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OPPORTUNITIES FOR CULTIVATION OF MEDICAL CANNABIS (*Cannabis sativa* L.) IN GREECE

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Abstract

The cultivation of Cannabis sativa L. for medical uses was legalized in Greece in March of 2018, ending the 90 years ban. The cannabis regulations in Greece attempt to protect the public health and safety by controlling for quality in a reactive manner. The necessary knowledge and know-how for this new crop were acquired by the Laboratory of Agronomy of the Agricultural University of Athens. In this review, the Greek legislation and licensing procedure are briefly presented. The essential relevant steps needed for making a production line are two. The installation permit for the production unit is the first step and then on the investment services sought to establish the conditions under which authorized investment. In the case of greenhouse facility, considering the crop requirements (temperature and photoperiod), the cultivation is suggested for Southern and Central Greece regions. The production process flow is endless during the year, and the duration of the biological cycle is 13-14 weeks. Finally, the required mechanical equipment, human resources, and final products for 1-hectare production with all the necessary conditions to cover GMPs are described.

Key words*: cannabis, Greek legislation, location criteria, medical use, production line.*

INTRODUCTION

1. Historical review

The origin of word cannabis is from Greek kannabis (κάνναβης or kánnavis). Herodotus, the Greek Historian, in 5th century B.C.E., described extensively about the Scythians and their ways of using cannabis (Grimmer, 2013). Later, circa 40-90 C.E., the Greek physician, pharmacologist and botanist, Pedanius Dioscorides wrote about the medical qualities of cannabis and mentioned about treating pains of the ear. During the declines of the Greek Empire, the knowledge pass to European and Byzantines through Rome and Dioscorides texts. In 1855, in a Bavarian text about pharmacology, cannabis was mentioned as a plant which was indigenous in the East and Persia and was cultivated in Europe and Greece. The big gab from ancient time was closed between 1870 and 1880, while the Piraeus port was developed and constituted the major trade depot in the Aegean region (Abel, 1980). During this period, immigrants from Egypt, Cyprus, and countries from the Middle East lived moved to the port because of work, and they brought their recreational habit, which was hashish (Stefanis et al., 1975).

In 1906, the Greek government introduced customs restrictions and tax on cannabis cultivation, accepting British pressures, extinguishing the Greek grapes market.

In 1919, the Treaty of Versailles banned the cultivation and marketing of hashish due to addiction and harmful effects on health. Greece has enacted the hash trade ban for ten years until 1st January 1936 (Papadopoulos, 1974).

2. Chemotype of cannabis

Cannabis components are many, while from the Cannabinoids, the well-known for their healing properties are cannabidiol (CBD) and tetrahydrocannabinol (Δ^9-THC).

Some of the cannabinoids come from raw cannabis, and others are produced after heating. They can be found more in the bud of blooming plant or before blooming. There is also the possibility to appear only after drying. However, in cannabis, there are also terpenoids that give a characteristic fragrance to the plant.

There are three cannabis chemotypes: the drug type, the fibre type and the intermediate type, which are easily distinguished by their Δ^9-THC content that represents the psychoactive constituent of the cannabis plant. The drug type is characterized by a high Δ^9-THC content (>2%), high in resin and is mainly found in good climatic conditions areas and sufficient sunshine. The fibre type has a low Δ^9-THC content (<0.5%) as opposed to high CBD content (>0.5%) and is cultivated for paper, cloth and litter production. The Δ^9-THC content in the fibre type doesn't exceed 0.03%. Intermediate type characterized by the high content of Δ^9-THC and CBD (>0.5%) (Kinghorn et al., 2017).

3. Legislation in Greece

In Greece, the medical cannabis cultivation is governed by the law 4523/2018, which was drawn up in 2018. For the granting of approval for installation and authorization, the applicant must submit documents for all stages (production, excise, transport, storage, supply of raw materials and substances of cannabis varieties of *Cannabis sativa* L. with a tetrahydrocannabinol (THC) content greater than 0.2%, the production, import and marketing of propagating material, processing unit, processing and production of finished medicinal products of cannabis). The final product will be purchased either in the state monopoly or exported. The supporting documentation for the installation approval and operating license is valid for 5 years. Any amendments require new supporting documents. On the basis of legislation, the cultivation will take place under enclosed conditions (greenhouse or indoor), the production area must be fenced off. In addition, there will be private security guards. The quantity of propagation material introduced is limited up to 30 kg of seed per hectare. Any infringements and incomplete data due to refusal or concealment are subjected to sanctions. These sanctions have correction deadline to withdrawal of approval (Hellenic Republic, 2018a, b).

The starting material for the manufacture of a herbal medicinal product can be a medicinal plant, a herbal substance or a herbal preparation.

Herbal medicinal product should be provided with the herbal substance data. For the purpose of ensuring the consistency of the finished product, particular attention should be paid in the agricultural production, including the selection of seeds, cultivation, and harvesting conditions. In order to succeed it, instructions are given in the Herbal Medicinal Product Committee (HMPC) guidance document entitled "Guideline on Good Agricultural and Collection Practice for starting materials of herbal origin".

There are five activities that receive the application of Good Practice. The guidance document of Good Agricultural and Collection Practice (GACP) provides the appropriate instructions for cultivation, collection, and harvesting of plants, algae, fungi, lichens, and collection of exudates. In addition, it includes the activity of cutting, drying of plants, algae, fungi, lichens, and exudates. The guidance document of Good Manufacturing Practice (GMP) is followed by 4 activities. Part II of the GMP guide is responsible for the proper operation of cutting, drying of plants, algae, fungi, lichens and exudates, expression from plants and distillation and comminution, processing of exudates, extraction from plants, fractionation, purification, concentration or fermentation of herbal substances. Part I of the GMP guide provides all the instructions that should be followed by the above-mentioned activities, including the further processing into a dosage form and packaging as a medicinal product.

Depending on the herbal material (active substance, intermediate or a finished product), the GMP classification is applied differently. Manufacturer assumes the proper choice of GMP classification for the medicinal product, additionally is responsible that the activities follow the marketing authorization-registration. GACP is applicable for the initial steps in the field, while GMP for further steps.

In that case, the quality of the product within the approved specifications should be ensured that it is acceptable that the activity of expression from plants and distillation will take place in the field and will be an integral part of harvesting, given that cultivation is in accordance with GACP. These situations should be regarded as exceptional and justified in the relevant marketing authorization - registration documentation. GMP principles undertake the proper operation of the activities that carried out in the field. Furthermore, GMP inspections occur during the activities by the regulatory authorities in order to evaluate compliance (European Commission, 2008).

PRODUCTION PROCESS/LINE

1. Selection of the region, location of the greenhouse cannabis production

Cannabis cultivation in a greenhouse is based on control of the environment in such a way as to provide the conditions that are most favorable for maximum yield. The location of the greenhouse and its orientation are factors that greatly influence the production potential. Solar radiation during winter, temperature, wind, and soil are needed to evaluate the suitability of a region (Mavrogiannopoulos, 2017). Solar radiation is indispensable for plant growth as well as for heat. Sunlight offers greenhouse plants optimal full-spectrum light, yet the day length is not enough. A region with high solar radiation can significantly reduce the use of technical light and therefore the cost. With regard to temperature, there are many areas in Greece where there are relatively high minimum temperatures in the winter and low maximum in the summer. Moreover, there is the option of areas, where the snow accumulation could be avoided because it is dangerous for construction. A prerequisite parameter is the water availability and the heavy metal contamination in water. Soil quality is not a significant parameter for medical cannabis cultivation as the plants are grown in pots. Wind direction and speed in a region could cause significant energy loss in heated greenhouses and can sometimes be a dangerous factor for the construction. For the reasons mentioned above, greenhouse orientation must be carefully considered during the installation. Also, the greenhouse location should be 1000 meters away from schools (Hellenic Republic, 2018b).

Greece is characterized by a predominant Mediterranean climate, with mean annual temperatures ranging from 12 to 19°C. Although, there is a remarkable range of micro-climates and local variations, most of the regions of Greece meet the demands of cannabis cultivation. Considering the crop requirements (temperature, photoperiod or light duration) in a case of greenhouse facility, the suggested areas include the whole region of Central, West, and South mainland of Greece. More particularly, regions of Thessaly, Central Greece, and Peloponnese could be preferred.

2. Production process

The production process is based on clone plants and until now the pharmaceutical final products *Cannabis sativa* L. will be (a) Dried inflorescence of *Cannabis sativa* L., and (b) *Cannabis sativa* L. (THC Oil) pharmaceutical oil which are pesticide free. For each stage, *Cannabis sativa* L. plants will be coded for safety and reference to yield (Mediavilla et al., 1998).

2.1. Growth and maintaining of mother plants

The cultivation begins with growing or introduction of the mother plants which are: i) feminized cannabis seeds, in order to be developed the first mother plants or, ii) already developed mother plants which can be imported. Mother plants should be healthy and have plenty of stems so that if one is removed, it will not harm the plant. In the first instance, seeds are imported and planted in biodegradable jiffy pots. Temperature, moisture air and light condition must be correct for seeds to germinate (Hall et al., 2014). Seed germination, depending on cannabis strain as the conditions in chamber room are standard. Seedlings should be exposed to cool fluorescent light (18 h photoperiod) for the initial vegetative growth (Clarke & Watson, 2002). When the plants have 2-6 leaves, they are transplanted. The growth of mother plants will last 8-9 weeks and will only take place once, at the beginning of production. The growth of plants from feminized seeds will be done in a chamber at 20 hours of light/day, 50-70% RH and 24-26°C. Great care must be taken to prevent mother plants from flowering because the clones use stored carbohydrates to grow a new root system (Kinghorn et al., 2017). In the second case, the already developed plants are kept in the controlled chambers as mentioned above. The mother plants must be stored in chambers with the appropriate equipment in order to maintain the desired conditions. In order to ensure that a mother plant provides vigorous cuttings, the fertilization schedule must be modified to suit long living of them, and the mother plant's age must be noticed.

2.2. Growth of clone plants

Since the mother plants will be at the ideal stage, then the second stage of the production process, propagation, is followed. The plant clones are transported and stored in a suitable place to form a rhizome and a completely new plant. There are two methods for propagation, vegetative propagation or tissue culture. With both methods, the genetically identical version of the donor plant is achieved. By using this method, the crop genetic uniformity will be developed, provided that the propagating conditions are controlled (Clarke & Watson, 2002). Tissue culture propagation constitutes a common way in plant science research, and it is successfully applied in the field of cannabis cultivation. It is a complicated method than vegetative propagation; however, the potential value of this method is appreciated by producers due to high volume management of numerous varieties and strains. An apical branch is about 6-10 cm containing at least two branches, as at least one node must be covered by soil. This branch is cut at a 45° angle straight below the node and dipped in distilled water immediately. Then, the first 2 cm of the cut is dipped into a root hormone and is planted in pots (5 x 5 cm). Plants are regularly irrigated and kept under controlled environmental conditions. In particular, the growth of clone plants requires more than 18 hours of light/day, 80-90% RH, and 24-26°C. The growth of clone plants lasts for up to 4 weeks. The rooting begins in two to three weeks, and this is followed by transplantation to larger pots (e.g. 30 x 30 cm) after six weeks.

2.3. Vegetative growth of clone plants

When plants acquire the appropriate root system, they are transplanted into 20-liter pots and transported to the greenhouse where they remain for 4-5 weeks at steady conditions photoperiod 18-24 hours of light/day, 50-70% RH and 24-29°C.

2.4. Flowering plant growth

At the flowering stage, the plants are transported to a greenhouse with 12 hours of light/day, 50% RH and 20-25°C for 5 to 6 weeks. The plant clones remain there until harvesting. By cutting the inflorescences, the plant crop residues are destroyed (burning or composting) and the soil from the pots is sunburned in a constructed area outside the greenhouse.

2.5. Harvesting

After the flowering stage has been completed, the plants are cut at the base of the overhang and placed in large basins to be transported to the site where the central leaf-foliar and inflorescence separation will take place. When 75% of hair- like structures turn brown, the flowers are ready to harvest (UNODC, 2009). Pots with soil and root system are transported out of the greenhouse, into the sun-cleansing area. In the area of solar decontamination, the contents of the pots are dispersed, the roots are transported to the composting site, and the soil remains there.

2.6. Central leaf-foliar and inflorescence separation

With the stem removal machine, the inflorescences and leaves are also gently removed from the stem. Once the plant has been cleaned down, the branches are separated from the stem, and then the branches are passed through the holes.

2.7. *Trimming*

Trimming constitutes one of the most important aspects of cannabis cultivation and production. The breech leaf is removed from inflorescence by special machines. The trimming machine can save a significant amount of money compared to paying a crew of hand trimmers, especially for large operations. Trimmer Machine will be used for trimming, as it offers the ability to adapt to more inflorescence conditions (i.e., strains, conditions, moisture levels, flower density etc.). A wet trimmer has the advantage to keep the moisture of flower, and thus the context of flower does not be destroyed. In case of the dry trimmer, flowers are dried up to 8-9% humidity.

2.8. Dehydration of inflorescence

The inflorescences after trimming are deposited for 12 days in a drying chamber at 40-45°C. Generally, it is recommended that the drying temperature maintained between 40-45°C because many terpenoids (molecules that are partly responsible for the psychoactive effects but also largely responsive to the odor of the plant) evaporate at temperatures above 45°C. Unplanned drying moisture levels should generally be between 45-55%. Higher moisture levels are associated with mold appearance. Lower moisture levels tend to dry the products very quickly. If the plant material dries very quickly, chlorophyll will fail to convert, which will lead to suboptimal the average organoleptic characteristics (Tang et al., 2015; Kinghorn et al., 2017).

2.9.A.1. Packaging of dried inflorescence of Cannabis sativa L.

Dry inflorescences are packed in special 500 g or 1000 g vacuum packs or FDA-approved polyethylene bags placed in sealable fiber drums (short term: 18-20°C; long term: 10°C) (Kinghorn et al., 2017).

2.9.A.2. Storage of dried inflorescence of Cannabis sativa L.

The inflorescences are stored in a dark warehouse, 30% H and 22°C.

2.9.B.1. Extraction of pharmaceutical oil of Cannabis sativa L. *(THC Oil)*

Liquid cannabis is a concentrated liquid extract of either herbal cannabis material or cannabis resin. The reason that liquid cannabis is produced is to concentrate the psychoactive ingredient THC. Immediately after drying, they are placed in the extraction machine. The extraction process is done with CO_2. This process is also referred to as Extract Liquid and is today a popular technology for fast and non-transmissible extraction in the food industries and pharmaceutical industries. It is important that in the extraction machine are also placed the waste generated during the trimming process and thus reduces the production losses.

2.9.B.2. Packaging of pharmaceutical oil of Cannabis sativa L. *(THC Oil)*

The oil is packed in 10, 50, 150, 250 and 500 g dark glass oil packs.

2.9.B.3. Storage of pharmaceutical oil of Cannabis sativa L. *(THC Oil)*

The packaged *Cannabis sativa* L. pharmaceutical oil (THC Oil) is stored in a dark warehouse, 30% RH and 22°C. A major concern when storing *C. sativa* is the stability of many of the cannabinoids, e.g. the optimum Δ^9-THC content. Degradation of Δ^9-THC is negligible during processing, especially when the material is well-dried and sealed; however, it is still extremely sensitive to oxygen and UV light, and slow degradation occurs during room temperature storage through oxidation to cannabidiol (CBD). Also, Δ^9-THC readily converts to (-)-Δ^8-*trans*-tetrahydrocannabinol (Δ^8-THC) under thermodynamic control. Therefore, the preferred conditions for long-term storage are low temperature and absence of light (Kinghorn et al., 2017).

THE ENVIRONMENT OF THE PLANT AND THE MECHANICAL EQUIPMENT

1. The above-ground part and its environment

In addition to the proper construction and location of the greenhouse, which they are significant for a successful production, it is crucial to have the equipment, which allows the precise regulation of environmental factors that influence the growth of plants, but primarily they provide GMPs. Additionally, the variation of Δ-9-tetrahydrocannbinol in cannabis products is high, and be attributed in climatic and growing conditions (Kinghorn et al., 2017). The equipment of a greenhouse for medical cannabis consists of devices for artificial lighting, shading, sun shading curtains, heating, CO_2 enrichment, irrigation, nutrient solution disinfection, and automation. The choice between equipment with similar capabilities and distinctive features should be based on the duration of its use, operating costs and best economic result.

1.1. Duration of light

An important factor for continuous production is light. For medical cannabis cultivation, natural light is not enough, and it often requires artificial light to supplement illumination up to 20 h per day at a density of 120 μmol m^{-2} s^{-1} and above. Flowering is affected by the night length, and often it is necessary to the night length falls below their critical photoperiod, when the plant is during this particular stage. For shading, blackout curtains are used. The growth of plants is affected by:

a. Radiation spectrum (wavelength), for photosynthesis, photoreduction and photomorphogenesis
b. Intensity, for photosynthesis, photomorphogenesis and phototropism, and
c. Duration, for photosynthesis

The wavelength of 400-700 nm (Visible light) is important for cannabis and its photosynthesis. Artificial lighting is used in different ways. In the mother room, there is a complete replacement of the lighting while in the vegetative and flowering stage the light is complementary, in periods with low daylight. While the total hours required for each stage of development are stable, the quantity and range of artificial light required is determined by various factors such as daytime, sunshine, latitude and weather, and, finally, greenhouse permeability light (Albright et al., 2000).

It has been demonstrated that the photosynthetic ability of plants in light correlates better with the number of photons (mol m^{-2} s^{-1}) than with power units (Wm^{-2}) (McCree, 1972). Thus, artificial light will be substituted by High Pressure Sodium lamps (HPS), which are efficient lamps in the 400-700 nm (100 lm W^{-1}) range. Light intensity was set to ~450 μmol m^{-2} s^{-1} measured from the canopy top (de Wit, 1965). The emission spectrum is very concentrated in the yellow-orange-red range (500-650 nm) but is quite low in the blue range (450-500 nm). High Pressure Sodium lamps are widespread in greenhouse cultivations and are used during the flowering cycle of crops such as medical cannabis cultivation (Critten, 1993). The cost of artificial light is quite high, and it costs both in the initial installation and the duration of electricity consumed.

1.2. Ventilation

In order to ensure uniform fresh air in greenhouse, a ventilation system is preferred to keep stable conditions. Hot air is extracted, and appropriate filters introduced fresh air from the outside, and, as a result, the temperature in the greenhouse is not increased. In Greek conditions, the needs for ventilation are high from spring to late autumn (Carpenter & Willis, 1959).

Ventilation must be dynamic (or mechanical), i.e., the interior and exterior pressure differences greenhouse will be created by mechanical means to ensure stable conditions and no problems with GMP's. Ventilation is a critical control point because it depends on the reduction of the high temperature of the greenhouse due to the high intensity of the solar radiation. In a greenhouse of medical cannabis, it is more important as there is artificial light. Ventilation also exhausts vapors due to the transpiration of plants and offers full exploitation of CO_2 (Ganguly & Ghosh, 2011).

For the purpose of creating the homogenous conditions and keeping a controlled environment during cold/humid hours, the ventilation may not be sufficient to a lower temperature inside the greenhouse. On the other hand, high air velocities in the greenhouse result in excessively high transpiration with negative effects on cannabis clones growth.

1.3. Heating

Heat and consequently temperature have an effect on the growth and production of cannabis clone plants. Temperature affects photosynthesis, respiration etc. (Walker et al., 1982). It is also a factor that has its effect on the production cost in the greenhouse after artificial light. A greenhouse for medical cannabis belongs to fully heated greenhouses that offer the optimum temperature.

During the day, solar radiation is the main source of energy for heating (Kampkes et al., 2000). On a cloudless day or early in the morning or on a day with low outside temperatures, sunlight is not enough, and the room temperature is below the desired levels.

Cannabis production must not be affected by temperature drops because at the harvest stage the inflorescences will be at a different stage, so they cannot be harvested at the same time. For heating in a cannabis greenhouse, central heating with hot water or air heaters will be used to complete the air distribution to achieve a uniform distribution of air (Nederhoff, 2006).

Temperature regulation enables production planning, quantity increase and improved product quality throughout the year, and the production of pharmaceutical cannabis is important as the production flow is continuous. Moreover, stationary humidity reduces plant diseases and improve buds quality (Nederhoff, 2006).

1.4. Humidity control

The humidity is one of the determinants of the greenhouse environment. It usually tends to be high due to the evaporation of the crop. The management of humidity belongs to environmental control strategies (Labidi et al., 2017). However, humidity encourages diseases and other problems in a growing environment, while the use of pesticides is not allowed in medical cannabis cultivation.

1.5. Enrichment with carbon dioxide

The rate of photosynthesis affected not only by the availability of light and carbon dioxide (CO_2) but also by the ability of the photosynthetic mechanism that engages the CO_2. Enriching the greenhouse with CO_2 pointed to enhance the production of the crop through the enrichment of the greenhouse atmosphere (Akilli et al., 2000).

The enrichment of the greenhouse with CO_2 gas should be done during the day, when, the photosynthesis is done, the windows are closed, and the ventilators are off (Chalabi & Zhou, 1997). In particular, ventilation should begin one hour after dawn, and continue until sunset. It is a necessary element for producing inflorescences throughout the year (Heij & van Uffelen, 1984). The enrichment method commonly used in Greece is the liquid CO_2 evaporation, which is in a high-pressure tank and distributed in the greenhouse via a series of pressure regulating valves (Mavrogiannopoulos, 2017).

2. The underground part and its environment

2.1. Irrigation, water and oxygen

The water along with oxygen are the most important factors in the root environment. The irrigation system is fully automated with a drip method which offers the best control over the amount of water. It is the most widespread watering system in closed-type crops. Black plastic tubes of 12-20 mm in diameter are used on which drippers are installed or incorporated. The tubes are usually placed on the ground surface, one for each plant line or one for two plant lines. In the second case, from the center tubes start very thin tubes of 1-2 mm diameter ending in each pot. The end of the tube is secured to a specific pile close to the plant (Kim et al., 2015).

2.2. Fertilization - pH

The fertilization of the medical cannabis crop will be done along with irrigation. The optimum substrate pH for the plant is from 6.5 to 7.2 (Papastylianou et al., 2017). In hydroponic growth, the nutrient solution is best at 5.2 to 5.8, making cannabis well suited to hydroponics, and thus indoor production, because this pH range is hostile to most bacteria and fungi. (UNODC, 2009).

CONCLUSIONS

A few years ago, any discussion of medical cannabis was kept under wraps. Today, the medical cannabis cultivation is a great opportunity. The cannabis industry has many strengths such as human resources needs. For one-hectare productive unit, around 50 scientific or technical staff is needed. Additionally, new medicines will be produced to manage epilepsy, depression or chronic pain. This new industry for Greece encourages new businesses for product design. The main lack of the Greek market is the familiarization of people with this kind of medical products. Until now, for the approval granting for construction, 32 application forms have been submitted. In the next months, more application forms are expected as the consumers believe in the health benefit of cannabis as a medicine. Greece has great prospects for growth and build of a medical cannabis valley.

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