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Cannabis, factors affecting it and treatment of diseases in humans

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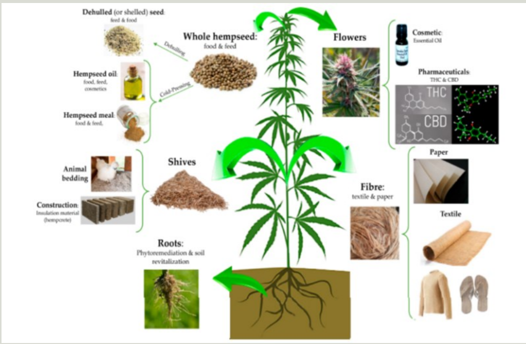
Abstract



Cannabis sativa L. is spreading as a specialty crop. This diploid plant from Central Asia contains various phytochemical compounds and secondary metabolites. Secondary metabolites include cannabinoids, flavonoids, terpenoids, stilbenoids, terpenoids, alkaloids, and lignans. Despite the presence of numerous psychoactive substances in the plant, it is required as a very important agricultural crop for fiber and medicinal purposes, and in many countries the cultivation and use of the plant for medicinal purposes is legal. Therefore, ecological identifications of this valuable plant and knowledge of its phytochemical compounds can be considered. Hemp also has many medicinal properties, and studies show that its derivatives can have beneficial effects on the treatment and improvement of some diseases. This review article discusses the cultivation techniques, the biosynthetic pathways of the secondary metabolites present in this plant, and the factors that influence the reduction or increase of its medicinal properties.

Keywords: Cannabis, Secondary metabolit, N, P, K elements, treatment of diseases

1.Introduction

The cannabis plant is a highly variable species in terms of botany, genetics, and chemical composition (1). Hemp is an industrial medicinal plant native to Central Asia. This ancient crop came to China from Central Asia and has been cultivated there for more than 4500 years. And because of its valuable properties as a source of food, fuel, fiber, medicine, and narcotics, it has been widely used by people around the world for thousands of years (2,3). Despite the negative reputation that this plant has had as a drug in recent years, it is still considered a very important agricultural plant in terms of fiber and medicinal plants today (4).
Cannabis with the scientific name *Cannabis sativa* L. Cannabis plant is a diploid plant (2n=20) with a karyotype consisting of nine autosomes and one pair of sex chromosomes (X and Y), with a

karyotype consisting of nine autosomes and one pair of sex chromosomes (X and Y), dioecious, herbaceous, annual and 1 to 3 meters high or even higher. And there are different varieties and forms. Cannabis has opposite leaves along the stem, but the closer we get to the end of the stem, the simpler the leaves become. The leaf blade of cannabis is divided into 5 to 7 deeply toothed lobes and ends in a long petiole. In their natural state, the flowers are male and female and are located at two separate bases. One of the characteristic features of male cannabis flowers is that they are arranged in a complex and hang from a base at the end of the stem. Each of these flowers has 5 stamens inside the perianth. The female flowers generally have the same texture as the male, with the difference (5,6). The seeds of cannabis (*Cannabis sativa* L.) contain nutrients that are very valuable for health. The seeds of this plant contain about 19-38% oil, 20-38% protein, 27-36% fiber and 6-4% minerals. Tocopherols, carotenoids and some phenolic compounds can be mentioned as other components with nutritional value. The medicinal effects of cannabis are attributed to the presence of cannabinoids (7). Cannabinoids are terpenophenolic secondary metabolites formed in the trichomes of cannabis plants. To date, more than 100 cannabinoids have been discovered and studied. The most interesting and well -studied compounds in this class are delta-9-tetrahydrocannabinol (THC) and cannabidiol (CBD). The ratio between THC and CBD content is a good indicator for distinguishing between "fiber type" and "drug type"(4). Other important cannabinoids with little or no psychoactive effect are cannabidiolic acid (CBDA), cannabigrole (CBG), cannabichromene (CBC), cannabinol (CBN), cannabicyclol (CBL), and cannabidiol (CBND). These compounds are metabolized by the enzymatic conversion of cannabirulic acid (CBGA) and cannabidivaric acid (CBDVA), respectively (7). To clarify the phytochemical discussion of cannabinoids, they can be easily classified into three groups: acidic cannabinoids, neutral cannabinoids, and "artifacts." This convenient classification of cannabinoids is shown in Figure 1(8). Considering the importance of cannabis as a medicinal plant and the increasing demand for cultivation of this plant for various purposes, including medicine, this article reviews the results of the study of various factors on the biosynthetic, physiological, and biochemical properties of the cannabis plant.

1-1- A history of the hemp plant

Cannabis (*Cannabis sativa* L.) is a widespread species in nature, found in various habitats from sea level to the temperate and mountainous regions of the Himalayas, where it probably spread 10,000 years ago. The ancient cultivation of this plant makes it difficult to pinpoint the origin of its distribution (1). The first medicinal use of this plant was also recorded by the emperors of China. This plant is mentioned in Hindu scriptures and ancient books left in Iran in 600-700 BC (9). Even in ancient Egyptian mummies, evidence of cannabis cultivation as food or medicine has been found. Therefore, the origin of this plant is believed to be in Central Asia (8). This plant is considered one of the oldest sources of food and textiles. Historical evidence shows that the first paper made from hemp fibers was produced in China 100 years before Christ (9). The cultivation of hemp for fiber production became common in Western Asia, Egypt, and later in Europe between 1000 and 2000 BC. It also became popular in Europe after 500 AD. This product was first brought to South America (Chile) in 1545(1). It is worth mentioning that during more than a thousand years of hemp cultivation, different products were obtained and used from this plant, and today the narcotic varieties of this plant are known as marijuana and the fibrous varieties are known as hemp. The fibrous and industrial hemp varieties have no narcotic effect and can be grown and used industrially on a large scale without any problems. The annual trade of fibrous varieties of this plant of about 100 to 2000 million dollars shows its economic value (9).

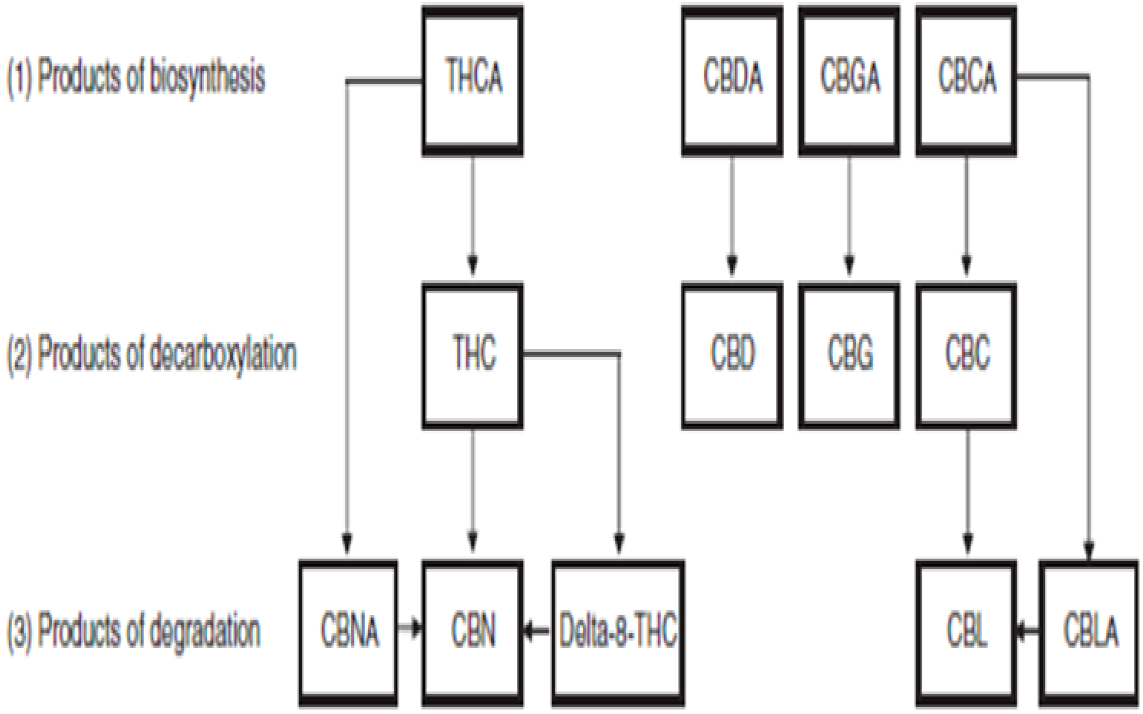


Figure 1. shows the classification of relationships between cannabinoids in cannabis. Three different groups can be distinguished: 1) Cannabinoids produced by plant biosynthesis, 2) Cannabinoids resulting from natural decarboxylation, 3) Degradation products caused by factors such as ultraviolet radiation, oxidation or isomerization.

1-2- Ecological characteristics

Cannabis is a short-day plant by its ecological characteristics, and its flowering period is generally dependent on genetic factors and short days, with the actual time of flowering onset varying according to weather conditions, location, and agricultural practices The length of the photoperiod (photoperiod) for this plant is reported to be 9 to 14 hours. The diversity of cannabis genotypes in terms of photoperiod length depends on the different species and environmental conditions. This plant is spring-flowering and is grown in different regions from early to mid-spring when weather conditions and temperature are favorable. Fiber hemp has a shorter growing season, so the temperature needed during the growing season to produce fiber is lower than when growing hemp for seed production. Reports have also shown that cannabis will turn green at a temperature of 20 to 30 degrees Celsius from the third day and will be completely green after 7 days. On suitable soils, hemp produces the greatest quantity of products, both quantitatively and qualitatively. Clay-sand soils with a pH of 4.7-5.6 are suitable for growing cannabis. On the other hand, salty, too cold, too heavy or too light soils are not suitable for the cultivation of this plant (9).

1-3- Phytochemical compounds in cannabis

Cannabis is very complex in terms of phytochemical compounds and more than 480 different chemical compounds have been identified in the hemp plant. Some of these compounds belong to primary metabolites such as amino acids, fatty acids and steroids, while cannabinoids, flavonoids, stilbenoids, terpenoids, lignans (phenolic amides and lignanides) and alkaloids are secondary metabolites of cannabis. Therefore, cannabis can be considered as a real plant producing secondary metabolites, which is very important in the pharmaceutical industry (10).

In fact, from this versatile plant, it is possible to produce various industrial products such as fibers, thermal insulation materials and bioconstruction; seeds, flour and oil with important nutritional and functional characteristics; and obtain bioactive compounds in the pharmaceutical industry (Figure 2).

Figure 2: Multiple uses of the hemp plant: in general, every part of this plant can be used in a specific industrial field (11).

1-3-1- Cannabinoids

This group has devoted the most studies to the hemp plant and they are 22-carbon terpenophenolic compounds, of which 70 types have been found so far, which can be divided into ten types of main structures. Cannabinoids D9-THC, CBD, CBN, CBG, CBC and CBND are the most common compounds found in cannabis (10,12). THC is the most important cannabinoid found in cannabis, and studies have shown that the use of extracted THC alone has similar medicinal effects to the use of the whole plant. CBD is another cannabinoid. The importance of this plant is that it has different medicinal effects (9,12).

1-3-2- Flavonoids

Flavonoids play a role in many functions such as biochemical, physiological and ecological processes of plants and are very important in human and animal nutrition and health. More than 20 flavonoids have been reported in cannabis. Cannabis flavonoids have been identified and isolated in flowers, leaves, small branches and pollen grains. There is no evidence of the presence of flavonoids in the tubers of this plant. Conflavin A and Conflavin B are methyl isoprenoid flavones that are specific to cannabis. Preliminary studies show that extricates without THC and CBD from C. sativa can decrease the cataleptic impacts of THC in mice, and this impact can be switched by organization of prostaglandin E2 (PGE2). In subsequent investigations, it was determined that these properties are related to conflavin A and B, and it was moreover expressed that these prenylated flavonoids can hinder PGE2 generation in human rheumatoid synovial cells and give anti-inflammatory benefits that are roughly 30 It is more effective than aspirin (9,10,13).

1-3-3- Stilbenoids

Stilbenoids are phenolic compounds that exist in all plant families. These compounds have a structural role in plants and are used in defense and induction mechanisms, growth inhibitors and latent factors. Also, stilbenoids are components of root wood and have anti-microbial and anti-fungal activity, or they are insect repellants. About nineteen stilbenoids have been identified in cannabis, which have been isolated in the stem, leaves and resin (9,10).

1-3-4- Terpenoids

Terpenoids or isoterpenoids are another main group of plant metabolites. The isoprenoid pathway produces primary and secondary metabolites. In primary metabolism, isoprenoids act as phytohormones (gibberellic acid, abscisic acid and cytokinin) and membrane stabilizers (sterols) and can be used in respiration (ubiquinone) and photosynthesis (chlorophyll and plastokinin). have a role While as secondary metabolites, they participate in defense mechanisms (phytoalexins). 120 terpenes have been identified in hashish: 61 monoterpenes, 52 sesquiterpenoids, 2 triterpenes, one diterpene and 4 terpenoid derivatives (10).cannabis could be a productive maker of terpens and these compounds are thought to contribute to the helpful viability of cannabis arangmenta through the 'entourage effect',by acting in combination ith cannabinoids (14,15).

1-3-5- Lignans (phenolic amides and lignanamides)

Cannabis fruits and roots produce 11 phenolicamide and lignamide compounds. N-trans-coumaryl-tyramine, N-trans-feruloyltyramine, N-trans-caffeoyltyramine are phenolic amides. Cannabis A -, B -, C -, D -, E -, F -, G - and grosamide are lignanamides. Phenolic amides are accumulated in chemical defense responses in plants. Similarly, phenolic acids play an important role in flowering, sexual organs and resistance (9).

1-3-6-Alkaloids

Alkaloids are another major group of secondary metabolites in plants. Alkaloids are nitrogen compounds with little biological activity that can be obtained from amino acids. 10 alkaloids have been identified in cannabis. Choline, norine, isoleucine betaine, muscarine which are pre-alkaloids. Cannabisativine and Anhydrocannabisativine are polyamines derived from spermidine. Pyridine and pyrrolidine have also been identified in cannabis. These alkaloids are extracted from the tissue of roots, stems, leaves, pollen grains and seeds of the cannabis plant (9,10).

1-4- Biosynthesis of cannabinoids

1-4-1- Place of synthesis of cannabinoids

Trichomes are specialized structures consisting of plant epidermal cells, which are mainly located on leaves, stems and hollow organs. These cells protect plants against biotic and abiotic stresses and produce and accumulate a number of specialized metabolites. In terms of morphology and the ability to secrete secondary metabolites, the two main types of trichomes, non-glandular and glandular, are different. Glandular trichomes are present in about 30% of all species of vacuolated plants and multicellular and specialized structures are responsible for the biosynthesis and secretion of a wide range of secondary metabolites. These particular metabolites are of interest because they can be used as natural toxins, food additives and medicine (12). Cannabis plant can be called a forgotten medicinal treasure. The most interesting thing is the compounds that are found in the secretions of the trichomes on the surface of the cannabis plant. These compounds include terpenoids, flavonoids and cannabinoids. It has been shown that cannabinoids, cannabigerolic acid (CBGA and THCA) cause cell death in some plant and insect cells through apoptosis. These results indicate that cannabinoids act as plant defense compounds, which is a common function of plant secondary metabolites (8). The hemp plant collects phytocannabinoids and terpenes in the glandular trichomes located throughout the aerial parts of the plant and with the highest concentration on the female flowers. Non-glandular trichomes are seen on the surface of most angiosperms and some gymnaperms and bryophytes. And they play a role in filtering sunlight, protecting against herbivores (12). On the other hand, non-glandular trichomes are found on the surface and root tissues. Therefore, phytocannabinoids do not accumulate in the root tissue. Glandular trichomes collect cannabinoids in a balloon-shaped cavity filled with secretory vesicles. When the trichome is ruptured, for example at high ambient temperatures or as a result of herbivory, its contents form a sticky coating on the surface of the plant, which is regulated by the viscous and non-crystalline properties of cannabinoids. (figure 3). The amount of cannabinoids formed is positively correlated with increasing temperature and heat stress, as well as with low soil moisture and low mineral nutrient content (13). The second category of metabolites with high abundance and even greater chemical diversity in cannabis glandular trichomes are monoterpenes and sesquiterpenes. These volatile terpenoids are responsible for the distinct aromas of different cannabis strains (14).

-2-4-1 The biosynthetic pathway of cannabinoids

In all accepted biosynthetic pathways for cannabinoids until 1964, cannabidiol (CBD) or cannabidiolic acid (CBDA) was considered the key intermediate, apparently made from a monoterpene and oleotol or oleoleic acid, respectively. However, researchers have shown that cannabigerol (CBG), a common precursor of cannabinoids, is biosynthesized through the condensation of geranyl diphosphate and oleitol or oleoleic acid (OA). After that, they concluded that cannabidiol (CBD), delta-9-tetrahydrocannabinol (THC) and cannabinol (CBN) are all derived from cannabigerol (CBG) and differ mainly in the way this precursor is cycled.

Our better understanding of cannabinoid biosynthesis came when Shoyama et al. (1975) (15) concluded that neither free phenolics (non-carboxylic acid) of cannabinoids nor cannabinolic
acid (CBNA) are produced by the living plant.
become Instead, they accepted that biosynthetic methods based on geraniol and a polyketoacid lead to the production of acidic cannabinoids. Similar results were obtained after studying some types of African cannabinoids by Turner and Hadley (17). It is now known that cannabinoids are produced by plant metabolism in the form of carboxylic acids, where the substituent group in the carboxyl (-COOH) is located in the 2 position. Studies conducted by C13-labeled glucose have confirmed that geranyl diphosphate (GPP) and OA are specific mediators in the biosynthesis of cannabinoids (8).
The biological synthesis of cannabinoids involves the integration of key steps in polyketide and isopranoid metabolism. Hexanoic acid is used as the initiator molecule of polyketide and is most likely produced from C18 fatty acids, which are continuously saturated, peroxygenated and broken into C6.

The biosynthesis of important cannabinoids involves two direct precursors. The polyketide pathway generates oleoleic acid (OA) from a short-chain fatty acid intermediate (hexanoyl-CoA), while the methylerythritol 4-phosphate (MEP) pathway provides geranyl diphosphate. Slow(14).

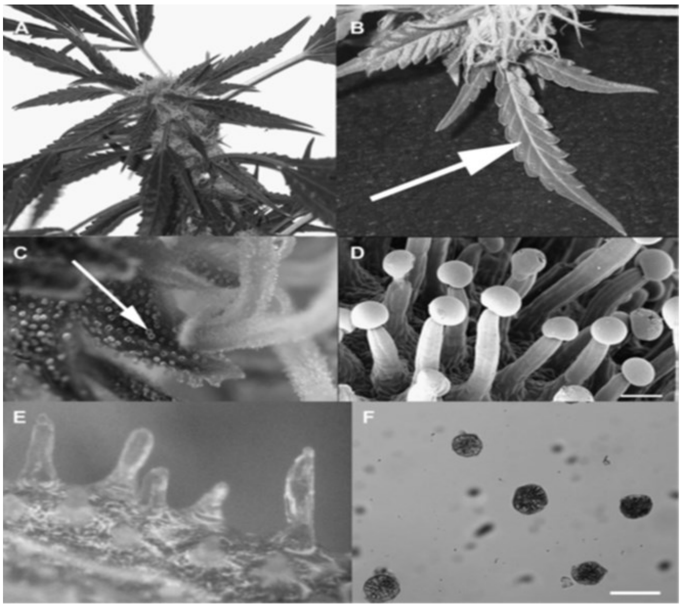


Figure 3: Isolation of glandular trichomes from petals of female inflorescences. A) Female inflorescence eight weeks after germination. B) leaves cooperating with the female inflorescence. C) Glands on the petals of the female inflorescence. D) Electron image of Capita glands. E) The image of the leaflets after removing the glands. F) Image of isolated glands. Image E and F are with a scale of 80 micrometers (16).

OA is produced from hexanoic acid in the cytosol. GPP is synthesized by the plastid non-mevalonate-dependent isopronoid pathway (MEP), the first specific biosynthetic step is the synthesis of geranyl diphosphate and oleoleic acid (OA) into CBGA, catalyzed by the enzyme prenylase geranyl diphosphate:oleoleoleate geranyltransferase (GOT). CBGA is a transmembrane aromatic prenyltransferase. Further oxidation of THCA leads to the formation of CBNA, which is still formed after harvesting the plant material, and large amounts may not be usable due to improper storage conditions(8). Figure 4 shows the common pathway between the biosynthesis of cannabinoids and terpenoids.

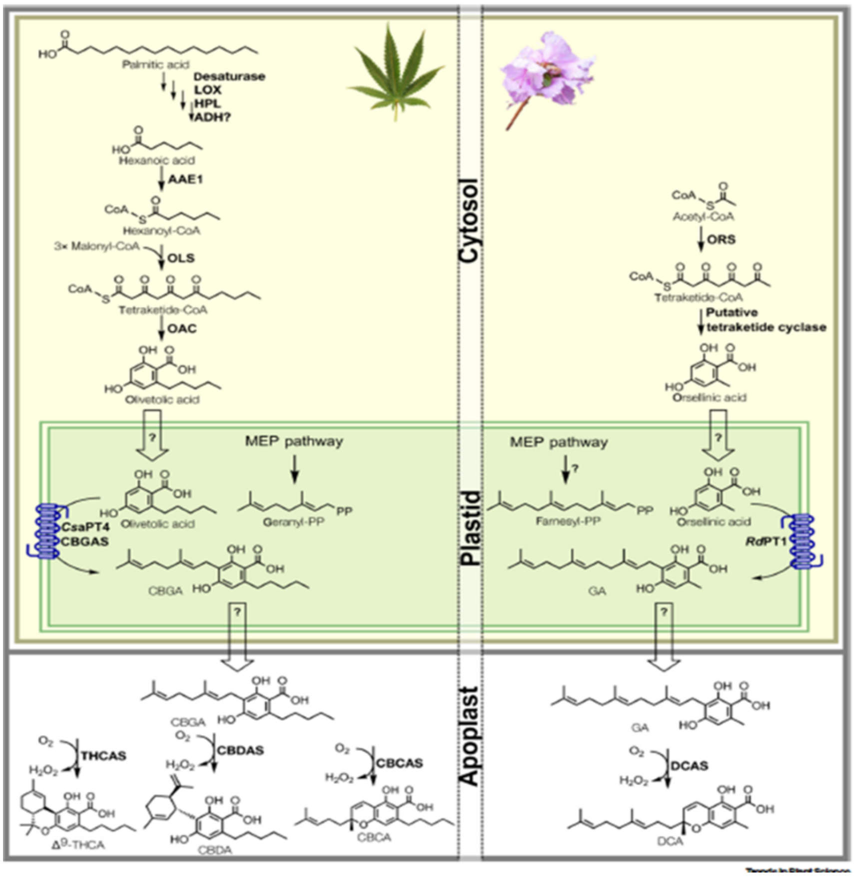


Figure 4: Common biosynthetic pathway between cannabinoids and terpenoids

The synthesis of cannabinoids is catalyzed by a series of synthase enzymes that compete with each other for the reaction with cannabigerulic acid. The last step in the synthesis of cannabinoids involves the conversion of cannabigerolic acid (CBGA) to tetrahydrocannabinolic acid (THCA) by the enzyme THCA synthase. And finally, THCA is decarboxylated to THC. On the other hand, CBGA is decarboxylated by CBDA synthase to cannabidiolic acid (CBDA) and then to cannabidiol (CBD). The reduced metabolic products of these acids are formed non-enzymatically by exposure to heat (16). Figure 5 shows the decarboxylation pathway of some important cannabinoids_(7). THC is known as a psychoactive substance that binds to the endocannabinoid receptor in vertebrates, while CBD is a non-toxic compound.

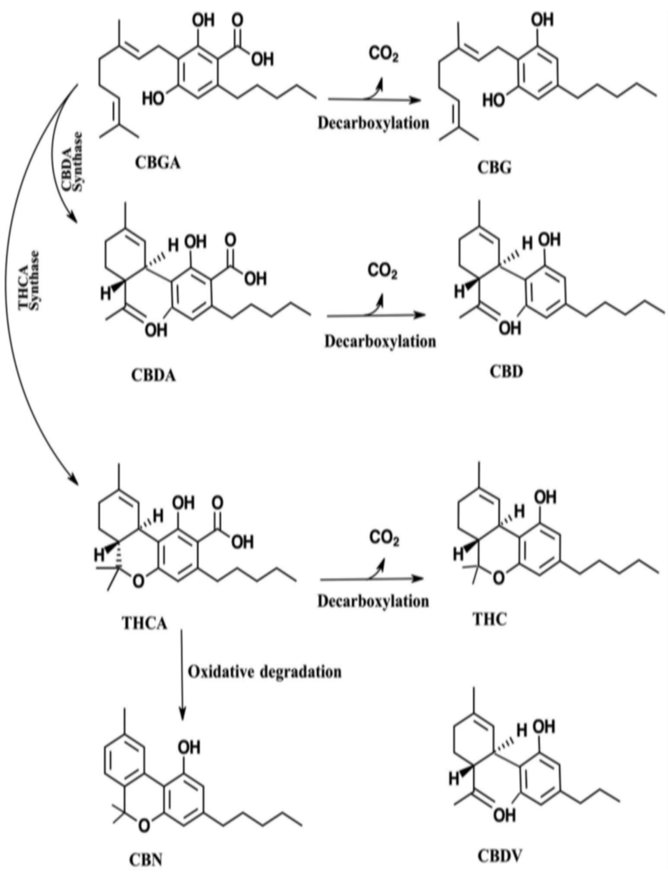


Figure 5: Decarboxylation pathway of cannabinoids

1-4-3---The role of hexanoyl COA in the biosynthesis of cannabinoids

Cannabinoids are a rare example of plant polyketides biosynthesized from hexanoate or hexanoyl COA precursors. Many plants and microbes use acyl coenzymes A as initiator polyketides. The detection of hexanoyl-CoA in cannabis flowers indicates that this compound is present in cannabinoid biosynthesizing tissues. Amounts of CBDA have also been detected in leaves, stems, and roots, but at lower concentrations than in flowers.

Therefore, hexanoyl-COA has a higher concentration in female flowers. In the studies conducted in 2012, it was found that the acyl cannabinoid enzyme activating genes (CsAAE1) are involved in the biosynthesis of cannabinoids. In fact, CsAAE1 was the most abundant transcript in EST (expressed sequence tag) and quantitative data from reverse transcriptase polymerase chain reaction show that the expression of CsAAE1 in trichome cells was 100 times higher than in other tissues. On the other hand, laboratory studies have shown that recombinant CsAAE1 activates hexanoate and other short and medium chain fatty acids. In this way, hexanoyl coenzyme A provides the synthetase for the synthesis of cannabinoids. The large number of transcripts encoding desaturases and lipoxygenase suggests that hexanoate may be formed via a pathway involving oxygenation and degradation of unsaturated fatty acids. Phylogenetic studies show that CsAEE1 does not possess a peroxisome receptor. As a result, it is directed to the cytoplasm and enters the pathway of cannabinoid biosynthesis. CsAAE3 encodes a peroxisomal enzyme that activates a variety of fatty acids, including hexanoate (18).

1-4-4-The role of transcription factors in regulating the expression of secondary metabolite synthesis genes

Accurate measurement of gene expression can identify the type of cell or tissue in which the gene is expressed and detect the level of gene expression in a specific biological state or changes in gene expression in response to environmental stress (19). Many secondary metabolites are valuable for their medicinal properties. Due to their beneficial effects on health, the biosynthesis of secondary metabolites has been the main subject of many researches. Many transcription factors are of interest due to their role in regulating biosynthetic pathways at the level of transcription and can form a dynamic regulatory network that controls the time, range and spatial distribution of gene expression required for the biosynthesis of secondary metabolites. Also, many transcription factors have been identified that play a role in regulating the biosynthesis of secondary metabolites in tuberous trichomes(12,20). Based on the functional annotation, cannabis has 1225 transcription factors, which are classified into 56 families according to the similarity of their DNA binding sequence with the binding domains of three large families, MYB, Bhlh and AP2/ERF. However, cannabis transcription factors are relatively low compared to model plants such as Arabidopsis, rice and maize (12). THCA synthase gene expression analysis by I.J. Flores-Sanchez et al showed that THCA synthase mRNA was present only in cannabis plant tissues such as leaves and flowers that contain glandular trichomes. This article can express the importance of THCAs in the growth and development of trichomes. Since CsAP2L1, CsMYB1 and CsWRKY1 are important regulators of the expression of cannabinoid biosynthetic genes and regulate the expression of THCAs in tuberous trichomes. In the study conducted by Yuanyuan Liu et al (12), the promoter and regulatory region of THCAs that drive expression in trichomes were investigated. The measurement of transcriptional activity showed that while CsAP2L1 acts as a transcriptional activator, CsMYB1 and CsWRKY1 act as transcriptional repressors. Examination of different tissues of Purple Kush (a type of marijuana) revealed that THCAS, CsAP2L1, CsMYB1 and CsWRKY1 show higher expression in trichome than other tissues such as root, stem and leaf. As a result, their findings show that cannabinoid biosynthesis is under tissue-specific and developmental control, at least in part, through the action of several transcription factors that were identified and pointed out. Such transcription factors have the potential to provide tools for biotechnological manipulation of cannabinoid levels. Since esters such as salicylic acid and GABA are used for mass production of THC and CBD. In a study, the increase of the secondary metabolites of cannabis, namely THC and CBD, was investigated by Elistor compounds.

The results of this study showed that signaling compounds such as salicylic acid (SA) and GABA promote the genes involved in the biosynthesis of THC and CBD. On the other hand, the expression study of the target genes THCAS, CBDAS, OLS and PT as well as quantitative analysis showed THC and CBD compounds. That the highest level of THCAS activity occurs in the concentration of 0.1 mM GABA and 1 mM salicylic acid. Therefore, the results suggest that salicylic acid and GABA can affect the cannabinoid biosynthesis pathway by stimulating the expression of key genes and ultimately causing a change in the amount of final products (19). In 2009, Marks et al (16) used RNA isolated from trichomes to produce a cDNA library containing more than 100,000 expressible sticky sequences (EST) in order to identify candidate genes affecting the synthesis of delta-9-tetrahydrocannabidiol. Candidates were identified at each step of biosynthesis leading to THCA. According to their studies, it was found that many genes of the biosynthetic pathway are preferentially expressed in glands.

As already mentioned, one of the metabolites required for the synthesis of THCA is hexanoyl coenzyme A, which can be made by synthesizing denevo fatty acids or breaking down existing lipids. Of course, qPCR analyzes support the denevo pathway. The results of RT-PCR and heterologous expression show the presence of THCA synthase in the apoplastic space of the trichome gland locally. On the other hand, many ESTs encoding transcription factors and two MYB genes are expressed in trichomes. It has been suggested that due to the similarity of cannabis MYB genes to genes found in other plant species, these genes may play a role in regulating the growth of trichomes and THCA synthesis (16,21).

1-4-5-Acidic cannabinoids

It is known that cannabinoids are produced by plant metabolism in the form of carboxylic acids, where the substitution group is located at the 2nd position of a carboxyl part (-COOH). Acidic cannabinoids produced by C.sativa include Δ9-THCA, CBDA, CBGA and CBCA. These compounds do not show any psychoactive effects. Usually, acidic cannabinoids produced by plant metabolism contain a pentyl side chain derived from the OA fragment.

The combination of GPP with divarnic acid instead of OA in cannabigrovarinic acid (CBGVA) leads to the production of cananoids with propyl side chains. The three known cannabinoid synthase enzymes are not selective for the length of the alkyl side chain and convert CBGVA to the propyl homologues of THCA, CBDA and CBCA. All chain lengths from methyl to pentyl have been found naturally in cannabinoids, probably all due to mixing with shorter OA chain homologues. Side chains are important in determining the affinity, selectivity, and pharmacological potency of cannabinoids for receptors. Many other acidic cannabinoids, including monomethyl and other types of esters, have been identified over the years (8,13).

1-5- Cannabinoid receptors: CB1 and CB2

Cannabinoid receptors are a group of receptors belonging to the G-protein family. And it has a protein structure consisting of seven membrane-enveloping helices along with intervening intracellular loops and a C-terminal domain that can be related to G-proteins from the G i/o family. The ligands of these receptors are known as cannabinoids and endocannabinoids depending on whether they are obtained from external or internal sources.

1-6- Cannabis classification

Cannabis means cane-like, while sativa means planted. And this means that this plant is propagated through seeds, not through a perennial plant with roots. According to the modern classification system, the genus Cannabis together with the genus Humulus belong to the cannabis family. During many centuries, different types of cannabis have been produced as a result of breeding and selection. So far, there is no general agreement for the classification of this plant. And the classification of different groups of hemp plant goes back to

the time of Linnaeus in the late 18th century.
UNODC (1956) has divided hemp into three groups:
1- fibers (hemp); Tall and branchless plants with poor seed production.
2- Oil seed; Short and early plants with abundant seed production.
3- medicinal cannabis; Short and branched plants with dark green leaves
Schultz, Klein, Plowman, and Lockwood (1974) (22) highlighted three species of this genus: C. sativa L, *C. indica* Lam and *C. ruderalis*. Other authors refer to the same divisions at the subspecies level with only one species *C.sativa* L. Small and Cronquist (1976)(23) have divided the single species of *C.sativa* into two subspecies, sativa and indica, each of which has domestic and wild varieties. In the subspecies *C.sativa* there are domestic and wild types:
sativa var.sativa (domestic), *C.sativa* subsp. *Sativa* var. *spontama* (Wild), *C.sativa* subsp. *indica* var. *indica* (domestic) and *C.sativa* subsp. *indica* var *kafiristanica* (wild).
The chemical diversity and morphological characteristics found in cannabis have led some taxonomists to agree and suggest that cannabis should be considered a multispecies genus with several individual species including: sativa, indica, and ruderalis. However, it is usually accepted that cannabis is a species and has a single species C.sativa. On the other hand, the classification of narcotic cannabis is complicated by years of prohibition, which has led to informal and clandestine breeding programs, which have resulted in decades of crossbreeding and hybridization without genetic records (5,25).

1-6-1- Classification of cannabis based on the amount of THC and CBD production

The medical benefits of compounds obtained from cannabis are undeniable, on the other hand, the subtle differences in the chemical nature of these compounds can be pharmacologically effective (16). The content and composition of cannabinoids among cannabis plants is very variable (6). Hemp plants are divided into marijuana and hemp based on the amount of THC and CBD production. Marijuana produces a high ratio of THC to CBD, while hemp has a low ratio of THC to CBD. Published studies show that the transcription levels of THCAs and CBDAs may be the determining

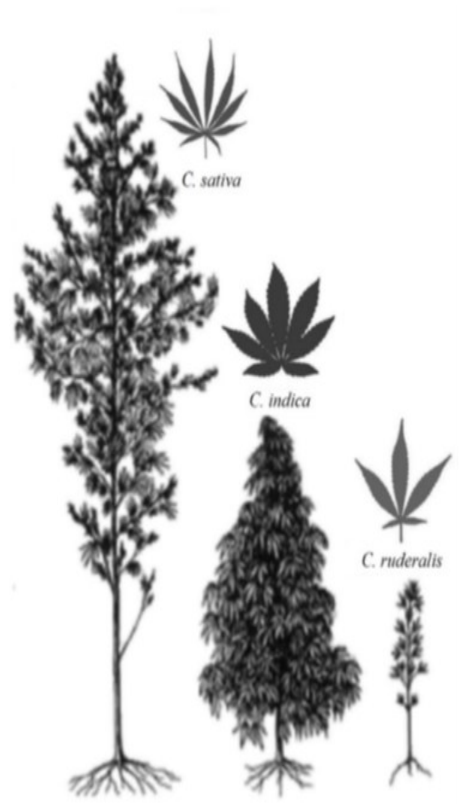


Figure 6: Species of cannabis (27)

factors for the synthesis of the THC/CBD ratio, although detailed information about the mechanisms for changes in the expression of these genes has not been revealed (24). However, among the most important factors affecting the final performance of hemp seeds and biomass, we can mention climatic factors, i.e. the effect of weather conditions that determine cannabinoids in plants, genetic predisposition and also agricultural factors (29).

1-7- Cannabis cultivation techniques

1-7-1- Cultivation in the open space

The hemp plant can be propagated through seeds and its life cycle is completed between 4 and 6 months depending on the type and time of cultivation. Its height can reach five meters (16 feet). The germination process is usually completed between 3 and 7 days, and the initial seedling growth stage usually ends between 2 and 3 months. After this, the plant is characterized by an increase in biomass and overall growth during long days (vegetative growth).

It is very easy to distinguish the gender of the flowers at this stage. At the end of summer, with the shortening of the days to 12-14 hours or less depending on the latitude and genetic characteristics, the cannabis plant enters the reproductive phase. Female flowers die at the same time as male flowers mature and pollinate. The seeds produced after flowering have a combination of the characteristics of the two parents as a result of cross-fertilization. This method is mostly used to grow hemp to produce fiber or seeds with less than 0.2% THC.

1-7-2- Cultivation in indoor environment

This method is usually used to increase resin production and remove unwanted male plants. So that the complete growth cycle, quality and quantity of biomass can be adjusted under controlled environmental conditions (6-8 weeks). Indoor cultivation requires an effective hydroponic system to receive nutrients and oxygen. However, a number of different techniques have been proposed for the indoor cultivation of cannabis. For example: standing aeration method, nutrient shell technique and aeroponic technique. In hydroponic growth, a nutrient solution in a specific pH range (5.5-6.5) is needed for maximum plant absorption and growth. Artificial light and compressed CO2 gas are needed to control photosynthesis, plant biomass, and flowering in indoor culture. For indoor cultivation, lamps including fluorescent lamps (FL), metal halide lamps (MH), and high pressure sodium lamps (HPS) are usually used.

1-7-3- Cultivation in a laboratory environment

This method has the advantage of being under control, independent of environmental factors (climate and geographical location), non-contamination of the produced plants with microorganisms and high efficiency. This method allows the propagation of different varieties of cannabis through seeds, although one of the biggest problems of this method is the high level of heterozygosity, which can lead to significant changes in secondary metabolites from one generation to another. In the early 1980s, the callus of different parts such as cotyledons, stems, young leaves, buds, petioles and roots were used. Recently, the use of meristematic callus has been studied. But so far no specific results have been provided (5).

1-8- The effect of the light spectrum on the cannabis plant

Light is one of the most important environmental parameters affecting plant growth and development (25). It exerts a wide range of effects on the activity of photosynthesis and photomorphogenic reactions throughout the life of the plant. The most important part of the light spectrum for plants, PAR (400-700 nm), is in the range of visible light. Today, it is widely accepted that the wavelength and intensity of light can affect photosynthesis and photomorphogenesis. Light plays an important role in cannabis cultivation both in terms of quality (spectrum) and quantity (intensity) (26). Lydon et al. (1987) (27) reported an increase in THC concentration in cannabis plants treated with UV-B radiation. which shows the possible protective role of cannabinoids against ultraviolet rays. They stated that there is a linear relationship between the content of THC in the flower tissue and the amount of UVB in the medicinal cannabis plant. While it does not affect other characteristics such as physiology, leaf morphology and the content of other cannabinoids (such as CBD) in medicinal and fibrous plants. The content of THC in flower tissue increased from 25% to 35% when the effective daily dose of UVB increased from zero kJ/m2 to 13.4 kJ/m2 (26). Since the final output of the hemp plant is important for its producers and consumers, the cultivation of the hemp plant will be different from other crops. The yield of the product cannot be evaluated only based on the dry weight of the flowers, but the content of the chemical compounds of the final product is very important. Dry shoot yield may be given on the basis of mass per plant (grams per plant) or mass per unit area of growth. Currently, there is no standard unit to indicate the yield of dry sprouts. In recent years, the unit of mass per watt of electrical energy consumed by the lighting system (g W-1) has been used because it indicates the relationship between light intensity, cannabis growth and the efficiency of the lighting system. *Cannabis sativa L.* produces hundreds of different chemical compounds, which are known as phytocannabinoids and have different medicinal properties. Each type of cannabis plant produces and stores different combinations of secondary metabolites in different proportions. The formation of the characteristics of cannabinoids depends on environmental and chemical factors, so this issue is very important for the producers of the characteristics of cannabinoids depends on environmental and chemical factors, so this issue is very important for the producers of the medicinal compounds of the cannabis plant, in order to produce continuous and uniform cannabinoids with the desired medicinal properties.

For this reason, many cannabis producers are moving their growing medium to grow rooms and closed spaces. Since the most important factors for cannabis cultivation are quality, intensity and photoperiod. In these rooms, it is possible to control temperature, humidity, CO2 concentration, intensity and quality of light spectrum. Therefore, it provides the possibility of continuous cultivation of hemp plant and harvesting up to six times during the year for the producers. On the other hand, growing cannabis indoors requires a lot of energy due to the high demand for light and indoor cooling, since cannabis is a plant adapted to high radiation levels and hot temperatures. Various types of lighting have been reported in cannabis grow rooms, including fluorescent lamps (CFL or T5), metal halide lamps (MH), HPS lamps, induction lamps, light emitting diodes. Light (LED) or a combination of different types of light is used. Different lamps have completely different light spectrums. Ordinary bubble lamps (tungsten-fluorescent) in which a wire is melted and the light shines from it has a range of spectrum from violet to infrared, while moonlight lamps (fluorescent) and mercury and moonlight lamps have a very small amount of red waves and no infrared waves.

These types of lamps are cold because they do not have infrared waves, while in normal lamps, only about 5% of the electrical energy is converted into light waves that can be used by the plant, and the rest is lost as heat. be made This efficiency in moonlight lamps is more than 15%. In horticultural sciences and agricultural industry, it has long been known to manipulate plant morphology and metabolism with light spectrum. Also, studies conducted by researchers show that the spectrum of light has an effect on the quality of cannabinoids and the production of secondary metabolites.

A study compared the effect of three light spectrums including one HPS and two types of LED (AP673L and NS1) on the morphology and cannabinoid content of cannabis clones. The spectrum produced by HPS was 96% PAR and was strongly concentrated with green/yellow light (68%), orange/red light (21%) and less with violet/blue light (8%). In comparison, the spectrum of AP673L produces a spectrum equal to 93% of PAR and was mostly focused on orange/red light (59%), green/yellow (20%) and violet/blue light (14%). For the NS1 spectrum, the PAR was equal to 94% and focused on green/yellow light (37%), orange/red light (33%) and violet/blue light (24%). The percentage of UVA in HPS was 1%, 0% in AP673L and 2% in NS1. In mature conditions, the plants grown under two LEDs were shorter and more compact than those under HPS treatment due to the increase in red light and blue light emission (26).

Namdar et al. (2019) (28) showed that cannabis plants grown under LED light, instead of growing vertically towards the light source, spread their branches horizontally and expressed the possibility that it may be due to Use this method to get more light to all the flowers. Also, Namdar et al. (2019) (28) and Magagnini et al. (2018)(29) stated that cannabis grown under LED light enriched with blue light has a shorter height than plants grown under normal light.

On the other hand, plants grown under HPS were significantly taller and had higher stem dry weight compared to plants under LED light treatment. Tibbitts et al. (1983) (30), Wheeler et al. (1991) (31) reported that plants grown under HPS may have unbalanced morphology and excessive leaf elongation due to low R:RF ratio and low blue light emitted from these lamps. Show the stem.

In fact, the reduction of R:RF ratio activates several transcription factors involved in auxin biosynthesis, which leads to an increase in the longitudinal growth of plants. The quality of light can affect the flowering of plants and sometimes photoperiod (short day, long day) may work. According to the studies of Namdar et al. (2019) (28), the short-day cannabis plant under LED light shows a 40% reduction in flowering compared to normal light, although it is associated with a 66% increase in total cannabinoids.

As mentioned, usually in the path of cannabinoid biosynthesis, the amount of CBGA increases in unripe flowers and finally it is converted into THCA by specific enzymes. According to the conducted studies, LED light can be effective on the distribution of CBGA, in fact, the growth method under LED light creates changes that can be seen in the reproductive stage as well.

Namdar et al. (2019) (28) observed an increase in the amount of CBGA and reduced conversion to THCA in cannabis plants that spent the vegetative period under LED light and the reproductive period under HPS light. In another study, Magagnini et al. (2018) also reported a significant increase in CBGA in cannabis plants that flowered under LED light.

They also expressed the reduction of THC concentration in flowers treated with HPS compared to LED. Meanwhile, the reduction of THC led to the reduction of CBD, THCV and especially CBG, which ultimately increased the ratio of THC in HPS treatments compared to LED. So that HPS shows a higher ratio of THC compared to LED treatment. Most studies emphasize that the quality and quantity of light affects the synthesis of cannabinoids in the growing plant.

So MAHLBERG and HEMPHILL (1983) (32) concluded in their research that the quality and quantity of light can affect the concentration of delta-9-tetrahydrocannabinol (Δ9-THC), although other cannabinoids, especially CBC It undergoes optical changes. They observed the accumulation of high levels of CBC, and the change in the ratio between this cannabinoid and delta-9-tetrahydrocannabinol (Δ9-THC) in plants under green, blue, and red filtered light, as well as darkness. Also, they believed that the high ratio of CBC to Δ9-THC in filtered light conditions and plants grown in darkness shows the importance of CBC in light stress conditions. Therefore, the mechanism of cannabinoid synthesis can be partially deactivated in light-stressed leaves, but when such leaves are exposed to daylight, it is reactivated and leads to the production of cannabinoids in the plant. In this part of the current review, we present the effect of different light spectrums on cannabis growth. The conducted studies show that LED and HSP lights can be suitable options for the growth of cannabis plants due to the beneficial changes in growth and the amount of cannabinoids, however, there is still a need for more extensive studies on the effect of quality and There is a quantity of different light spectrums on the growth, photomorphogenesis and metabolism of the cannabis plant.

1-9- The effect of food elements on cannabis plant

It is well known that environmental conditions affect secondary metabolites and their accumulation in plants. Exogenous factors such as water supply, moisture, salinity and nutrient availability affect the production and concentration of secondary metabolites such as alkaloids, phenols and terpenoids (33). Mineral nutrition is one of the main factors affecting growth, The growth and performance of plants and the availability of nutrients in the soil strongly affect the growth and development of plants (33,34). When the soil is depleted of certain nutrients, severe limitations in biomass production occur. Nutrient deficiency may induce nutrient reabsorption as an important physiological process. which is used as an important strategy to store nutrients. This process in plants that grow in soils with limited nutrients or under stress, leads to a greater ability to absorb nutrients and as a result, better growth (34). Optimal concentrations of mineral nutrients in plant and root tissues are different and possible for each nutrient (33). depend on plant species. Nitrogen (N), phosphorus (P) and potassium (K) are three minerals that are very ubiquitous in plants and play a vital role in many aspects of plant metabolism.

T.Lošák and R. Richter(35) showed in their studies that the use of nitrogen supplements in the leaf and flowering stages of the poppy plant leads to an increase in the yield of alkaloids in the capsules. Also, the highest level of morphine was found in plants after treatment with high doses of nitrogen. The content and composition of secondary metabolites in plants are influenced by genetics and environmental factors. While genetics determines the production potential, environmental conditions cause changes in the quantity, quality and distribution of active compounds in the plant. In this way, the characteristics of secondary metabolites are the result of interactions between environmental and physiological processes. Legal restrictions have hindered the progress of academic research on cannabis over the past decades (33). Legal restrictions have hindered the progress of academic research on cannabis over the past decades (33). Considering that the medicinal activity of cannabis plant is attributed to its various secondary metabolites. Understanding how to regulate the biosynthesis and accumulation of secondary metabolites in different plant organs is needed. On the other hand, hemp (HEMP) has a deep and large root system and has a high ability to absorb nutrients and water from the roots. Although hemp contains high amounts of macronutrients, most of them can be returned to the soil at a significant level through the above-ground biomass as well as through the roots. In the same way, approximately one third of the total potassium required by the crop can return to the soil through the inner part of the stem during the watering phase of the field. For these interesting features, hemp can be used in crop rotation to stabilize nutrient levels and improve soil properties (36). Mineral nutrients and especially nitrogen are among the main environmental factors affecting plant growth, physiology and metabolism (37). Nitrogen is a nutrient that has the highest consumption in plants and is an essential part of most metabolic processes, especially the synthesis of secondary metabolites, so its availability in the soil is very effective not only on biomass but also on the synthesis and final yield of the product. N input is one of the critical factors for plant growth and performance and is recognized as a primary limiting factor in many agricultural systems (34,37). Water and nitrogen insufficiencies are major imperatives in hemp generation(45). The relationship between the availability of nutrients and the yield of hemp products is a very important issue in hemp cultivation. This article supports the idea of joint regulation of nitrate transporters, genes related to N metabolism, transcription factors and genes involved in the synthesis of secondary metabolism as part of the complex mechanism of dealing with biotic and abiotic stresses. Therefore, this gene family can provide potential targets for genetic improvement in hemp as well as other fiber crops, improving tolerance to abiotic stresses, nitrogen absorption, and finally production of biomass and secondary metabolites (34). The results of various studies show that nitrogen consumption is usually very high during the first month of cannabis plant growth. Therefore, this fertilizer is used in hemp cultivation fields at the time of planting. The use of N fertilizers has a positive effect on the height of hemp plants, the biomass of fibrous varieties and the content of seed protein in seed-producing species. So, the consumption of high amounts of nitrogen fertilizers leads to an increase in the longitudinal growth of the hemp plant, which leads to greater strength of the plant in the soil. On the other hand, insufficient amounts of nitrogen lead to a decrease in plant performance, which is very evident in the quality of the produced fiber. PC Struik et al (2004) (38), in a study, stated that the response of hemp plants in nitrogen-rich soils to nitrogen fertilizers is very small. Therefore, based on the studies, it is suggested that the amount of nitrogen fertilizer used should be determined according to the amount of nutrients in the soil (soil fertility). Considering the limited information about the effects of nutrients on cannabis plant with medical use, the results of Bernstein, N et al.'s 2019(39) studies on cannabis plant (medical) can be interesting. Also, it was said in previous articles, nitrogen supplement in hemp plant leads to increase in height and biomass. While in the case of hemp plant with medicinal use, very little response was observed using fertilization treatments with P or K. But this information only applies to medical cannabis, where the concentration of therapeutic cannabinoids is far more important than total biomass or fiber length. In another study conducted by Saloner and Bernstein in 2021(37), cannabis plants showed a significant increase in inflorescence biomass under the treatment of 160 mg/L of nitrogen, while higher amounts of nitrogen (320 mg/L) g/L) did not induce significant effect. But it led to several pheno-

phenotypic and physiological responses including: increase in photosynthetic pigment concentration, leaf osmotic potential, plant N and N-NO3 concentration, and decrease in gas exchange parameters.
They also observed an overall decrease in the concentration of most cannabinoids and terpenoids with increasing available nitrogen, although it did not affect or lead to the production of some compounds, for example, alpha-pentene, beta-pentene and myrcene. It was produced on the spur of the moment. On the other hand, the increase in decarboxylation of THCA and CBDA with increasing nitrogen supply shows that the optimal physiological state causes the decarboxylation of cannabinoids in the plant. And the lack of N, which causes physiological disorder and delay in the decarboxylation of cannabinoids in the plant, which shows the importance of secondary metabolites in stressful conditions.

1-9-1-The effect of the element phosphorus (p)

Phosphorus (P) is an essential macromolecule for plant metabolism and growth. Due to its function as a structural element in phospholipids and nucleic acids, it plays a key role in the transport of carbohydrates inside the plant as well as in the transport of intracellular energy. Due to its important role as an energy carrier, P plays a role in many key biosynthetic pathways such as fatty acid synthesis, aerobic respiration, photosynthesis and glycolysis (40). Phosphorus nutrition has long been of interest in cannabis cultivation. Breeders often supply plants with a relatively high concentration of phosphorus (above 200 mg/L) at the flowering stage, based on the belief that this will promote flower growth. However, there is little evidence to support this (41). Studies on the effect of phosphorus nutrition on the functional-physiological characteristics and the content of cannabinoids in two cultivars of medical cannabis, namely Royal Medic (RM) and (DQ) Desert Queen, respectively, with a high ratio of THC to CBD and a balanced ratio of THC and CBD, evaluated. The research results showed that biomass accumulation and morphological growth of the plant were not significantly affected by concentrations higher than 30 mg/liter. And the response to lower concentrations was different between cultivars and tissues. At low concentrations of phosphorus, the reduction of root and shoot biomass was shown without affecting the ratio of branches. Also, the concentration of photosynthetic pigments, chlorophyll a and b, decreased under P deficiency in RM. As for the concentration of cannabinoids, the increase in the consumption of phosphorus resulted in a decrease in the concentration of the tested cannabinoids, especially THCA and CBDA (Figure 7).

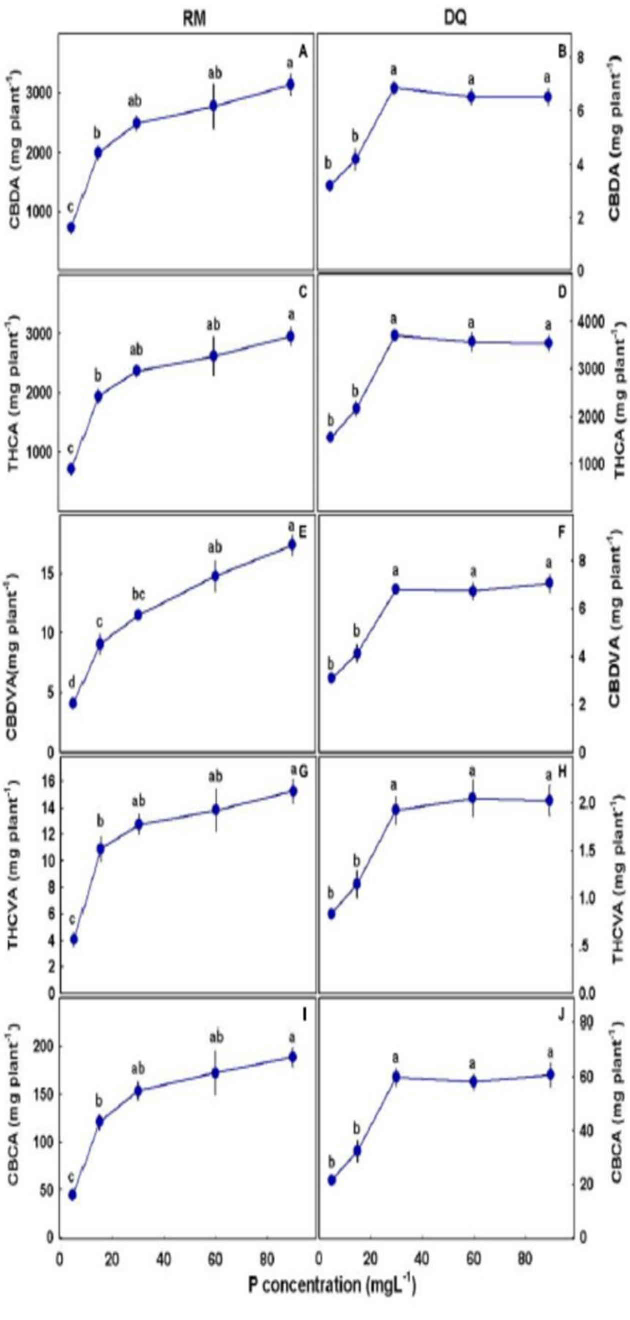


Figure 7: The effect of phosphorus application on the yield of cannabinoids in two varieties of medical cannabis, RM and QM(40).

However, the yield and performance increased, which shows that the values of 30 mg/L for DQ and 30-90 mg/L for RM are optimal. Based on this, it can be stated that the effect of phosphorus nutrition on cannabinoids may depend on the genotype and should be considered in genetic differences to optimize consumption (40).

Studies by COFFMAN and GENTNER (42) in 1977 show that there is a direct relationship between maximum plant growth and Δ9THC yield with soil phosphorus along with high levels of nitrogen or medium to high K. So that C. sativa plants accumulated Mn up to 1800 ppm under phosphorus deficiency conditions without showing signs of toxicity, while plant growth was negatively correlated with Mn concentration. Other studies also show that the response of medical cannabis to increased phosphorus supplementation depends on the organ and composition. So, the concentration of the main cannabinoids THC, CBD, CBN and CBG in the upper flowers of the plant is not affected by the increase in P treatment (Figure 8). The concentration of THC was reduced by 16 and 19% in the leaves of the flower by phosphorus and NPK supplementation, respectively, while the concentration of CBN showed a decrease only in the lower flowers of the plant (Figure 8, A). Indeed, for most of the cannabinoids studied, including THC, CBD, and CBG, P supplementation increased the content in the center or bottom of the plant without affecting the top surface of the plant (Figure 9) (39).

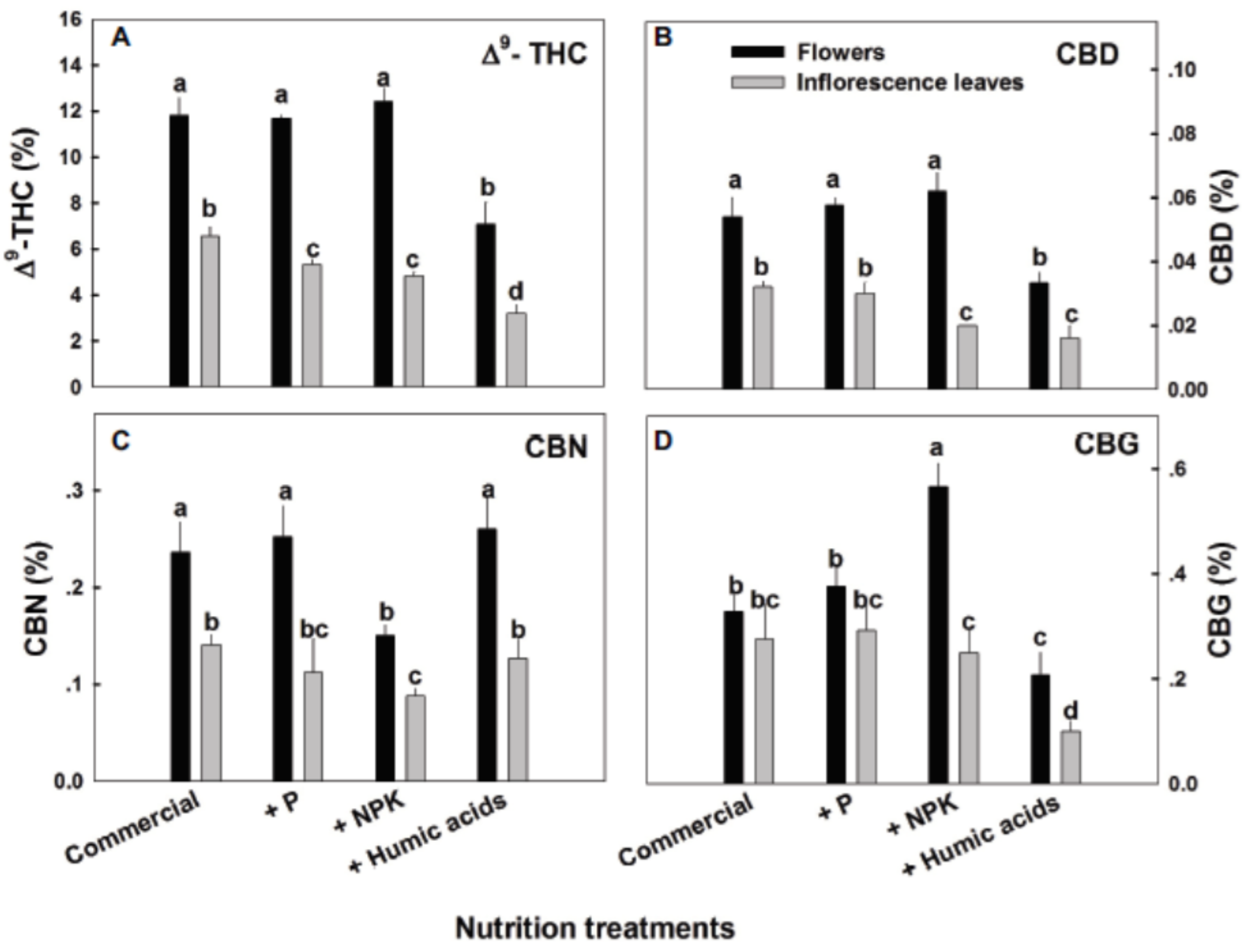


Figure 8: The concentration of the main cannabinoids in the flowers and leaves of the medical cannabis plant under the influence of food supplements (39).

1-9-2- Effect of potassium

K plays a role in many physiological and metabolic processes, including photosynthesis, transport of absorbed substances, protein synthesis, enzyme activity, regulation of stomata and osmotic regulation. And therefore, it is not surprising that it plays an essential role in the growth and development processes (33). The information obtained from the study of the effect of potassium consumption on two genotypes (RM and QM) of the medical cannabis plant has shown that low amounts of K have similar effects in both genotypes, but high amounts of K have various effects in the genotypes. shows In the case of RM genotype, an increase in growth was observed in response to values higher than 175 ppm, as well as an increase in leaf and root biomass, stem thickness and internode height. But the values of 240 ppm provided limiting effects. Therefore, 175 ppm is known as the optimal concentration for RM genotype. For the QM genotype, the values of 60-175 ppm were not effective on plant growth, while it was surprisingly observed that the values of 240 ppm of k led to an increase in growth and development in this genotype (33). This difference in response to K supply may be due to differences in plant tissue sensitivity to K (eg, main stem vs. lateral shoot). Also, the phenological stage of the plant (for example, the vegetative or reproductive stage) can be a factor in the response of hemp to K supply (41).

1-9-3- The effect of humic acid

HA is derived from humic substances, known as humus, microbially metabolized organic matter that constitutes more than 60% of soil organic matter in the world (39). Humic substances, as a part of organic substances of humus, soil, are compounds that arise from the physical, chemical and microbiological transformation of biological molecules (48).

Humic acid in combination with different mineral fertilizers, acid can improve soil quality, increase the amount of fertilizer consumption, improve yield and product quality (49) (Yang Li et al., 2019). It also plays an important role in the initial stabilization of soil grains (48). Therefore, HA as a biological stimulus directly affects plant growth and development through nutritional, hormonal or secretory pathways. Therefore, it can also play a role in the biosynthesis of secondary metabolites (39). Bernstein, N et al. reported in 2019 (39) based on their studies that humic acid (HA) dietary supplement reduced THC, CBD, and CBG levels in flowers, inflorescence leaves, and fan leaves. While P or NPK treatment did not affect the cannabinoid content in fan leaves, with the exception of CBCT, which was reduced by 29% with NPK treatment, HA significantly increased THC, CBD, CBG content. It reduced CBC, THCV, CBCT and CBL in fan leaves. On the other hand, they observed that the concentration of nutrients N, P, K and Ca and micronutrients Mn, Zn and Fe increased at least in one vegetative organ of medical cannabis (leaves or stems). But effects on mud were found only for Mn concentration. They concluded that the accumulation of these metals may cause the production of cannabinoids.

1-10- Medicinal effects of cannabis plant on the human body

In a study by Callaway(44) and his colleagues in 2005, they evaluated the effect of daily oral consumption of 30 ml of hemp oil in atopic dermatitis patients for 8 weeks in order to find out its medicinal properties. The results of this study showed that hemp oil effectively improves skin quality and pathological symptoms by increasing the plasma levels of gamma linoleic acid (GLA), stridonic acid (SDA) and litoleic acid (LA), which leads to a decrease Dry skin, itching and use of skin medications by patients. It has also been suggested that GLA is rapidly metabolized in the skin to the anti-inflammatory DGLA, which also leads to the suppression of the ability of polymorphonuclear neutrophils (PMN) to produce leukotriene B4 (LTB4). On the other hand, SDA increases EPA levels in red blood cells and plasma phospholipids, which acts as an anti-inflammatory. Decreasing the level of ceramides in the stratum corneum is one of the important factors in atopic dermatitis due to its importance in the function of the skin barrier. Meanwhile, the increase in plasma LA level can increase the amount of ceramide in the skin layer. The authors observed a decrease in TEWL values, indi-

-cating that less water is lost through the skin after using hemp oil.

The amount of total polyunsaturated fatty acids (PUFAs) in patients' plasma increased significantly after daily oral consumption of sesame oil, and due to the known role of these fatty acids in immune responses, the formation of new skin cells by cells Facilitate basic skin problems and help improve atopic dermatitis. They consider the presence of GLA and SDA in hemp oil as a factor for replacing delta-6-desaturase with the rate-limiting enzyme and thus improving the symptoms of atopic dermatitis.

Another study on hemp oil was conducted by Mamber et al. in 2020(45) on the expression of the immune response gene of human small airway epithelial cells (HSAEpC) in chronic obstructive pulmonary disease (COPD). The results of their studies show that hemp oil extract was able to create significant effects on the expression of 37 tested genes. So that six genes (CSF2, IL1RL1, IL4, IL13RA2, IL17A and PPARG) were regulated in all three dilutions (1:400, 1:800 and 1:1600). Two other genes (CCL22 and TSLP) show positive regulation, while six genes (CLCA1, CMA1, EPX, LTB4R, MAF and PMCH) were negatively regulated at 1:400 and 1:800 dilutions. . Especially, reducing the expression of CLCA1 and CMA1 genes can have positive effects in the treatment of COPD.

On the other hand, the positive regulation of many genes, such as IL4, CCL22 and TSLP, encode cytokines and chemokines that are involved in anti-inflammatory responses and Th2-type immunity. Finally, it has been stated that hemp oil extract has the potential to help reduce inflammation, restore Th1/Th2 balance. and can improve other symptoms in COPD, it is also possible that it plays a role in other autoimmune diseases that use the TH2 immune response pathway. The authors stated that the use of cannabis extract in diseases such as asthma and allergies that have an abnormal TH2 immune response is contraindicated.

Study at 2021 evaluated the effect of cannabis products on the control of CDKL5 deficiency disorder (CDD), a severe, treatment-resistant form of primary epilepsy, in children. As current treatment options are often ineffective or associated with adverse effects, it forces families to seek alternative treatments for their children, including cannabis-derived products. The authors stated that more than two-thirds of the 70 people surveyed perceived improvement in seizures either temporarily (16%) or permanently (54%). And less than a quarter reported that cannabinoids had no effect on seizure improvement, while fewer reported that seizure control worsened.

However, the active use of cannabinoids was not associated with a reduction in the frequency of seizures and the number of antiepileptic drugs used compared to non-users. This issue indicates the need for more investigations to understand this issue. Also, the authors observed other favorable effects of cannabis use, such as: improving sleep, feelings/mood, growth and eating/digestion/appetite, the most common benefits of which were besides improving seizures, increasing alertness/attention and improving cognition. Therefore, it can be said that cannabis products may have benefits beyond seizure control (46).

In 2013, Soheila Rezapour-Firozi and et al (47) investigated the effect of hemp oil and evening primrose oil along with a warm diet on the control of MS. For this purpose, patients were divided into three groups. Group A was treated with a diet of complementary oils in the amount of 18 to 21 grams per day (6 to 7 grams, three times a day) with the recommended hot nature diet, group B was treated with olive oil in the amount of 18 to 21 grams per day (6 to 7 grams, three times a day) and group C treated with complementary oils 18 to 21 grams per day (6 to 7 grams, three times a day) for 6 months. The results of this study indicate that supplemental oils alone (with or without hot nature diet) can have a therapeutic effect on MS.

The amount of pro-inflammatory cytokines IL-17 and IFN in group A and C (mainly group A) decreased, while in group B, it was associated with a significant increase. They stated that complementary oils along with hot nature diet leads to blocking of pro-inflammatory cytokinin synthesis pathways and blocks the expression of IL-17 cytokinin.

In fact, by targeting the key mechanisms of the disease, it acts like one of the approved treatments for modulating the immune system, such as beta interferons and glatiramer acetate (47).

Conclusion

Cannabis is among very special plants due to its high diversity. This plant has very complex phytochemical compounds, the most unique of which are cannabinoids. Therefore, cannabis can be considered as a real factory producing secondary metabolites, which is very important in the pharmaceutical industry. Each type of cannabis plant produces and stores different combinations of secondary metabolites in different proportions. The formation of the characteristics of cannabinoids depends on environmental and chemical factors, so this issue is very important for the producers of the medicinal compounds of the cannabis plant, in order to produce continuous and uniform cannabinoids with the desired medicinal properties Considering the extensive medicinal properties of cannabinoids, the methods of growth, harvest, processing and use are progressing towards an important place in pharmaceuticals.

Various factors are important in the growth and breeding of the cannabis plant. Light, both quantitatively and qualitatively, can play an important role in the cultivation of cannabis, so that studies have shown that there is a linear relationship between UV-b radiation and the amount of THC in the cannabis plant. This is despite the fact that LED and HSP lights can be suitable options for the growth of cannabis plants due to the beneficial changes in growth and the amount of cannabinoids, however, there is still a need for more extensive studies on the effect of the quality and quantity of the spectrum. There are different light effects on the growth, photomorphogenesis and metabolism of the cannabis plant. Nutrients also had interesting effects on the hemp plant, so that according to the study, the consumption of high amounts of nitrogen fertilizers will increase the length growth of the hemp plant, which leads to greater strength of the plant in the soil. to be On the other hand, insufficient amounts of nitrogen cause a decrease in plant performance, which is very evident in the quality of the produced fiber. Considering the limited information about the effects of nutrients on the hemp plant, more research in this field can be useful. In addition to the importance of cannabinoids, hemp plant products, including its oil, can have beneficial effects in the treatment of many diseases such as: epilepsy, MS, skin eczema, etc., which these cases show. The importance of the need for more research about this valuable plant.

Reference

1. F.Thomas B, A.Elsohly M. The Botany of Cannabis sativa L. In: The Analytical Chemistry of Cannabis. ELSEVER; 2016. (Editor; vol. 59).
2. Salami SA, Martinelli F, Giovino A, Bachari A, Arad N, Mantri N. . It Is Our Turn to Get Cannabis High: Put Cannabinoids in Food and Health Baskets. Molecules. 2020;4036(4):25 (18).
3. Russo, E, Guy, G.W., Whittle, B.A., Robson, P.J. History of cannabis as a medicine The medicinal uses of cannabis and cannabinoids. Pharm Press. :1–16.
4. Stiasna K, Presinszka M, Vyhnanek T, Trojan V, Mrkvicova E, Hrivna L, Havel L. ANALYBISIS OF GENES FROM CANNABINOID BIOSYNTHETIC PATHWAY. MENDELNET. 2015;442–6.
5. Farag S, Kayser O. The Cannabis Plant: Botanical Aspects. Biol Pharmacol Diagn Treat. 2017;3–12.
6. van Bakel H, Stout J.M,Cote A.G,Tallon C.M, Sharpe A.G, Hughes T.R and Page J.E. The draft genome and transcriptome of Cannabis Sativa. Genome Biol. 2011;(12:R102).
7. Fathordoobady F,Singh A,D. Kitts D & Pratap Singh A. Hemp(Cannabis Sativa L.)Extract: Anti-Microbial Properties,Methods of Extraction, and Potential Oral Delivery. Food Rev Int. 2019;664–84.
8. Hazekamp A, T. Fischedick J, Llano Dı´ez M, Lubbe A, L. Ruhaa R. Chemistry of Cannabis. In 2010. p. 52.

9. Asadi S, Moghadam H ,Naghdi Badi H, Naghavi MR, Salami SAR. A Review on Agronomic, Phytochemical and Pharmacological Aspects of Cannabis (Cannabis sativa L.). 2018;

10. Flores-Sanchez I and Verpoorte R. Secondary metabolism in cannabis. Phytochem Rev. 2008; (7:615–639).

11. Farinon B , Molinari R,Costantini L and Merendino N. The Seed of Industrial Hemp (Cannabis sativa L.):Nutritional Quality and Potential Functionality for Human Health and Nutrition. Nutrients. 2020;(12, 1935).

12. Radosavljevic-Stevanovic N, Markovic J, Agatonovic-Kustrin S, Razic S. Metals and organic compounds in the biosynthesis of cannabinoids: a chemometric approach to the analysis of Cannabis sativa samples. Nat Prod Res. 2013;28:511–6.

13. Rea K. A,Casaretto J. A, Al-Abdul-Wahid M.S, Sukumaran A, Geddes-McAlister J, J. Rothstein A, A. Akhtar T. Biosynthesis of cannflavins A and B from Cannabis sativa L. Phytochemistry. 2019;162–71.

14. Hurgobin B, Tamiru-Oli M, T. Welling M, S. Doblin M, Bacic A, Whelan J and G. Lewsey M. Recent advances in Cannabis sativa genomics research. New Phytol. 2020;230: 73–89:17.

15. Grof Ch.P.L. Cannabis, from plant to pill. Br J Clin Pharmacol. 84 2463–2467.

16. Liu Y, Zhu P, Cai C, Haughn G, E. Page J. Three novel transcription factors involved in cannabinoid biosynthesis in Cannabis sativa L. Plant Mol Biol. 2021;

17. Gülck T and Lindberg Møller B. Phytocannabinoids: Origins and Biosynthesis. Trends Plant Sci. 2020;25(10).

18. Jordan J. Zager , Lange I, Srividya N, Smith A and Lange B. Gene Networks Underlying Cannabinoid and Terpenoid Accumulation in Cannabis. Plant Physiol. 2020;180:1877–97.

19. Shoyama Y, Yagi M, Nishioka I, Yamauchi T. Biosynthesis of cannabinoid acids. 1975 Oct;14 (10):2189–92.

20. Carlton E. Turner, Kathy Hadley. Constituents of Cannabis sativa L. II: Absence of cannabidiol in an african variant. JPharmSci. 1973;62 (2):251–5.

21. Marks M.D,Tian L, P. Wenger J,N. Omburo S, Soto-Fuentes W, He J,R. Gang D,D. Weiblen G, A. Dixon R. Identification of candidate genes affecting Δ9-tetrahydrocannabinol biosynthesis in Cannabis sativa. J Exp Bot. 2009;60(13):3715–26.

22. Stout J, Boubakir Z, J. Ambrose S,W. Purves R, E J. The hexanoyl-CoA precursor for cannabinoid biosynthesis is formed by an acyl-activating enzyme in Cannabis sativa trichomes. Plant J. 2012;71(3):353–65.

23. Jalalia S, Salamia S.A,Sharifib M, Sohrabi S. Signaling compounds elicit expression of key genes in cannabinoid pathway and related metabolites in cannabis. Ind Crops Prod. 2019;133:105–10.

24. Patra B, Schluttenhofer C, Wu Y, Pattanaik S, Yuan L. Transcriptional regulation of secondary metabolite biosynthesis in plants. Biochem Biophys Acta. 2013;1829:1236-1247.

25. Sirikantaramas S, Taura F,Tanaka Y, Ishikawa Y, Morimoto S ,Shoyama Y. Tetrahydrocannabinolic Acid Synthase, the Enzyme Controlling Marijuana Psychoactivity, is Secreted into the Storage Cavity of the Glandular Trichomes. Plant Cell Physiol. 2005;46(9):1578–82.

26. Schultes, R. E., Klein, W. M., Plowman, T., & Lockwood, T. E. Cannabis: an example of taxonomic neglect. Harv Univ Bo¬tanical Mus Leafl. 1974;23:337–67.

27. Small, E., & Cronquist, A. A practical and natural taxonomy for Cannabis. Taxon. 1976;25:405–35.

28. S. Monthony A, R. Page S, Hesami M, Maxwell P. Jones A. The Past, Present and Future

of Cannabis sativa Tissue Culture. PLANTS. 2021;185(10):28.

29. 29.Malík M, Velechovský J, Tlustoš P. The overview of existing knowledge on medical cannabis plants growing. Plant Soil Env. 67:425–42.
30. 30.Aryal, N., Orellana, D.F. & Bouie, J. Distribution of cannabinoid synthase genes in non-Cannabis organisms. J Cannabis Res 1. 2019;(8).
31. 31.Poniatowska J, Wielgus K, Szalata M, Szalata M, Ozarowski M, Panasiewicz K. Contribution of Polish agrotechnical studies on Cannabis sativa L. to the global industrial hemp cultivation and processing economy. sciendo. 2019;65(2):14.
32. 32.Eichhorn Bilodeau S, Wu B-S, Rufyikiri A-S, MacPherson S and Lefsrud M. An Update on Plant Photobiology and Implications for Cannabis Production. Front Plant Sci. 2019;296(10).
33. 33.Jin, D., Jin, S.X. and Chen, J. Cannabis Indoor Growing Conditions, Management Practices, and Post-Harvest Treatment: A Review. Am J Plant Sci. 2019;(10):925–46.
34. 34.Lydon J, H. Teramura A,Coffman C.B. UV-B RADIATION EFFECTS ON PHOTOSYNTHESIS, GROWTH and CANNABINOID PRODUCTION OF TWO Cannabis sativa CHEMOTYPES. Photochem Photobiol. 1987;46(2):201–6.
35. 35.Namdar D, Charuvi D, Ajjampura V, Mazuz M, Ion A, Kamara I, Koltai H. LED lighting affects the composition and biological activity of Cannabis sativa secondary metabolites. Ind Crops Prod. 2019;132:177–85.
36. 36.Magagnini G,Grassi G,Kotiranta S. The Effect of Light Spectrum on the Morphology and Cannabinoid Content of Cannabis sativa L. Med Cannabis Cannabinoids. 2018;(1):19–27.
37. 37.Tibbitts T.W, MorganD.C and Warrington I.J. Plants under Four Combinations of High-pressure Sodium, Metal Halide, and Tungsten Halogen Lamps at Equal PPFD. Am Soc Hortic Sci. 1983;108(4):622–30.
38. 38.Wheeler R.M, Mackowiak C.L, Sager J.S. Soybean Stem Growth under High-Pressure Sodium with Supplemental Blue Lighting. 1991;83(5):903–6.
39. 39.Mahlberg, P.G. and Hemphill, J.K. Effect of Light Quality on Cannabinoid Content of Cannabis sativa L. (Cannabaceae). Bot Gaz. 144:43–8.
40. 40.Saloner A, Sacks MM and Bernstein N. Response of Medical Cannabis (Cannabis sativa L.) Genotypes to K Supply Under Long Photoperiod. Front Plant Sci. 2019;10:1369.
41. Landi S , Berni R , Capasso G , Hausman J ,Guerriero G and Esposito S. Impact of Nitrogen Nutrition on Cannabis sativa: An Update on the Current Knowledge and Future Prospects. Mol Sci. 2019;20, 5803.
42. Lošák T, Richter R. Split nitrogen doses and their efficiency in poppy (Papaver somniferum L.) nutrition. PLANT SOIL Env. 2004;50 (11):484–8.
43. Angelini L.G,Tavarini S ,Cestone B, Beni C. Variation in mineral composition in three different plant organs of five fibre hemp (Cannabis sativa L.) cultivars. agrochimica. 2014;58-No.1.
44. Saloner A, Bernstein N. Nitrogen supply affects cannabinoid and terpenoid profile in medical cannabis (Cannabis sativa L.). Ind Crops Prod. 2021;167:113–516.
45. Tang K, Fracasso A, C. Struik P, Yin X, Amaducci S. Water- and Nitrogen-Use Efficiencies of Hemp (Cannabis sativa L.) Based on Whole-Canopy Measurements and Modeling. Front Plant Sci. 2018;9:14.
46. Tang K , Struik P.C Yin X, Calzolari D, Musio S,Thouminot C, Bjelková M, Stramkale V, Magagnini G , S.Amaducci. A comprehensive study of plant-

-ing density and nitrogen fertilization effect on dual-purpose hemp (Cannabis sativa L.) cultivation. Ind Crops Prod. 2017;107:427–38.

47. Bernstein N, Gorelick J, Zerahia R and Koch S. Impact of N, P, K, and Humic Acid Supplementation on the Chemical Profile of Medical Cannabis (Cannabis sativa L). Front Plant Sci. 2019;10:736.

48. Shiponi S and Bernstein N. Response of medical cannabis (Cannabis sativa L.) genotypes to P supply under long photoperiod: Functional phenotyping and the ionome. Ind Crops Prod. 2021;161:113–54.

49. Bevan L, Jones M and Zheng Y. Optimization of N, P, K for soilless production of Cannabis sativa in the flowering stage using response surface analysis. 2021;

50. Coffman, C.B. and Gentner, W.A. Responses of Greenhouse-Grown Cannabis sativa L. to Nitrogen, Phosphorus, and Potassium. Agron J. 1977;69:832–6.

51. Eladia M. Peña-Méndez, Josef Havel, Jiří Patočka, Humic substances. compounds of still unknown structure:applications in agriculture, industry, environment, and biomedicine. J Appl Biomed. 2005;(3):13–24.

52. Li Y, Fang F, Wei J,Wu X,Cui R, Li G, Zheng F,Tan D. Humic Acid Fertilizer Improved Soil Properties and Soil Microbial Diversity of Continuous Cropping Peanut: A Three-Year Experiment. Sci Rep. 2019;9:12014:9.

53. Callaway J, Schwab U,Harvi I ma, Pirjo Halonen, Otto Mykkänen, Pekka Hyvönen, Tomi Järvinen. Efficacy of dietary hempseed oil in patients with atopic dermatitis. 2009;87–94.

54. W. Mamber S, Gurel V, Lins J,Ferr F, Beseme S, McMichae J. Effects of cannabis oil extract on immune response gene expression in human small airway epithelial cells (HSAEpC): implications for chronic obstructive pulmonary disease (COPD). J Cannabis Res. 2020;14.

55. Dale T, Downs J, Wong K,Leonard H. The perceived effects of cannabis products in the management of seizures in CDKL5 Deficiency Disorder. Epilepsy Behav. 2021;108152(122):9.

56. Rezapour-Firouzi S, Arefhosseini S.R, Farhoudi R, Ebrahimi-Mamaghani M, Baradaran B, Sadeghihokmabad E, Mostafaei S,Bagher Fazljou S.M, Torbati M, Sanaie S, Zamani F. Immunomodulatory and therapeutic effects of Hot-nature diet and co-supplemented hemp seed, evening primrose oils intervention in multiple sclerosis patients. Complement Ther Med. 2013;(21):473–80.