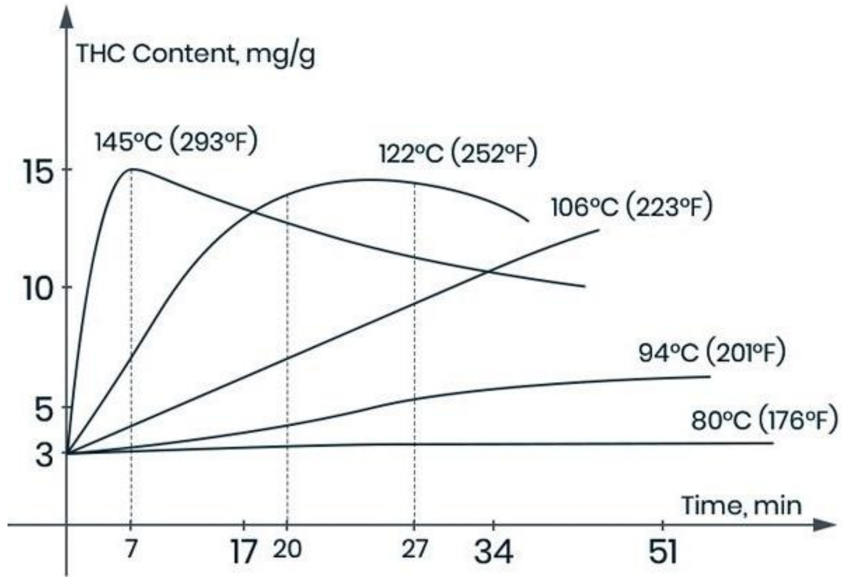

Figure 2. Effect of heating time and temperature on the THC content of an n-hexane cannabis extract after heating on the glass surface in an open reactor (https://activegearguy.com/blogs/fun-facts/decarboxylation-decarb-a-necessary-chemical-reaction)

Heat and time can also cause other forms of cannabinoid degradation to occur. For example, CBN (cannabinol) is formed through the degradation and oxidization of THC, a process that can occur alongside decarboxylation. CBN accounts for a much more sedative and less directly psychoactive experience (Citti et al., 2018).

It is important to keep tight temperature control applying cannabis to various technologically applications. While heat is needed to decarboxylate the acids into the active form of cannabinoids our bodies can use, extreme temperatures can destroy many of the important plant materials that contribute to positive health outcomes, like terpenes. Each individual terpene may have its own therapeutic health benefits, but also carries its own sensitivity to heat. If cannabis is heated above 300°F, need to run the risk of denaturing many important plant compounds (Fiorini et al., 2020).

For this process, a digital oven-safe thermometer is recommended so that the temperature that works best for the final product can be monitored and assessed. Additionally, it is recommended to limit the number of oven openings during the decarboxylation process, as this significantly changes the oven temperature. Opening the door will cause the temperature to drop and change the reliability of the weather and temperature recordings (Eichler et al., 2012).

Table 2. Content of the cannabinoids before and after decarboxylation by the Kief and Cannabis Trim (Patrick Lynch, 2020. Way of Leaf. https://wayofleaf.com/education/decarboxylation)

Cannabinoid	Before decarboxylation (Content in %)		30 minutes of decarboxylation (Content in %)		60 minutes of decarboxylation (Content in %)	
	Kief	Cannabis Trim	Kief	Cannabis Trim	Kief	Cannabis Trim
THCA	24.5	6.5	2.6	2.9	0.1	0.2
THC	3.8	0.6	25.4	4.8	25.5	6.9
CBDA	0.6	0.2	0.3	0.2	0.3	0.1
CBD	0	0	1	0	0.1	0.1
CBN	0.4	0	1	0	1.4	0
Moisture	0	3.4	0	4.5	0	0
Total cannabinoids	29.3	7.3	30.3	7.9	27.4	7.3

2.2 Other factors that impact of decarboxylation process

There are many factors that will impact the results of the final product when decarboxylating cannabis. Here are a few additional considerations to keep in mind:

- The strain of cannabis used: The type of cannabis flower used will affect decarboxylation time and temperature recommendations. Each type of cannabis contains different amounts and ratios of different cannabinoids and terpenes. Because each cannabinoid and terpene decarboxylates at different temperatures, need to consider the best temperature and cooking time for your particular species.
- The freshness of product: There will be noticeable differences in the final product depending on the freshness of the material you start with. The concentration of cannabinoids will vary depending on the freshness of the starting material, which will affect the final product.
- Equipment variability: If an oven or other equipment such as a cooker, slow cooker or instant cooker is used, there will be small variables in the cooking equipment that may affect the final product. Different vessels will have different temperatures when placed in the same setting, which is why it is recommended to use a digital thermometer during the process.
- Uniformity of product size: The size of the cannabis flower buds upon decarboxylation will have an impact on the final product. If the cannabis flower buds are loosely broken up by hand, that will cook differently than cannabis buds that have been run through a grinder and now have a small, uniform texture. Additionally, decarboxylating finely ground cannabis powder, also known as kief, will require much shorter cooking times to prevent burning and denaturing of the important compounds in the plant.

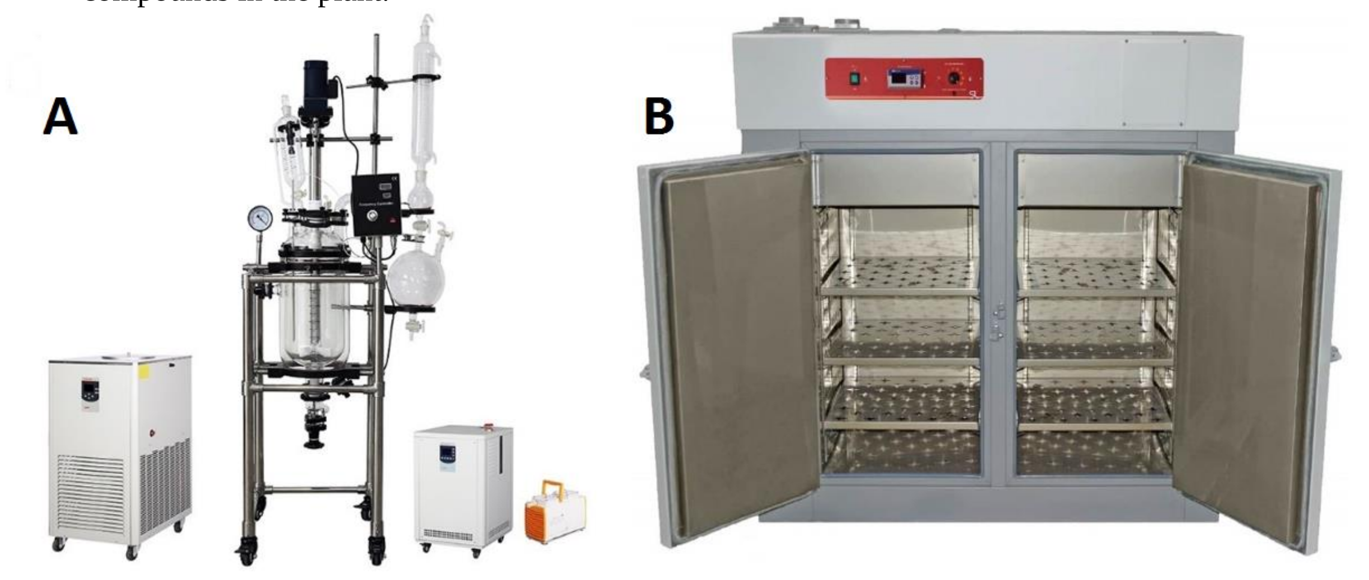

Figure 3. Examples of equipment for decarboxylation process of: A) Cannabis crude oil (Decarboxylation Jacketed Glass Reactor) and B) Dried (and grinded) cannabis flowers or biomass (Manufacturing Ovens)

3. Conclusions

In order to produce a quality cannabis extract that will be used for medical purposes, the process of decarboxylation must be included in the production process of cannabis preparations. This is a key process in the production stages of medical cannabis extracts. The process of decarboxylation involves chemical conversion under the influence of high temperature or other co-factors (as a time) of inactive forms of cannabinoids, by removing their carboxyl group, into active forms of cannabinoids that will be responsible for the therapeutic effect of cannabis preparations.

Manufacturers of medical cannabis products include decarboxylation in their production protocols as a phase before cannabis extraction (decarboxylation of raw material / dried flowers) and as a phase after extraction (decarboxylation of crude oil). The most important parameters to perform a good decarboxylation process are time, temperature, and of course, the choice of quality decarboxylation equipment.

From the review of published literature data, it can be concluded that the highest concentration of THC (about 15 mg/g) is obtained when the material is decarboxylated at 122°C for 27 minutes. As for the conversion of CBDA to CBD, a higher temperature is required, about 150°C, for about 30 minutes.

Also, from the review of the literature, a change in the content (in %) of the main cannabinoids can be noticed, before and after decarboxylation content. For example, the content of CBDA before decarboxylation was 0.6%, and 1 hour after decarboxylation decreased to 0.3%. Whereas, the CBD content before decarboxylation was 0%, and after 30 minutes it increased to 1%. Regarding the content of THCA: before decarboxylation it was 24.5%, and 1 hour after decarboxylation it decreased to 0.1%. The THC level before decarboxylation was 3.8%, but after 1 hour of decarboxylation, it increased to 25.5%.

The decarboxylation of dried cannabis flowers, as well as crude oil, remains a process of further research by manufacturers and scientists in the field of medical cannabis. The interest in this area is great, so in the future manufacturers and researchers are expected to publish more specific information and direct data on this important process in the production of cannabis extracts for medical purposes.

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