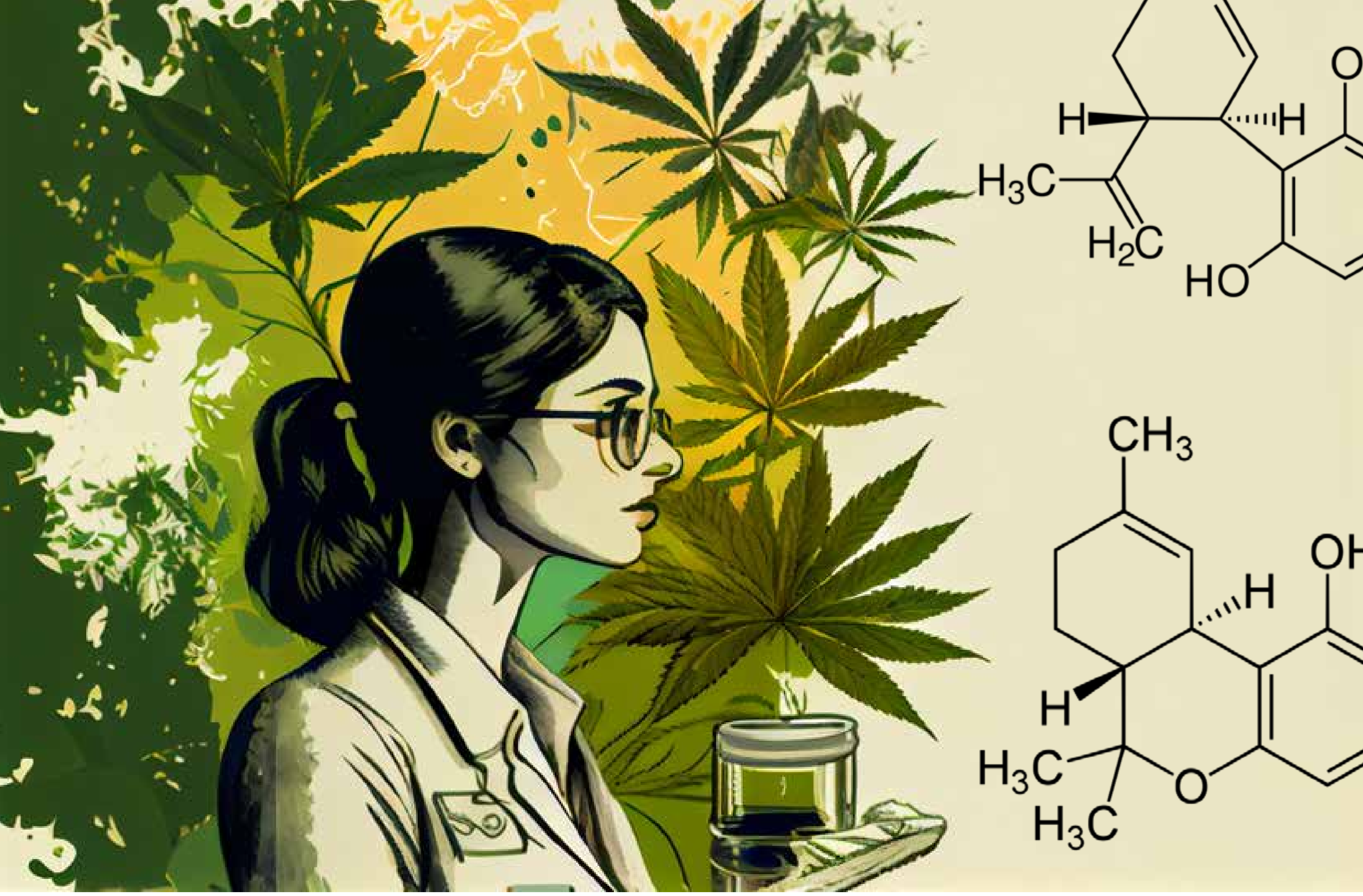


WHITEPAPER

Cannabis Workflow

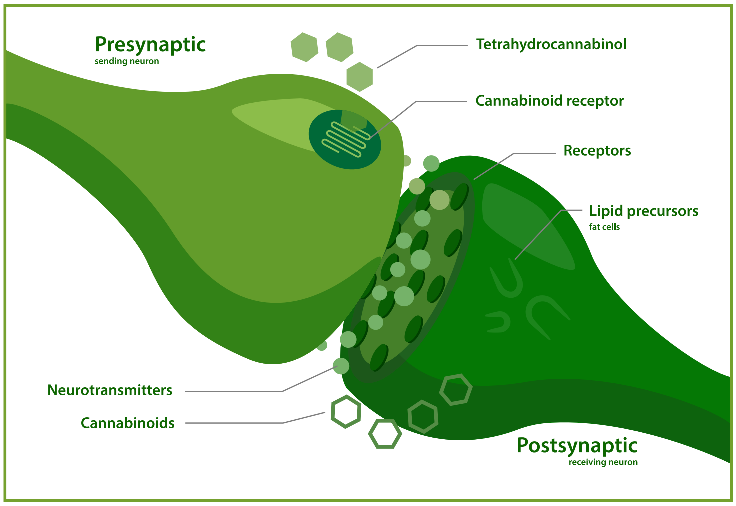
Obtaining hemp extracts safely and efficiently

Greater freedom to cultivate and use hemp in many parts of the world is not the only thing making the hearts beat faster of people who consume cannabis because of its intoxicating effects. Probably the oldest medicinal and useful plant cultivated in humanity's history, it is also rich in metabolic products that have pharmacological and therapeutic potential. In addition to pharmaceutical companies, manufacturers of food and dietary supplements as well as beverages and personal care products have set a goal of expanding on this potential. And for good reason: It is estimated that the global cannabis market will generate sales of around EUR 50 billion in 2023, with an increase of 15 percent per year by 2027 [1]. A worthwhile business, and not least with over-the-counter hemp products.

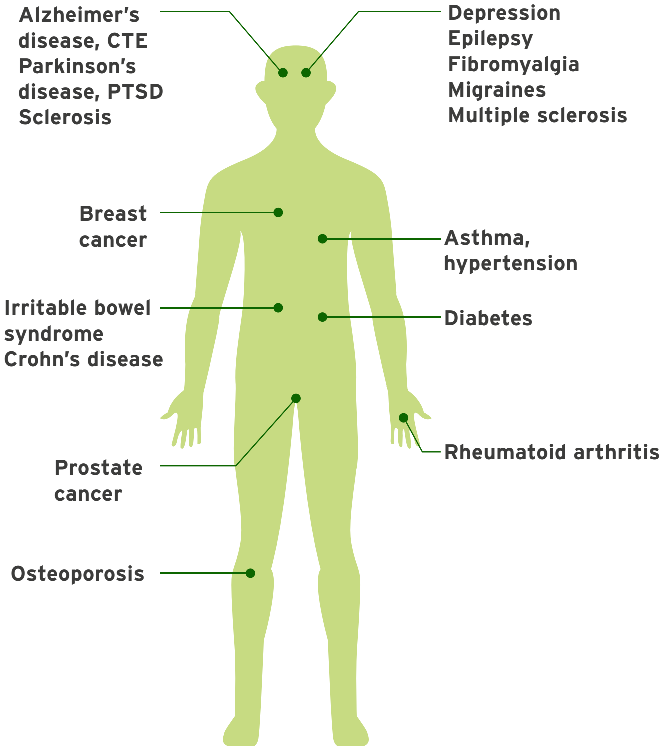
However, these products are subject to strict controls, and they must not contain Δ^9-tetrahydrocannabinol (THC) in significant quantities, which is the active ingredient attributed with the intoxicating effect of cannabis. On the other hand, the question arises of how to yield the highest possible quantities of the hemp products that are meant to have the desired commercial benefits. Extraction technology will be hugely important here. This white paper highlights various common methods that are widely used to extract the cannabinoids THC and CBD. This white paper also highlights the role played by temperature, which must be regulated and maintained at the optimal level, a topic of great importance for the success of the overall process.

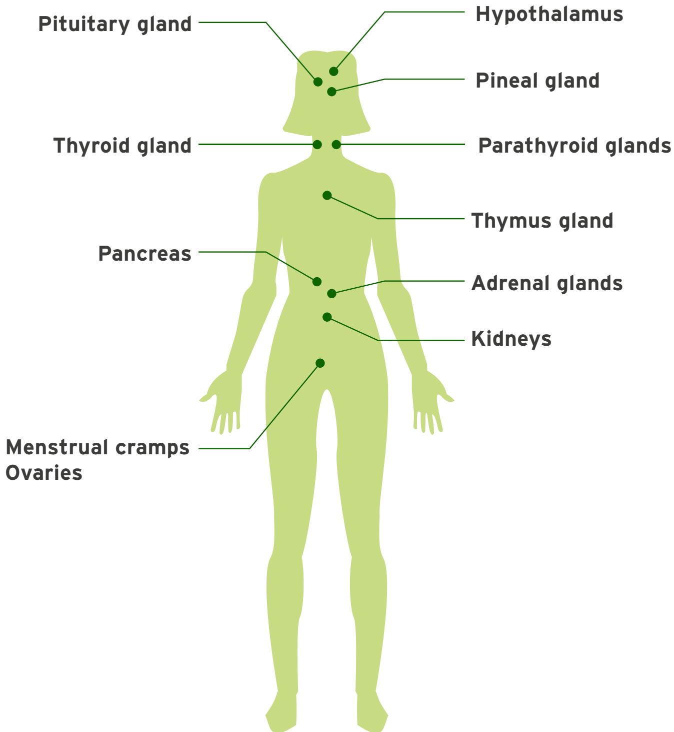
[Text from: Guido Deuβing & Silja Moser-Salomon]

Cannabis, a plant genus belonging to the hemp family, is probably the oldest known useful and medicinal herb. According to the latest findings, this plant was first domesticated in East Asia in the early Neolithic period [2]. From China, it made its way around the globe via India and the early civilizations of the Near East. Its spread was not solely due to the extraction of plant fibers, as hemp can be used to make rope, cord, nets, thread, and yarn [3]: Historical sources dating back to 2000 BCE suggest that cannabis was grown primarily for purposes of drug consumption. This intoxicating plant then spread to the widest corners of the world: to Africa in the 13th century, to Latin America in the 16th century, and from the Indian subcontinent to North America in the 20th century [2].



CBD is also used for neuropathic pain.





Integrating CBD into everyday life can have a positive effect on mind and body.

To date, more than 530 different and chemically distinct compounds, which originate from the primary and secondary metabolism of the hemp plant, have been identified.
These include approximately 110 cannabinoids, the most important of which currently being Δ9-tetrahydrocannabinol (THC) and cannabidiol (CBD), as well as 140 terpenoids. The latter are of particular importance due to their organoleptic properties, their potential for chemical fingerprinting of different varieties, and their synergistic interaction with cannabinoids. [7]

In addition to its intoxicating effects, which are attributed in particular to Δ9-tetrahydrocannabinol (THC), it was known early on that cannabis also had health-promoting potential. In China, for example, it has been used to treat a wide range of conditions, including constipation, gout, malaria, rheumatoid arthritis, fever, appetite loss, excess phlegm, and speech difficulties [4]. Today, the pharmacological potential of cannabis – with there being a distinction made essentially between two types, namely ***Cannabis sativa*** and ***Cannabis indica*** [5] – is considered to be assured. Its therapeutic effects have been demonstrated with regard to various conditions, such as chronic pain, multiple sclerosis (MS), epilepsy, and anxiety [6]. But what makes hemp such a useful pharmaceutical product?
Far from the initial, simplified view that only Δ9-THC carries the biological activity of cannabis, Flavio A. Franchina, Lea M. Dubois, and Jean-François Focant from the Molecular Systems, Organic and Biological Analytical Chemistry Group, at the University of Liège in Belgium, note that numerous studies have shown the importance and interaction of the various metabolites present in cannabis, leading to the discovery and isolation of new active compounds [7]. Depending on the type, cannabis contains different amounts of Δ9-THC as well as other endogenous metabolites, such as cannabidiol (CBD), also a cannabinoid. CBD is attributed, among other things, with having anti-seizure, anti-inflammatory, pain-relieving, anxiety-reducing, and calming effects [8]. Though individual cannabis metabolites demonstrated stronger effects than others, the balance and interaction between all of the metabolites is important for the overall effect of the hemp plant. Besides the significance for medical applications, this is also important for cannabis being used in food and cosmetics.

Extracting Active Ingredients from Cannabis, Step-by-Step

In order to market cannabis successfully on the commercial market, it is first necessary to have a firm understanding of the chemical composition of the primary and secondary metabolites contained in cannabis. In addition, the desired cannabis compounds must be isolated cleanly and efficiently, then concentrated in relevant quantities. Efficiency is a requirement. Various established, scientifically-based extraction techniques are used for this, and these methods have already proven themselves in a wide range of applications. In essence, these are three solvent-based extraction methods that separate the active ingredients from the plant material. Let's take a closer look at the basic steps of this process.

Extraction

With this separation method, one or more components are dissolved out from a mixture of several individual solid, liquid, or gaseous substances by means of a solid, liquid, or gaseous extraction agent. Preparing coffee in a standard household coffee machine is a common example of extraction, which is followed by a filtration process to separate the aromatic liquid phase from the extracted coffee powder.

Distillation

This method is a thermal separation process used to extract evaporable fluids or solvents from non-evaporable material, thereby isolating and collecting them via condensation. Apart from the distillation apparatus, no other basic materials, such as adsorbents or solvents, are required. The compounds are separated solely by applying thermal energy and allowing for the required boiling temperature. Distilleries, for example, use distillation to obtain spirits as a distillate from a mash mixture, i.e., fermented grain.

Supercritical fluid extraction

This method is a safe, non-toxic, environmentally-friendly procedure for extracting or removing active ingredients from plant sources, whereby suitably processed plant material is extracted with supercritical carbon dioxide (CO_2). This form of fluid extraction is used, for example, to decaffeinate coffee beans, extract nicotine from tobacco, manufacture essential oils, or extract hops in beer brewing. Similarly, this procedure is also used to extract a cannabinoid-rich resin from hemp. With this method, CO_2 is brought to a supercritical state by changing the pressure. In the supercritical state, carbon dioxide has characteristics which are between a gas and a liquid, with supercritical carbon dioxide being as dense as a liquid but having the viscosity of a gas.
The active ingredients are extracted from the cannabis while the supercritical carbon dioxide flows through a chamber containing the hemp material. When the pressure is finally reduced, the carbon dioxide evaporates, leaving behind a residue in the form of the solvent-free cannabis extract (see Fig. 1: Phase diagram of carbon dioxide).

By the way: By adjusting the temperature and pressure, CO_2 systems are capable of yielding extracts with a complete terpene profile. Sophisticated extraction devices also allow for fractionation and isolated extraction of the desired compounds. If the system has an integrated cooling unit, it is possible to liquify and recycle the carbon dioxide being used. On the other hand, using recirculated heat in the evaporator, with temperatures around 30°C, yields high-purity extracts, as this helps to completely remove the carbon dioxide from the extract. Consistent, precise temperature control of both compounds is crucial for safe, reliable process control as well as for high sharpness of separation and yields.

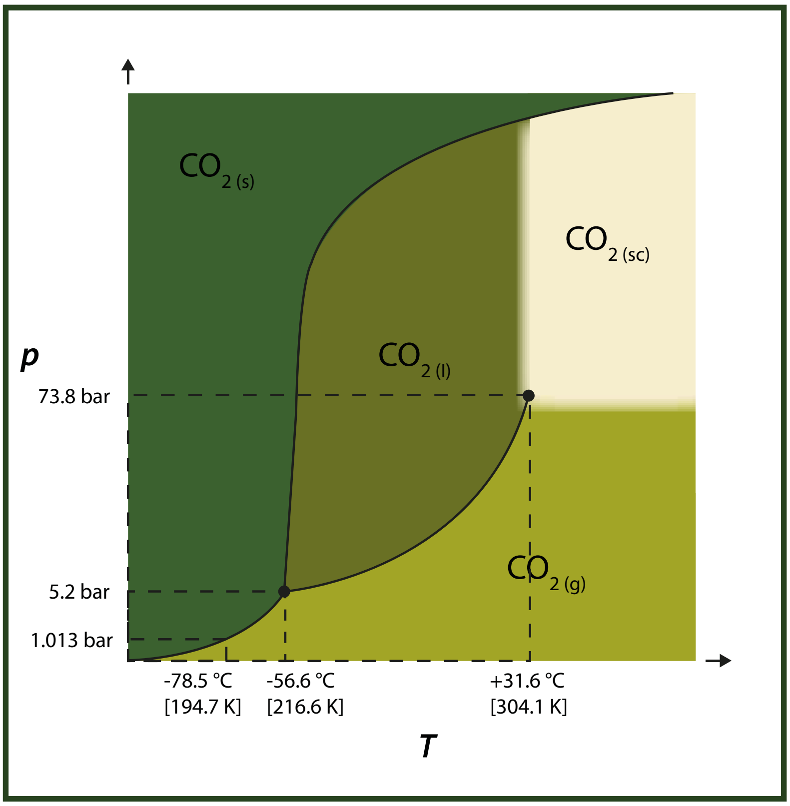


Fig. 1: Phase diagram of carbon dioxide

Vacuum distillation

Distillation under reduced pressure: Placing a liquid mixture under vacuum decreases the boiling points of the liquid to be separated, shifting the thermal equilibrium, which has a favorable effect on the separation capacity. However, under vacuum, the vapor density and distillation rate are also reduced, i.e., there are fewer molecules per unit of space. This affects the distillation rate, so distillation is often attempted under atmospheric conditions wherever possible because it is faster. On the other hand, the thermal load on temperature-sensitive components is reduced under vacuum, which in turn has a favorable effect on the distillation results. In addition, the process speed can also be improved by decreasing the heating times.

Fluid hydrocarbon extraction

One conventional method to extract active ingredients from a plant is to use liquid hydrocarbons with low molecular weights, like butane or propane, as seen in common household lighters. Liquid hydrocarbon is first passed and filtered through a bed of hemp material, resulting in a solvent extract containing the intended active ingredients and free of undesired matrix components. For further processing, a pressure reduction is required. This causes the liquid hydrocarbon to evaporate, with only a solvent-free, cannabinoid-rich extract remaining.
Special safety precautions are necessary when using liquid hydrocarbon extraction due to the flammability of this compound. Low temperatures are needed to keep the pressurized hydrocarbon in a liquid state. Recirculating temperature control units (TCUs) that allow cooling to -60°C (-76°F) and below simplify process control. At the same time, a heat distribution that is as homogeneous as possible is necessary to completely evaporate the hydrocarbon used and yield a solvent-free extract. The cooling and heating capacity of the TCUs must correspond to the required capacity for the size of the application.

Decarboxylation

This technique makes use of a chemical reaction, separating a carbon dioxide molecule from a molecule, which is often catalyzed at a higher temperature or enzymatically. The heat effect facilitates and promotes the extraction of the cannabinoids THC and CBD, which are normally present in the cannabis plant as pharmacologically inactive carbonic acids (THC-A and CBD-A). With decarboxylation, a carbon dioxide molecule is separated by applying heat, and both compounds are converted into their active phenolic forms (THC and CBD). Dried plant material is shredded and heated to 100–150°C for a specific period of time. In the case of extracts, decarboxylation is done following winterization by heating the resulting oil extract (100 to 160°C)

Winterization

This procedure is used to stabilize edible oils by crystallizing and filtering out flocculated fatty components, such as wax and high-melting glycerides, at temperatures up to 5°C. Winterization can be used to separate compounds with only slight differences, e.g., with similar boiling points, by making use of their melting points, i.e., via the liquid-solid phase transition instead of the liquid-gaseous phase transition.

Extraction with ethanol

Alcohol is able to easily pass through the cell walls and cell membranes of plants, gently dissolving out the substances contained in the cells. This property is also utilized when extracting cannabinoids from the cannabis plant, using food grade or USP (United States Pharmacopeia) grade ethanol as a solvent. Alcohol extraction has great variability with regard to the vessels and reactors used. However, the residence time of the plant material in the alcohol and the temperature are crucial for the extraction process. Widely used, ethanol is cooled to -20°C (-4°F) and then pumped into a cannabis container. If a jacketed container is used to cool the ethanol, a low-temperature TCU acts as a cooling source. Once the soaking time elapses, the solution is either filtered out, or the depleted plant material is removed like a tea bag from a cup.

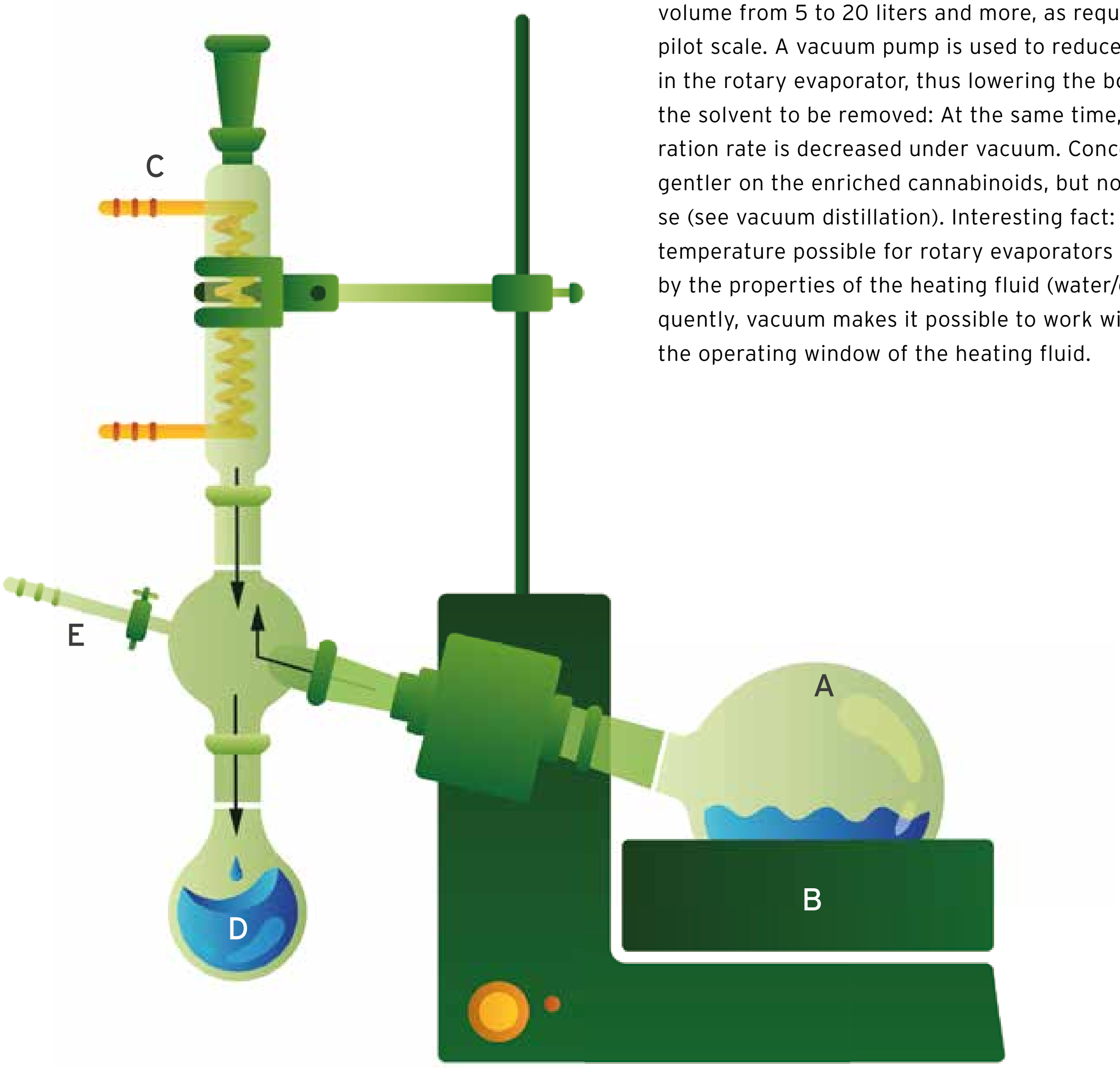
The resulting extract is concentrated by removing the ethanol in the form of an oil. Typically, rotary evaporators, falling film evaporators, or a discontinuous vacuum distillation system are used for this step.

Purifying the Cannabis Extracts

All of the extraction methods described yield an oil once the solvent used has been removed. In addition to terpenes, THC, CBD, and other cannabis metabolites, this oil contains vegetable waxes, lipids, and possibly also chlorophyll, which may precipitate once the oil is added to ethanol and stored at temperatures below the freezing point. Undesired matrix components can be removed by filtering. Depending on the respective intended purpose, further purification of the extract (winterization) and concentration is necessary to obtain a high-purity isolate that is also suitable for medical applications. Rotary evaporators are common and widely used for this.

Rotary evaporation

Since its invention in 1950, the rotary evaporator has been a valuable instrument for extracting high-purity isolates. Rotary evaporators are used to remove solvents under vacuum in a controlled manner. Rotary evaporators are available in different dimensions and with a flask volume from 5 to 20 liters and more, as required for the pilot scale. A vacuum pump is used to reduce the pressure in the rotary evaporator, thus lowering the boiling point of the solvent to be removed: At the same time, the evaporation rate is decreased under vacuum. Concentration is gentler on the enriched cannabinoids, but not faster per se (see vacuum distillation). Interesting fact: The maximum temperature possible for rotary evaporators is limited by the properties of the heating fluid (water/oil). Consequently, vacuum makes it possible to work within the operating window of the heating fluid.



Flow of evaporation process during rotary evaporation

How the evaporation process works:

Typically, the distillation flask (A) is half filled with solvent extract. The water bath (B) is heated to 30–40°C. The condenser temperature (C), controlled by a recirculating cooler, is adjusted to between -10°C and 0°C (reducing the heat-induced decomposition rate of the cannabinoids). Once the water bath and cooler have reached their target values, the distillation flask is rotated at 150 to 200 rpm, which draws the fluid into a thin film on the inner wall of the glass flask. This increases the surface area of the solution and the evaporation rate of the solvent. Applying a suitable vacuum to the system (E) lowers the boiling point. The vacuum must be adjusted so that the ethanol vapor temperature is between 15°C and 20°C. It condenses and collects in the distillate flask (D). The reproducibility can be optimized with just a few adjustments. Flow of evaporation process during rotary evaporation (see Fig. left)

As a side note:

If the evaporation rate increases due to a reduction of the vacuum and/or increase in the water bath temperature, this can cause the condenser to overload because the evaporation rate exceeds the condensation capacity of the recirculating cooler. In this case, ethanol vapor flows through the condenser into the vacuum pump, which, depending on the device, may not result in negative consequences but can lead to total failure of the pump. To increase the throughput, rotary evaporators can be upgraded on a case-by-case basis, e.g., with automatic vacuum control and refilling accessories (manual and automatic).

JULABO FT900 immersion cooler

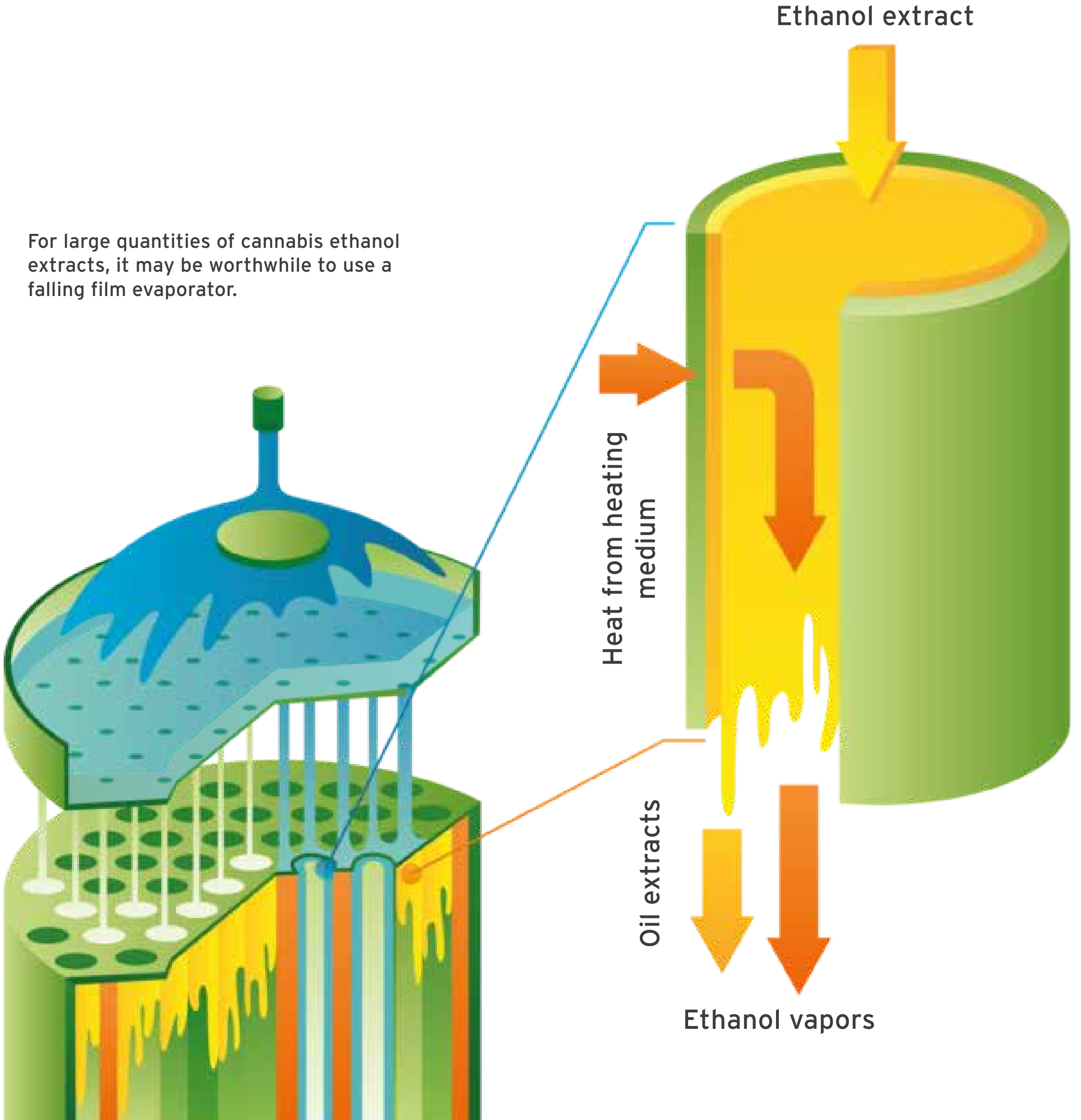
JULABO FT200 immersion cooler

Moreover, most vacuum pumps are equipped with a cold trap on top because of this. In this cold trap, volatile components penetrating into the main condenser are separated at -40°C to -90°C so that they do not reach the pump. An immersion cooler, such as a Julabo FT-200 or FT-900, is suitable for controlling the cold trap.

Falling film evaporation

When handling large quantities of cannabis ethanol extract, it may be worthwhile to use a falling film evaporator. Falling film evaporators are, in simple terms, vertically arranged tube bundle heat exchangers. Under vacuum, the ethanol solution flows through one or more externally heated pipes, which evaporates the ethanol. The vapor collects in a condenser or cold trap, while the cannabis extract, which has a higher boiling point, flows down the inner wall of the tube into a collection vessel. This procedure offers a high evaporation capacity with a short heat exposure time for the extract while also permitting continuous operation. However, this device requires heating circulators of suitable size in order to facilitate the evaporation process, as well as coolers to condense the ethanol vapor.

For large quantities of cannabis ethanol extracts, it may be worthwhile to use a falling film evaporator.



Deriving High-Purity Cannabis Extracts

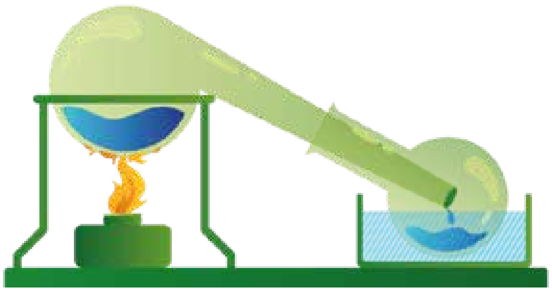
Last, but not least, medical and other applications require the use of high-purity THC and CBD extracts. In addition, Δ9-tetrahydrocannabinol (THC) should not be present in significant quantities in over-the-counter hemp or CBD products. Therefore, one important focus of process control can be to reduce the THC levels in order to eliminate its associated and expected psychoactive effect and to obtain a CBD-rich product.

Distillation processes are only suitable to a limited extent: While terpenes can be separated by distillation relatively well, THC (157°C) and CBD (160–180°C) do not do so. As such, THC cannot be distilled. However, the ratio between CBD and TCH can be adjusted to a limited extent by selecting suitable plant material (variety, cultivation). Suitable chromatographic procedures are needed to remove compounds using process technology.

Possibilities of vacuum distillation

OVERHEAD DISTILLATION

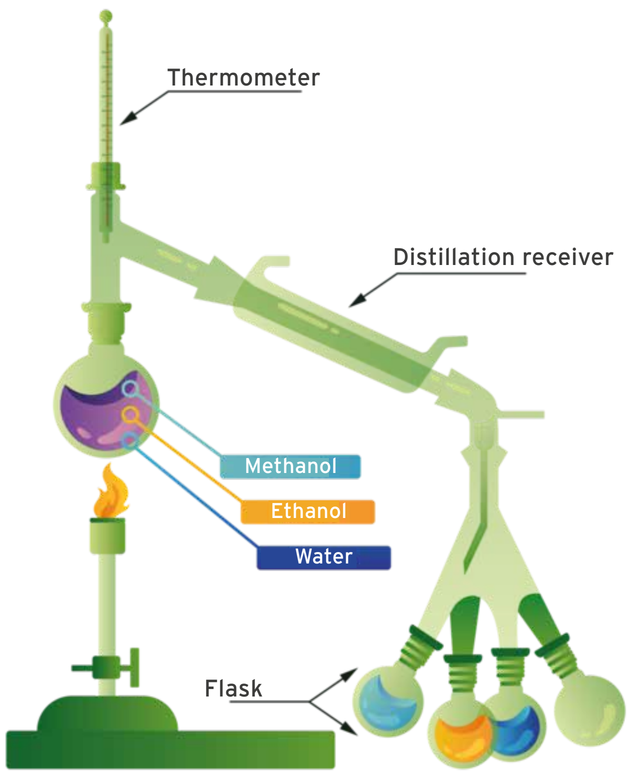
This is a simple distillative separation method for liquid mixtures. The oil is heated in a flask under vacuum (typically with a magnetic heating plate stirrer) with a short distillation head.
A recirculating cooler keeps the condenser cool and condenses the vapors. This form of distillation, which is used to separate solvents or occasionally also in the spirits sector, proves unsuitable for the extraction of cannabis extracts: The sample's long residence time in the flask, at high temperature under normal pressure, can cause decomposition of the cannabinoids.



Overhead distillation: This is a simple distillative separation method for liquid mixtures.

FRACTIONAL DISTILLATION

To achieve better separation results, liquid mixtures can be distilled in fractions, i.e., the distillate is concentrated in a separate collection vessel according to its boiling point. If the vapor temperature rises, indicating a new compound or mixing fraction, the position of the intake flasks is adjusted to isolate the different fractions.



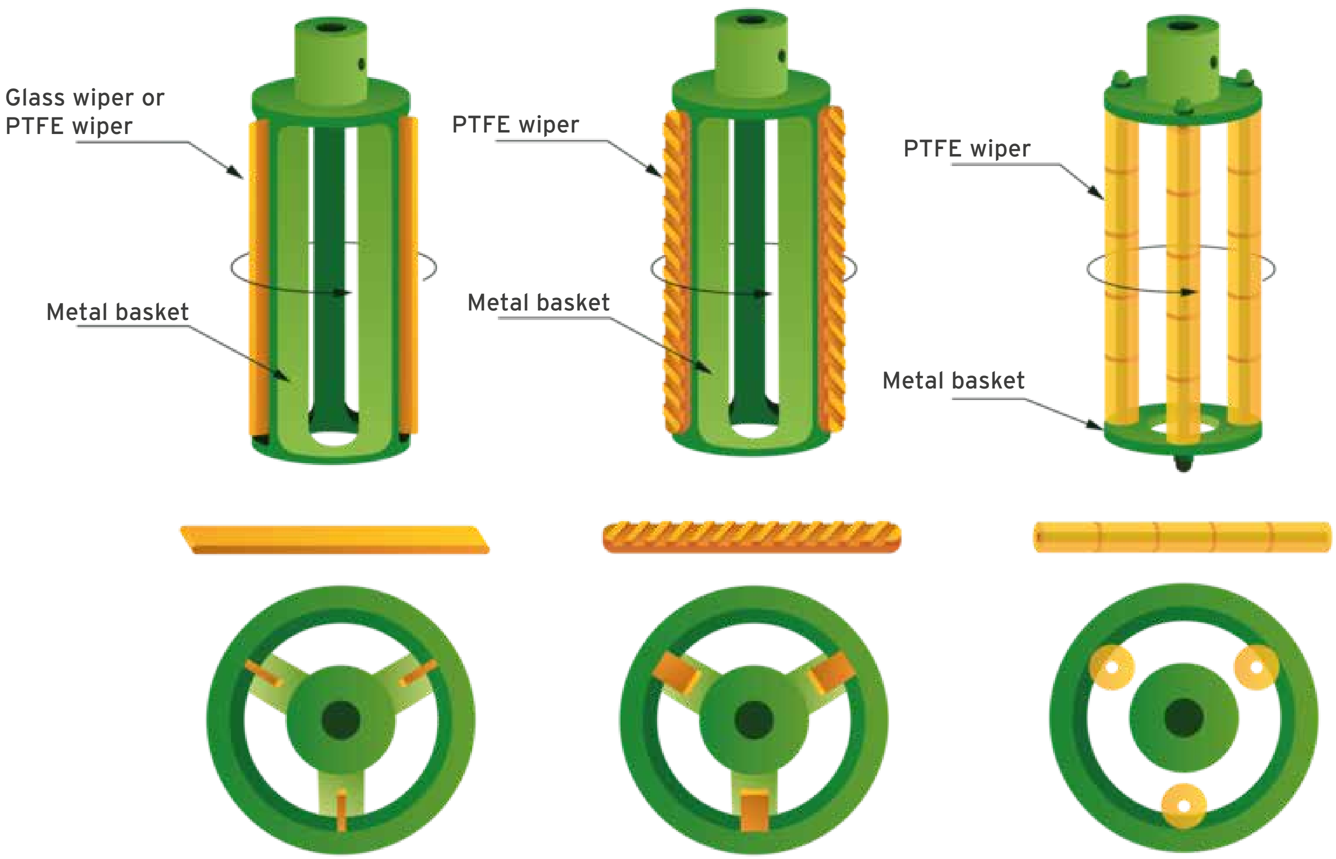
Fractional distillation: To achieve better separation results, liquid mixtures are also distilled in fractions.

THIN-FILM DISTILLATION

This horizontal or vertical distillation variant (wiped film) can be operated in batches or continuously: Depending on the application, the oil is applied, at atmospheric pressure or under vacuum (up to approx. 1 mbar), to the top of a heated vertical cylinder. Rotating scrapers or rollers draw the oil into a thin film on the heated surface.
The vapor can condense in different ways: By collecting in a short-path thin-film evaporator with internal condenser, or being physically separated by a thin-film evaporator with external column, thereby increasing the length of the condensation path. Collection vessels accumulate the condensate and high-temperature residue on the bottom. The oil's shorter exposure time to high temperatures is the main added benefit of this technique. Moreover, the ability to switch to continuous operation increases productivity. A recirculating heater controls the temperature of the feed tank and the wiper body, which has an external jacket.
Refrigerated circulators cool the condenser and cold trap. To obtain the desired compound composition in the distillate, it is necessary to optimize the feed rate, vacuum, and temperatures. The desired purity and composition of the distillate can be achieved by fine-tuning the process. Thin-film distillation is suitable for separating the terpenes from the heavy fraction, i.e., the cannabinoids and matrix residue in the sump.

SHORT-PATH/MOLECULAR DISTILLATION

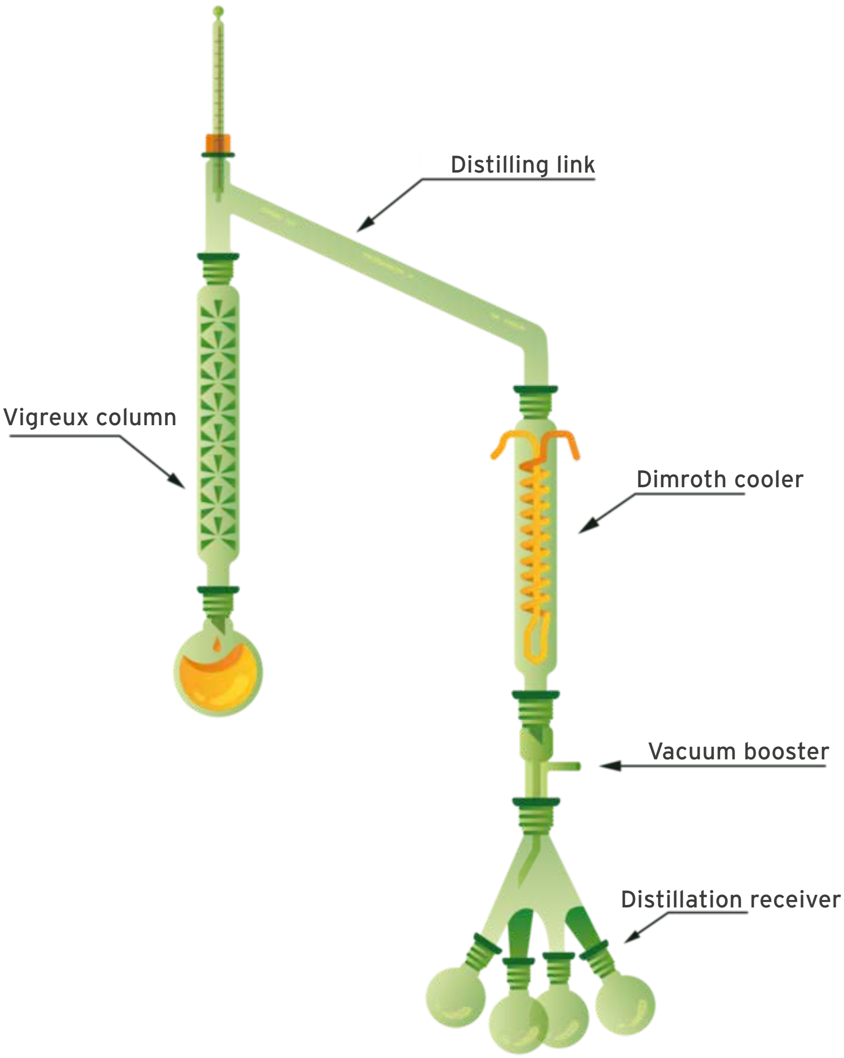
This method is a variant of wiped film distillation for use at high vacuum (less than 10^{-2} mbar). The evaporator and condenser must be close together, hence the term "short-path distillation". The vacuum, in turn, must be high enough that the free path of an evaporated molecule is longer than the distance between the evaporator and condenser. Under these conditions, the boiling point can be lowered to the maximum possible extent, and the cannabinoids in the vapor can be separated from the heavier sump fraction.



Thin-film distillation is suitable for separating the terpenes from the heavy fraction.

RECTIFICATION

Distillation with one column: Using one column improves the separation capacity of a distillation system. This column can consist of different column types (Vigreux, Oldershaw, etc.) that permit a finer separation of the compounds. For better understanding: In distillation, equilibrium is only reached once between the liquid and vapor phases. This occurs on the surface of the liquid, which is the first separation stage. The ascending vapor and descending condensate interact several times with the column (bottom column, packed column, etc.) – on each bottom of a bottom column or flowing along a packed column. This means that several separation stages can be realized, for example, up to 100 bottoms with a high-performance packing, which corresponds to 100 individual overhead distillers connected in series. In other words, the length of the fractionating column, with its ledges, trays, and packing, causes equilibrium between the vapor and liquid to be reached several times, which makes it easier to separate the components.



Rectification: The separation efficiency of a distillation system can be improved by distilling with a column.

Speaking of Temperature

When it comes to yielding cannabis extracts and cannabinoids in the desired purity and sharpness of separation, using the right equipment is a necessity. Controlling and monitoring the process temperature has proven to be crucial for success of the extraction process. The maximum extraction yield and purity can typically only be achieved when all process parameters are fine-tuned. A discussion with suppliers of fluid temperature control systems provides insight into the basic processes, methods, and standards already in use. This is the best way to select the right product. What is important here: When evaluating equipment, the temperature must be taken into account from the very beginning. High-quality fluid temperature control systems with the required heating and/or cooling capacities have a positive effect on material throughput, product quality, and uptime.

JULABO – The place to go for perfect temperature control technology

JULABO is one of the world's leading manufacturers of temperature control instruments for research, industry and science. For over five decades, our premium products have delivered the very best performance, always providing our customers with the exact temperature they need, when they need it. With professional expertise and passion, we are leading the way in the development of temperature control technology, driven by our responsibility as a premium supplier at the top of the global market.

By the way: If you are interested in taking a look at a modern distillation plant, which is operated by Pilodist GmbH in Meckenheim and temperature-controlled perfectly by JULABO laboratory circulators, click here or follow the QR code.

Not to get too far ahead of ourselves: Pilodist GmbH is a world-leading supplier of thermal separation systems used in research, development, and quality control. As this company's long-standing partner, JULABO ensures precise temperatures for all processes of its various distillation plants. JULABO uses various products, like heating circulators, refrigerated circulators, and immersion coolers, to control the temperature of Pilodist's systems. These make the following applications possible: Crude oil distillation, thin-film evaporators, distillation pilot plants, cannabis extraction.

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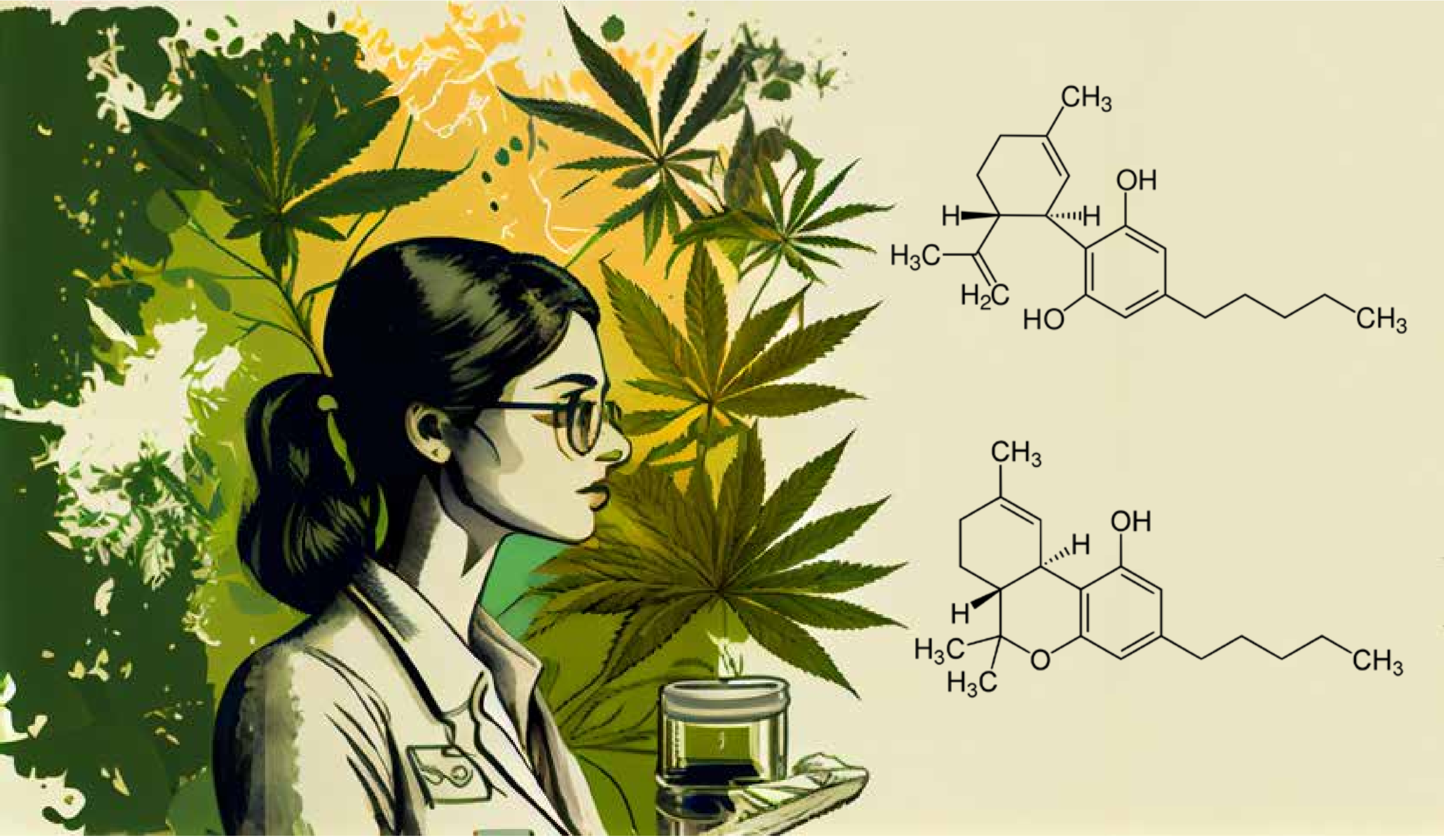

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