PHARMACIA

Pharmacia 70(4): 1385–1395
DOI 10.3897/pharmacia.70.e114938

Review Article

Regulation and control of the use of *Cannabis* and Cannabidiol in „novel foods"

Dobrina Tsvetkova[1], Lily Peykova[1], Lily Andonova-Dimitrova[2], Ivanka Pencheva[1]

1 *Department of "Pharmaceutical Chemistry", Faculty of Pharmacy, Medical University-Sofia, Dunav St. 2, Sofia 1000, Bulgaria*
2 *Bulgarian Pharmaceutical Union, Sofia 1000, Bulgaria*

Corresponding author: Dobrina Tsvetkova (dtsvetkova@pharmfac.mu-sofia.bg)

Received 30 October 2023 ♦ **Accepted** 6 November 2023 ♦ **Published** 30 November 2023

Citation: Tsvetkova D, Peykova L, Andonova-Dimitrova L, Pencheva I (2023) Regulation and control of the use of *Cannabis* and Cannabidiol in „novel foods". Pharmacia 70(4): 1385–1395. https://doi.org/10.3897/pharmacia.70.e114938

Abstract

Cannabis sativa L. is a medicinal plant from family Cannabaceae with many pharmacological activities. The recent appearance of a number of cannabis products in the pharmaceutical market has led to increased requirements for regulation and quality control. The control of *Cannabis sativa* L. is subject to the Psychotropic Substances Convention, which includes the addictive psychoactive delta-9-tetrahydrocannabinol (THC), and to the Narcotic Drugs Convention, which includes the illicit products: herbal and liquid cannabis, resin, extracts and tinctures of flowering or fruiting tops containing THC. Approved by the FDA for use in chemotherapy are Marinol caps. (THC) and Cesamet caps., containing the synthetic THC-derivative Nabilon. There is no harmonized European Union legislation on the use of cannabis and Cannabidiol (CBD), which antagonizes the THC-psychotropic effect. Legitimate products include seeds, oil, extracts, and seed tinctures of the industrial cannabis chemotype, containing primarily Cannabidiol and less than 0.2% THC. Sativex oral spray (THC/CBD = 1:1) is approved for muscle spasticity in multiple sclerosis. Cannabidiol was not used as a food ingredient in the European Union before 15.05.1997 and is a „novel food" according to Regulation 2015/2283. Flour; protein powder and cannabis seed oil are not „novel foods". Cannabidiol as Epidiolex is FDA approved for epilepsy forms Lennox-Gastaut and Dravet.

Keywords

Cannabis, Cannabidiol, „novel foods", regulation

Introduction

Medicinal use of *Cannabis sativa* L.

Cannabis sativa L. is a plant from family Cannabaceae and originated from Central oand South Asia. From plant have been isolated 278 cannabinoids, 221 terpenoids, 174 terpenes, 92 steroids, 63 flavonoid glycosides, 46 polyphenols, 19 flavonoids (Hussain et al. 2021).

Cannabis sativa L. is divided into the following subspecies: subsp. *sativa*; subsp. *indica*; subsp. *kafiristanca*; subsp. *ruderalis*; subsp. *spontanea*. It has been reported that in the 19th century the seeds of *Cannabis sativa* L. were used in medicine, mainly in the form of pressed oil or hemp milk. It has been described that *Cannabis sativa* L. can possess benefis against asthma, Bazedov's syndrome, bleeding, cystitis, decreased appetite, diarrhea, dysmenorrhea, gonorrhea, insomnia, malaria, migraine and stomach pain. Indian hemp (*Cannabis indica*) is known to be used towards convulsions, delirium tremens, depression, rheumatism, cholera and tetanus (Bridgeman and Abazia 2017).

In the 19th century, most European countries and the United States included *Cannabis sativa* subsp. *indica* (Lam.) E. Small & Cronquist in national pharmacopoeias

in the monographs: Herba *Cannabis indicae*; Tinctura *Cannabis indicae*; Extractum *Cannabis indicae* (Hall and Pacula 2003).

In 1964 is identified delta-9-tetrahydrocannabinol (THC), which is the main psychoactive component of cannabis, responsible for intoxication, and in high doses causies hallucinogenic effects (Zuardi 2006). The discovery of the first cannabinoid receptor (CB1) cannabinoid receptors in 1988 is important in the research of cannabis (Pertwee 1997).

Reasons for the increased control of cannabis products include: the absence of a standardized product; simultaneous application with other psychoactive substances and with alcohol; common use among adolescents and young people up to 30 years; insufficient clinical research; toxic effects of cannabis (Pertwee 1997).

These factors, combined with the lack of long-term studies on cannabis use in middle and advanced age, suggest that it is difficult to determine the exact role that cannabis plays in long-term health problems after 40 years (Hall and Solowij 1998).

Side-toxic effects

The need for increased control of cannabis products (Wodak et al. 2002) is due to its proven side-toxic effects (Hall and Solowij 1998) as follows: psychological acute effects: anxiety, depression, depersonalization, dysphoria, euphoria, relaxation (Harder et al. 2006), hallucinations, mania symptoms and psychosis (Henquet et al. 2005); effects on cognitive ability and psychomotor function: fragmentation of thoughts, impairment of attention and short-term memory; effects on motor function: increased motor activity, followed by impaired coordination, ataxia, muscle tremors and weakness (Pope et al. 2003).

There have been reported cases of acute cardiovascular death (Bachs and Morland 2001), acute myocardial infarction (Mittleman et al. 2001), cerebrovascular dysfunction (Moussouttas 2004), and increased risk of tumor development (Hall and MacPhee 2002) assossiated with cannabis use.

The increased control of cannabis products is necessitated by the increasing application of cannabis. In the European Union one out of every eight young people between 15 and 34 year has used cannabis. It has been described that nationally established use has ranged from 1% to over 20%. It has been shown that 1% of the population aged 15–64 years in the European Union smoke cannabis daily (Wodak et al. 2002). It has been demonstrated the decreased consumption from 2005 in Britain, Germany and Spain. In France and in the Scandinavian countries Denmark, Finland and Sweden it has been observed the increased application of cannabis (Wodak et al. 2002). Illegal products from cannabis are included into three main categories: cannabis plant, cannabis resin, and cannabis extract (Felder and Glass 1998).

Phytocannabinoids in *Cannabis sativa* L. and regulations

Phytocannabinoids are terpenophenolic compounds, with large amount in flowering tops, leaves, and resin of *Cannabis sativa* L., and low content in the stem and roots. As biologically active compounds phytocannabinoids exert psychoactive effects by binding to specific receptors in the brain (Felder and Glass 1998).

The addiction-inducing effects of cannabis and its effects on coordination, reactions, movement, memory, and especially learning in humans can be explainned by the interaction between the phytocannabinoids and endocannabinoid systems. It has been reported that the areas of the brain, which are most affected by these side effects of cannabis, are richest in cannabinoid receptors (de Fonseca et al. 2005).

Cannabinoids are Cannabigerol (CBG), and Cannabichromene (CBC), Cannabidivarine (CDV) (Fig. 1) (Grotenhermen 2003).

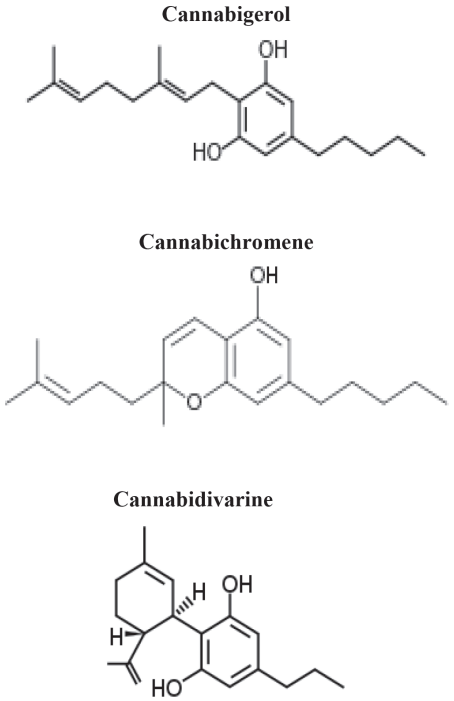

Figure 1. Chemical stuctures of Cannabigerol, Cannabichromene and Cannabidivarine.

Cannabis refers to the flowering or fruiting heads of *Cannabis sativa* L. (except the seeds and leaves, when they are not associated with the fruiting heads), from which the resin is not extracted, and which contain higher concentrations of Tetrahydrocannabinol (Musty 2004).

Extracts and tinctures from cannabis containing Cannabidiol are not allowed for medical use and are subject to increased control, due to the high risk of intoxication after abuse of these products, containing high concentrations of THC. Unresolved possession of extracts and tinctures from cannabis is subject to control and legislative restrictions (Bradford and Bradford 2016).

Marijuana is added in 1925 to the list I from the Second Convention on opium, which prohibited the export of resin from cannabis to countries that prohibited its use (Bradford and Bradford 2016). The United Nations Convention on Narcotic Substances (1961) increases control over the production, distribution, cultivation and use of cannabis products at the world level. There are four lists according to the Unified Convention (Convention 1961):

- List I: Substances that may be an object of abuse, comparable to that of cannabis, cannabis resin or cocaine.
- List II: Substances causing addiction, not greater than codeine.
- List III: Preparations intended for legal medical use, which according to the World Health Organization (WHO) are not subject to abuse and cannot cause harmful effects.
- List IV: Substances that are subject to abuse.

Cannabis, resin from cannabis, extracts and tinctures from cannabis, heroin and 15 other substances are included in the Unified Convention on Narcotic Substances of 1961 as substances in List I, whose properties give rise to dependence, pose a serious risk of abuse and are subject to the full control measures provided by the Union Convention (Convention 1961).

Cannabis and resin from cannabis are included in Schedule IV of the United Convention of 1961, which lists heroin and 15 other substances listed in Schedule I that are considered particularly dangerous by virtue of their value, risk of abuse and extremely limited medical and therapeutic value (Convention 1961).

Tetrahydrocannabinol and Cannabinol

Psychoactive cannabinoids delta-9-tetrahydrocannabinol (THC) and Cannabinol (CBN) (Fig. 2) (Grotenhermen 2003) are not present in the plant material, but are obtained during storage from the slow decomposition of the respective acids. High temperature is important for the acceleration of this conversion. It has been reported that under the influence of light Tetrahydrocannabinol breaks down to Cannabinol (Musty 2004).

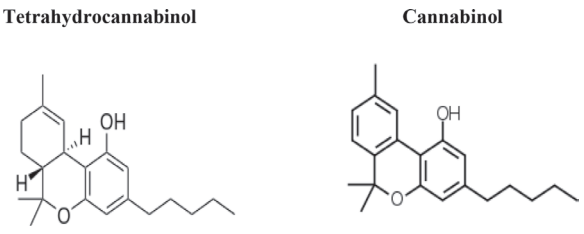

Figure 2. Chemical stuctures of Tetrahydrocannabinol and Cannabinol.

Tetrahydrocannabinol is agonist of the cannabinoid receptor CB1 located in the parts of the brain, responsible for coordination, movement, memory and thinking: cerebral cortex, cerebellum and basal ganglia. THC is isolated by Raphael Mechoulam in 1964. Tetrahydrocannabinol is indicated by the Convention on psychotropic substances from 1971 in the first of the four lists and its use is prohibited (Convention 1971).

Up to 1970 64 countries have ratified the Uniform Convention on Narcotic Substances for regulationg of the control of the spread, promotion, and use of cannabis products. According to legislation in one legal system, cannabis is considered fundamentally different from other drugs, and in other countries it is treated equally with all narcotic substances. Depending on the regulations governing the control of cannabis, the states are divided into the following groups: control, which is carried out in compliance with the requirements of the applicable law; control, which is based on calling for exceptions from legal requirements; control, which is based on exceptions, due to judicial presumption (Hall and Pacula 2003).

The International Convention on Narcotic Drugs recommends that countries that have signed these conventions apply the strictest controls on cannabis products, in accordance with national legislation. Some countries have used the freedom of judgment provided to them to abandon such recommendations for introduction and implementation on the most stringent regulatory measures in the control of cannabis (Hall and Pacula 2003).

This can lead to insufficiently strong and strict control, causing increased abuse of products with a high content of the main active ingredient Tetrahydrocannabinol, on which depends the strength of the effects of cannabis (Smith 2005).

The content of THC varies in products in different concentrations depending on the part of the plant: flowers (10–12%); leaves (1–2%); talks (0.1–0.3%); roots (< 0.03%) (Pitts et al. 1990).

The central stem and the main lateral stems contain little THC, but can be used in the production of cannabis oil. The emollient secretions of the plant, produced in glandular trichomes, are a source of products with a higher content of Tetrahydrocannabinol. Technical cannabis is concentrated technical extract from cannabis or from the resin of cannabis with the aim of concentrating THC (Rogeberg and Elvik 2016).

It is established that the acute effects are significantly increased according to the dose of Tetrahydrocannabinol. Combinations of growing conditions and varieties with a high THC content generate products with a maximum Tetrahydrocannabinol content, which is often 2 to 10 times higher than the THC concentration observed in illegal cannabis products produced in 1980. Studies in Switzerland in 2006 show the following concentrations of Tetrahydrocannabinol: 2%-12% in plant cannabis; 4%-25% in resin from cannabis, as the difference in concentration of THC varies depending on the specific characteristics of cultivation and method of production; 60% in the oil of cannabis (Baker et al. 1981).

CBD/THC ratio is important for psychoactivity and is genetically determined. CBD/THC ratio depends on: the combination of conditions of intensive indoor techniques for cultivation; specific methods in the production of cannabis products; use of varieties and plant parts with a high THC content (Hussain et al. 2021).

It has been established that cannabis, produced through intensive indoor cultivation, contains twice as much Tetrahydrocannabinol (Baker et al. 1981). Data for CBD/THC ratio in hemotypes of *Cannabis sativa* L. are presented in Table 1.

Table 1. CBD/THC in hemotypes of *Cannabis sativa* L.

Hemotype	CBD/THC ratio
Hemotype 1	1) CBD/THC > 1 (less than 0.2% THC – Regulation EC № 327/2002
	2) is related to the production of illegal products from cannabis
	3) its cultivation is criminalized, and the unregulated distribution, possession and use of products from this hemotype are subject to strict legal restrictions.
Hemotype 2	CBD/THC < 1 (more than 0.2% THC)
Intermediate hemotype 3	CBD/THC = 1 – for the production of herbal extracts of cannabis, included in the legal drug product Sativex oral spray

The combination of conditions of intensive indoor cultivation, specific methods in the production of cannabis products, and the use of varieties and plant parts that contain a high THC content, are very strong reasons to strengthen the control of unregulated cultivation of cannabis, and of production of illegal cannabis products, and for the enforcement of legal restrictions against their illegal distribution, possession and abuse (Bone and Waldron 1997/8). With this control, it is essential to develop analytical procedures with the application of reliable, accurate and sensitive methods for the identification and quantification of THC content. The application of this analytical control is mandatory in order to limit the use of products, containing high content of Tetrahydrocannabinol, which do not meet the requirements according to European regulations (Baker et al. 1981).

In 1992 has been proven the existence of synthesized in the human body endocannabinoids, which act as agonists on cannabinoid receptors (Kilaru and Chapman 2020). This discovery opens up possibilities for the use of cannabis-based products for medical use. In the last 20 years the research on *Cannabis sativa* L. is increasing in Britain, Italy, Spain, Switzerland and have been studyed the possible benefits of cannabis for medical purposes. Report of the British Medical Association from 1997 on the therapeutic effect of cannabis and the report from 1998 „Cannabis: the scientific and medical evidence" provides an evidence base to support further clinical trials to assess the potential for therapeutic use of the cannabinoids (Abrams 2018). The renewed scientific interest in cannabinoids is evidenced by the increasing number of cannabinoid drugs in the process of pharmaceutical development. Studies have established that indications for the use of *Cannabis sativa* L. include pain, migraine (Russo 1998), and cancer-related anorexia and cachexia (Ashton 2001).

Products containing phytocannabinoids

In Table 2. are summarized products containing phytocannabinoids.

Table 2. Products containing phytocannabinoids.

Products	Regulation (EC № 327/2002)
Marinol capsule (Dronabinol, THC)	Schedule III; FDA appetite stimulant in AIDS
Syndros oral liquid (Dronabinol, THC)	Schedule II (antiemetic in chemotherapy – FDA)
Sativex (Nabiximols) oral spray: THC and Cannabidiol = 1:1	muscle spasticity in multiple sclerosis, and pain associated with cancer
Cannador: Dronabinol and other cannabinoids	muscle spasticity in multiple sclerosis and postoperative pain
Cesamet caps: Cannabinoid-receptor agonist Nabilon – a synthetic derivative of Dronabinol	FDA, 1986 nausea and vomiting associated with chemotherapy

Marinol caps: Tetrahydrocannabinol (Dronabinol)

Product Marinol caps. contains Tetrahydrocannabinol (Dronabinol) and is approved for use by the USA Food and Drug Administration (FDA) for nausea and vomiting associated with cancer chemotherapy and for anorexia associated with weight loss in patients with AIDS (Iversen 2003).

Sativex oral spray: THC and Cannabidiol = 1:1

The medicinal product Sativex oral spray is a plant extract of cannabis and contains equal amounts of THC and Cannabidiol and is permitted in 17 member states of the European Union and Norway for buccal and sublingual application in the treatment of muscle spasticity in multiple sclerosis. In Canada, Sativex oral spray is licensed as an adjunct to treatment for the relief of symptomatic pain associated with multiple sclerosis (Zajicek et al. 2006), and pain associated with cancer (Holdcroft et al. 2006).

Cannador: Dronabinol and other cannabinoids

A product being investigated in clinical trials is Cannador, containing Dronabinol and other cannabinoids and is indicated for the treatment of spasticity and other symptoms associated with multiple sclerosis (Zajicek et al. 2006) and postoperative pain (Holdcroft et al. 2006).

All licensed products containing THC are subject to strict analytical quality control in order to guarantee safety in use and to allow in these products a concentration of Tetrahydrocannabinol above 0.2%, according to Regulation EC № 327/2002.

Cesamet caps: Nabilon – a synthetic derivative of Dronabinol

The cannabinoid-receptor agonist Nabilon is a synthetic derivative of Dronabinol and is approved by the FDA in 1986 in the form of Cesamet caps. for use in the treatment of nausea and vomiting associated with chemotherapy. The limited use of these synthetic cannabinoid receptor agonists is necessitated by the fact that the effective dose for

these cannabinoids is close to the dose that causes sedation or intoxication. This is an important reason for manufacturers of legitimate products, to carried out regular quality control through the introduction of analytical procedures for the identification and quantification of THC content, in order to guarantee the safety of consumption of permitted medical products from cannabis (Iversen 2003).

Regulations for Dronabinol

In recent years, the law regulating the use of cannabis has undergone notable changes. Dronabinol is he stereochemical variant of delta-9-tetrahydrocannabinol and in 1990 the Expert Committee of the WHO proposes Dronabinol to be insertinted in List II of the 1971 Convention. In 2003 The Committee on Narcotic Dependence recommends Dronabinol to be moved from List II, where substances have very limited therapeutic effect, to List IV of the 1971 Convention, where substances have known therapeutic utility with little risk to public health. The report of the Expert Committee of WHO recommends that all stereochemical variants of delta-9-tetrahydrocannabinol to be placed in List IV of the Convention of 1971, in order to avoid placing different stereochemical variants of the same substance under different control systems. In 2006 the WHO Expert Committee on Medicines concludes that Dronabinol exerts a moderate therapeutic effect and poses a significant risk to public health, but the risk is different from that of cannabis. As a result, it is recommended that Dronabinol and its stereoisomers be transferred from List II to List III of the 1971 Convention (Convention 1971).

Legislation in the European Union regarding cannabis use

There is no harmonized legislation in the European Union regarding the use of cannabis, but mostly national regulatory bodies oppose the decriminalization of cannabis. In recent years, European countries have seen notable legal changes related to the use and possession of cannabis (King et al. 2005). From 2001 The Dutch Government Agency for Medical Cannabis, in accordance with the terms of the 1961 Union Convention, allows for use medical cannabis products containing THC at least 1% and CBD at least 1% to 9% for relaxation on symptoms, resulting from multiple sclerosis, spinal cancer, chronic neurogenic pain and tics, associated with Tourette's syndrome. Medical use of cannabis is legalized in Netherland in 2003 (Gorter et al. 2005).

From 2012 there is a renewed debate about laws, prohibiting or allowing the use and sale of cannabis worldwide, in relation to the legalization of the sale and use of cannabis for „recreational" purposes in some USA states and Uruguay since 2012. National regulatory bodies of countries in the European Union oppose the legalization of cannabis for „recreational" use. Proposals to legitimately offer and use cannabis for „recreational" purposes could lead to an increase in cannabis use and its associated harms (Gordon 1987).

With regard to the recent European trend at the level of universal prevention, the general trend is the increased use of the standardized „Programme for Prevention EU-Dap", which has reduced accidental use of cannabis by 24 % in Italy, Spain, Poland, Czechia and Sweden (King et al. 2005).

In the European Union it is legal to cultivate cannabis plants for the branched fiber and can only use varieties with a Tetrahydrocannabinol content of not more than 0.2% (Regulation of EC 1307/2013).

In Table 3 are presented some legislation regarding cannabis use.

Table 3. Legislation in the European Union regarding *Cannabis* use.

Countries	Legislation in the European Union
Portugal	drug use has been decriminalized since 2000
Luxembourg (2001) Belgium (2003)	punishment for the use and possession of cannabis passed from deprivation of liberty to the globe
Nederlands (2003)	Medical use of cannabis is legalized in 2003
European Union (Regulation of EC 1307/2013)	Legal cultivation of cannabis varieties for seeds and fiber and with low content of THC and a high content of Cannabidiol
European Union (Regulation of EC 1307/2013)	0.2% – current legal upper limit of Tetrahydrocannabinol CBD/THC ratio must be greater than 1
Canada	0.3 % – current legal upper limit of Tetrahydrocannabinol

Legitimate products from *Cannabis sativa* L.

Legitimate products from cannabis (Table 4) are registered in the „Common Catalog of Varieties" and must contain less than 0.2% THC.

Table 4. Legitimate products from *Cannabis sativa* L.

Legitimate products from *Cannabis sativa* L.	Characteristics
Cannabis seeds	1) Ω6 : Ω3 fatty acids = 3:1 2) can be impregnated with flowering tops, or resin, which leads to detectable amounts of THC – strict quality control
Oil from *Cannabis* seeds	1) not contain THC 2) THC above the maximum permissible limit of 0.2%, in accordance with Regulation EC № 327/2002 can be detected in the oil during poor extraction and non-observance of the rules of Good Manufacturing Practice in the production – strict the quality control
Cosmetic products	cannabis extracts and cannabis tinctures, originating from the seeds and leaves that are not associated with the fruiting tops of the plant.

The seeds of *Cannabis sativa* L. in the form of pressed oil or hemp milk can exert potemtial benefits against: convulsions, delirium tremens, depression, insomnia, migraine, Bazedov's syndrome, asthma, stomach pain, diarrhea, cystitis. Industrial cannabis (industrial cannabis) includes a number of cultivars of *Cannabis sativa* L., which are intended for the extraction of seeds and fiber and are characterized by a low content of THC and a high content of Cannabidiol (CBD). In most European countries the current legal upper limit is 0.2% Tetrahydrocannabinol (EU Regulation 1307/2013), and in Canada the legal limit is 0.3% THC (Fischer et al. 1998).

The relationship of THC to CBD in *Cannabis sativa* L. is of importance for psychoactivity. According to Regulation EC 1307/2013 there is a requirement that the CBD/THC ratio must be greater than 1. The ratio of THC to CBD in *Cannabis sativa* L. is genetically determined in hemotypes, which differ in the amount of chemical substances: Hemotype 1: CBD / THC > 1 (less than 0.2% THC – Regulation EC № 327/2002); Hemotype 2: CBD / THC < 1 (more than 0.2% THC); Intermediate hemotype 3: CBD / THC = 1:1 (Zajicek et al. 2006).

Hemotype 2 is related to the production of illegal products from cannabis and its cultivation is criminalized, and the unregulated distribution, possession and use of products from this hemotype are subject to strict legal restrictions (Holdcroft et al. 2006).

Concentrations of cannabinoids vary significantly and depend on the propagation of the plant and the techniques for cultivation and processing (Sirikantaramas et al. 2004).

Cannabis seeds are a source of Ω-3-fatty acids. A 3:1 ratio of Ω-6- to Ω-3-fatty acids makes the oil from cannabis seeds high quality and nutritious. Although the seeds are encased in the part of the plant with the highest density of glandular trichomes and with the highest concentration of Tetrahydrocannabinol, the seeds themselves do not contain THC. Even though cannabis seeds are a legitimate product, they can be impregnated with flowering tops, or resin, which leads to detectable amounts of Tetrahydrocannabinol. This requires compliance with strict control measures when assessing the quality of cannabis seeds, even if they are a legitimate product (McLaren et al. 2008).

The development and observance of specific procedures for analytical control, including identification and quantification of the content of admixed THC is necessary, in order to prevent the distribution and use of products with a Tetrahydrocannabinol content of more than 0.2%, which is the maximum permissible limit, according to the requirements of Regulation EC № 327/2002. The essential oil from the cannabis seed does not contain THC and is a legitimate product, but Tetrahydrocannabinol can be detected in the oil during poor extraction from the flower seed (McLaren et al. 2008).

Non-observance of the rules of Good Manufacturing Practice in the production of essential oil leads to a serious health risk, due to the potential danger of content of impurity of THC above the maximum permissible limit of 0.2%, in accordance with Regulation EC № 327/2002. This fact has determined the need for strict control of essential oil. Optimizing the quality control of products containing CBD requires the development and application of reliable and highly sensitive analytical methods to identify and quantify Tetrahydrocannabinol in essential oil, with the aim of confirming that the oil does not contain more than 0.2 % THC (McLaren et al. 2008). The USA Food and Drug Administration maintains jurisdiction to regulate the use of Cannabidiol in food, beverages and dietary supplements (FDA).

„Novel foods"

With the aim of making the food authorization process more efficient, while ensuring high standards of food safety for consumers, from the Parliament and the Council of the European Union from 1 January 2018 is approved Regulation (EC) N:2015/2283, on „novel foods", which amends Regulation (EC) N:1169/2011 and replaces previous regulations: Regulation (EU) N:258/97 and Regulation (EU) N:1852/2001, which are in force till 31.12.2017 (UNODC 2007).

According to Regulation (EC) N:2015/2283, „novel food" is defined as food which was not used for consumption to a significant extent within the European Union before 1505.1997. According to the European Commission, „novel foods" can be: newly developed, innovative food; food, produced with the help of new technologies and production processes; food which is or has been traditionally consumed outside the European Union (UNODC 2007).

Before a „novel foods" to be placed on the market, is required an approval based on an assessment in accordance with the principles underlying „novel foods" in the European Union: „novel foods" must be safe for consumers and labelled. In the procedure for authorizing „new foods", the European Commission and the European Food Safety Authority (EFSA) work together to evaluate „novel foods" for consumption, according to Regulation (EC) N:2015/2283 (UNODC 2007).

Regulation (EC) N:2015/2283 included improvements introduced, in order to facilitate the addition of „novel foods" to the European Union market, while guaranteeing safety for consumers (Hall and Solowij 1998).

Actualization of Regulation (EC) N: 2015/2283 include:

1. expanded categories of new foods originating from plants, animals, microorganisms, cell cultures, minerals;
2. specific categories of foods (vitaminsq minerals, nutritional supplements);
3. food as a result of state-of-the-art technology (modified or new molecular structure, nanomaterials), which were not produced or used before 1997;
4. the introduction of a reference list of all permitted „novel foods" that may be placed on the market in the European Union. The reference list is kept up to date by the European Commission and is managed by Regulation (EC) N:2017/1023 for the implemen-

tation of the Commission in accordance with Regulation N:2015/2283;
5. centralized assessment of the safety of „novel foods" from the European Food Safety Authority (EFSA).

The reference list of all permitted „novel foods" is kept up to date by the European Commission and is managed by Regulation (EC) N:2017/1023 for the implementation of the Commission in accordance with Regulation N:2015/2283.

„Novel foods" originating from *Cannabis sativa* L.

In the European Union, the cultivation of varieties *Cannabis sativa* L. is allowed, provided that they are registered in the „Common Catalog of Varieties" and that the content of Tetrahydrocannabinol does not exceed 0.2%. According to the Catalog of „Novel Foods" of the European Union, foods and food ingredients from varieties of *Cannabis sativa* L., which contain less than 0.2% THC and are registered in the „Common Catalog of Varieties", are not considered as „novel foods" (UNODC 2007).

According to Regulation N:2015/2283, not considered as as „novel foods" the following products of the variety *Cannabis sativa* L., which contain less than 0.2 % Tetrahydrocannabinol, are not considered as „novel foods":- seeds; flour from seeds; protein powder from seeds; seed oil (UNODC 2007).

There are not documented data for use of other parts (excludung seeds; flour from seeds; protein powder from seeds; seed oil) of *Cannabis sativa* L. (including extracts from hemp products) as food in the European Union prior to 15 May 1997. Cannabidiol was not used as a food or nutritional ingredient before May 15, 1997 and it falls into the classification of „novel foods". According to the Catalog of Novel Foods of the European Union, extracts from *Cannabis sativa* L., containing CBD, are „novel foods", and their introduction on the market requires prior risk assessment and authorization according to the European Union regulation for „new foods". „Novel Foods" originating from *Cannabis sativa* L. and Cannabidiol are included in the Catalog of „Novel Foods" of the European Union (UNODC 2007). In the European Union there is a process to establish that except seeds, seed flour, seed protein powder and seed oil of *Cannabis sativa* L. (which are not considered „novel foods"), other parts of *Cannabis sativa* L. (leaves, flowers, extracts from various plant parts) were legally placed on the market as food in the European Union before 15 May 1997. In relation to this question, the European Commission has sought information from the Member States in 2018. If information is received from a member state of the European Union that other parts of *Cannabis sativa* L. have been legally placed on the market as food in the European Union before 15 May 1997, the catalog of „novel food" in the European Union will be updated. With regard to the part of the plant that is not considered to be covered by Regulation (EU) N: 258/97 on „novel foods" and whose access to the market is not the subject of this Regulation.

Pharmacologicil activity of Cannabidiol

Cannabidiol (CBD) (Fig. 3) is the principal biologically active, but psychoinactive component of *Cannabis sativa* L. The difference in structure of THC and CBD results in significant differences in pharmacological properties, the main of which is the psychotropic effect of Tetrahydrocannabinol, which is absent in CBD. Cannabidiol interacts with different receptors and has an antagonistic effect and reduces the psychotropic effect of THC.

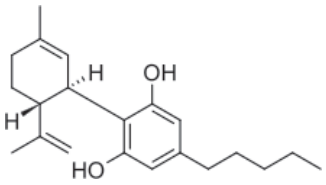

Figure 3. Chemical structure of Cannabidiol.

Cannabidiol has an indirect effect on the CB1 receptor located mainly in the brain. Cannabidiol modulates the release of neurotransmitters in a way that prevents excessive neuronal activity and reduces anxiety and pain, regulates cognitive function. CBD has been shown to have therapeutic benefits in cancer. The analgesic effect of Cannabidiol is the result of binding to cannabinoid receptors and reduction of various types of pain: chronic (Boyaji et al. 2020; Schilling et al. 2021), acute back pain (Eskander et al. 2020), pain in patients with malignant diseases (Darkovska-Serafimovska et al. 2018).

CBD may relieve symptoms of rheumatic diseases with musculoskeletal pain (Boehnke et al. 2022) and in arthritis (Frane et al. 2022). Cannabidiol exhibits a variety of pharmacological effects such as anxiolytic, antidepressive, antipsychotic (García-Gutiérrez et al. 2020), antiparkinsonian (Junior et al. 2020), anticonvulsive, antiinflammatory, antiemetic, and neuroprotective effects in dementia (Hermush et al. 2022). CBD has been shown to have effects on insomnia (Kaul et al. 2021) and sleep-disordered breathing (Suraev et al. 2020), lowers high blood pressure (Jadoon et al. 2017), and reduces cancer-related symptoms such as nausea and vomiting (Sawtelle and Holle 2021).

Cannabidiol products

In Table 5 are summarised products with Cannabidiol.

Table 5. Products containing Cannabidiol.

Products containing Cannabidiol	Application
Epidiolex (FDA approval on 28.06.2018)	for treatment of seizures associated with epilepsy: Lennox-Gastaut syndrome and Dravet syndrome
Epidiolex (FDA approval in 2020)	application against migraines caused by a genetic disease: tuberous sclerosis
Sativex (Nabiximol)	for the treatment of neuropathic pain
(-)-trans-Cannabidiol – for authorization as a „novel food" in the European Union	meets the requirements of Regulation (EO) N:258/97 for applicationa „novel foods" and on the European Framework Directive 2002/46/EC on food additives.

Currently there are no approved pharmaceutical products that contain Cannabidiol alone for the treatment of pain, as the only available pharmaceutical product that contains CBD and is used for the treatment of pain is Sativex (Nabiximol) (a combination product of THC/CBD in a ratio of 1:1). (Überall 2020). Sativex (THC/CBD = 1:1) is approved in several countries for the treatment of neuropathic pain associated with multiple sclerosis, chronic severe neuropathic pain and muscle spasms. Cannabidiol acts as a partial agonist at cannabinoid receptors, modulating the balance between excitatory and inhibitory neurotransmitters, which leads to muscle relaxation, responsible for improving spasticity and reducing excitability of the spinal cord (Russo et al. 2015).

Ready-to-use products containing CBD are considered medicinal products for medical purposes and can not be released on the market without permission. Until the middle of 2018 it is impossible to use CBD in medicinal products. In recent years, more and more research has been directed towards successful use of CBD as an anticonvulsant drug in children with epilepsy. Epidiolex contains Cannabidiol and is approved by the FDA on 28.06.2018 for the treatment of seizures associated with two severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome. In 2020 Epidiolex was approved from the FDA for the treatment of migraines caused by a complex of tuberous sclerosis, a rare genetic disease that causes the growth of benign tumors in the brain (Villanueva et al. 2021). Cannabidiol was not used in food or as a dietary supplement prior to becoming the active ingredient in the approved drug product Epidiolex. CBD is subject to exclusion from the definition of a dietary supplement and can not be sold as a dietary supplement (FDA).

According to the FDA, Cannabidiol cannot be sold in the United States as a dietary supplement, due to provisions in the Food, Drug, and Cosmetic Act regarding the use of dietary supplements that have previously been studied as medicinal ingredients. If a given substance has been approved for research as a new drug, clinical trials have begun and the existence of these trials has been publicly disclosed, before the substance is used in a food or supplement, then the substance falls outside the definition of a nutritional supplement or food. According to the FDA, Cannabidiol was not used in food or as a dietary supplement prior to becoming the active ingredient in the approved drug product Epidiolex, and therefore CBD is subject to exclusion from the definition of a dietary supplement and can not be sold as a dietary supplement (FDA).

Regulations for „Novel foods" originating from Cannabidiol in the European Union

In Table 6 are presented regulations for „Novel Foods" with Cannabidiol.

The previous status of Cannabidiol as a controlled substance on List I of the Unified Convention on Narcotic Substances of 1961 (Convention 1961) represents a significant obstacle to clinical trials, but changes in the law in recent years have removed this obstacle. The Expert Committee on Drug Dependence to the World Health Organization recommends CBD not to be included in the International Convention on Drug Control. In this case member states cannot oppose the free trade with licensed products containing CBD, if these products are legally produced in another member state within the area of the European Union (Hall and Pacula 2003).

Table 6. Regulations for „Novel foods" containing Cannabidiol.

Regulations for „Novel Foods"	Subject of regulations
European Union	the use of Cannabidiol as a subject of the unharmonized legalization and regulations
European Union Council on the legalization of Cannabidiol (19.11.2020)	emphasizes that Cannabidiol can not be qualified as a narcotic product
Regulation N:2015/2283 on „novel foods"	CBD purity and products with high levels of CBD
Regulation (EO) N:258/97 for applicationa „novel foods"	authorization of (-)-trans-Cannabidiol as a "novel food" in the European Union
Food Rapid Alert System	control of food products containing unresolved CBD

Cannabidiol is found in a variety of forms on the market. The most popular and most frequently used form is Cannabidiol oil. Also found in capsules, sprays, creams for massage, candies and drinks. Cosmetic products containing Cannabidiol are subject to control under legal quality requirements. Natural CBD is legal in cosmetics only when derived from cannabis extracts and cannabis tinctures, originating from the seeds and leaves that are not associated with the fruiting tops of the plant. Cannabidiol causes adverse effects such as diarrhea and fatigue and drowsiness (Iffland and Grotenhermen 2020). Due to this fact, the sourses containing CBD that are sold without purpose cannot be qualified unambiguously, since they can be used to produce different products with different purposes, which are in their own right subject to different laws and can be harmful for healt. Products containing CBD are subject to control according to legal requirements for different product categories and quality requirements. The purity of CBD and products with high levels of Cannabidiol are covered by Regulation N:2015/2283 on „novel foods" (UNODC 2007). Development of products containing CBD as „novel foods" is related to Cannabidiol therapeutic effects on symptoms of various diseases.

Once a product is classified as a specific product category, the relevant legislation applies. If the legal requirements regarding the specific purpose are not met, the product may not be distributed and may not be put on the market. End products are classified for each individual case, taking into account all factors, including composition, purpose and dosage. Different law enforcement bodies are responsible for control depending on the classification of the products. In case of doubt, the law enforcement body shall assess the product to the prescribed legislation and shall take the necessary measures (Hall and Pacula 2003).

In the European Union the use of Cannabidiol is not the subject of harmonized regulations. From a regulatory point of view, in the absence of evidence of significant

consumption, a preliminary registration approval procedure is necessary, in order to offer on the market a food product based on CBD.

The unharmonized legalization of CBD and dietary supplements requires a high level of vigilance regarding the law. For 3 years, 113 food products containing unresolved CBD have been reported to the Food Rapid Alert System. With the aim of making the food additive and food authorization process more efficient, while ensuring high standards of food safety for consumers, the European Commission announced that CBD and other cannabinoids will be classified as „new foods" and products containing CBD, require permission to be placed on the market in the EU as a nutritional supplement or ingredient. This regulation is recommended to apply to CBD extracts, synthetic CBD products as well as all other products with CBD, including CBD oil. Upon approval, manufacturers of CBD products will be required to conduct analytical tests, safety tests and prove safe consumption (Hall and Pacula 2003).

The grounds for the development of products containing CBD as a „novel foods" are related to the fact that Cannabidiol has therapeutic effects and affects the symptoms of various diseases. Yet no form of Cannabidiol is approved by European regulatory bodies for use in dietary supplements. Cannabis Pharma has submitted an application for authorization to market (-)-trans-Cannabidiol as a „novel food" in the European Union, intended for use by adults except pregnant and lactating and which also meets the requirements of Regulation (EO) N:258/97 for „novel foods" and on the European Framework Directive N:2002/46/EC) on food additives (Hall and Pacula 2003).

Methods for analysis of phytocannabinoids

The need for the development, validation and regular application of specific methods for the identification of cannabinoids and of highly sensitive analytical procedures for their quantification is due to the risk of serious adverse effects that can be caused by the consumption of both licensed and illegal cannabis products. For the quantitative determination of THC, CBN, CBD, THCA the following methods are described: high-efficiency liquid chromatography (Rustichelli et al. 1998) and gas chromatography-mass spectrometry GC/MS (Ilias et al. 2005).

A frequently used method for quantitative determination of THC, CBN CBD is gas chromatography with flame ionization detection (GC-FID), without and with derivatization. Until recently it was thought that Tetrahydrocannabinolic acid (THCA, the precursor to THC) is formed by cyclization of Cannabidiol acid (CBDA). More recent research provides evidence that THCA is formed from Cannabigerolic acid (CBGA) via oxidocyclization by the enzyme THCA-synthase. CBGA is a precursor to THCA, to CBDA and Cannabichromenic acid (CBCA), which through decarboxylation yield THC, CBD and Cannabichrome (CBC), respectively. With regard to the analytical approach it is possible to measure THCA and THC separately or to determine the total THC content (total THC, sum of free THC and THC, generated from THCA after decarboxylation).

This choice sometimes is made by national legislation. If there is no legal requirement for both approaches, common practice is to measure total THC, followed by decarboxylation of THCA into THC, as this best represents the pharmacological activity of the product. In GC analysis, the general THC content is determined without prior derivatization (silanization) (Fellermeier et al. 2001).

In the case that THC and THCA are to be analyzed separately, without decarboxylation to THCA, the non-thermally decarboxylated extract is derivatized by silanization prior to GC analysis. In gas chromatography, since the THC reference material degrades rapidly, quantification of THC can be performed with the reference internal standard CBN (Fellermeier et al. 2001).

Conclusion

The need for increased control and legal restrictions on the unregulated cultivation and distribution of cannabis is due to increasing use, lack of a standardized product, toxic effects and illegitimate products production of a chemotype containing little Cannabidiol and more than 0.2% THC (EC 327/2002). The development and regulation of CBD-products as a „novel foods" is based on the anti-inflammatory, anticonvulsant and analgesic effects of Cannabidiol.

The development and application of analytical procedures for identity, purity testing and validation of reliable, accurate and sensitive methods for quantifying the Cannabidiol content in „new foods" and the admixture of THC in them, has contributed to the strengthening of quality control and To guarantee the safety of the producer when consuming permitted medical products from cannabis, the content of Cannabidiol and „novel foods" from cannabis and to limit the use of products that do not meet the requirements according to European regulations.

Acknowledgements

This article was prepared with financial support from Grant 2022 Project N: D-207/03.08.2023, Contract N: 8186/22.11.2022, Medical University-Sofia, Bulgaria.

References

Abrams DI (2018) The therapeutic effects of *Cannabis* and cannabinoids: an update from the National Academies of Sciences, Engineering and Medicine report. European Journal of Internal Medicine 49: 7–11. https://doi.org/10.1016/j.ejim.2018.01.003

Ashton CH (2001) Pharmacology and effects of cannabis: a brief review. British Journal Psychiatry 178: 101–106. https://doi.org/10.1192/bjp.178.2.101

Bachs L, Morland H (2001) Acute cardiovascular fatalities following cannabis use. Forensic Science International 124(2–3): 200–203. https://doi.org/10.1016/S0379-0738(01)00609-0

Baker PB, Taylor BJ, Gough TA (1981) The tetrahydrocannabinol and tetrahydrocannabinolic acid content of cannabis products. Journal of Pharmacy and Pharmacology 33(6): 369–372. https://doi.org/10.1111/j.2042-7158.1981.tb13806.x

Boehnke KF, Häuser W, Fitzcharles MA (2022) Cannabidiol (CBD) in rheumatic diseases (musculoskeletal pain). Current Rheumatology Reports 24(7): 238–246. https://doi.org/10.1007/s11926-022-01077-3

Bone C, Waldron SJ (1997/8) New trends in illicit cannabis cultivation in the United Kingdom of Great Britain and Northern Ireland. Bulletin on Narcotics 49/50(1/2): 117–128.

Boyaji S, Merkow J, Elman RNM, Kaye AD, Yong RJ, Urman RD (2020) The role of Cannabidiol (CBD) in chronic pain management: an assessment of current evidence. Current Pain Headache Reports 24(2): 1–4. https://doi.org/10.1007/s11916-020-0835-4

Bradford AC, Bradford WD (2016) Medical marijuana laws reduce prescription medication use in medicare part D. Health Affairs 35(7): 1230–1236. https://doi.org/10.1377/hlthaff.2015.1661

Bridgeman MB, Abazia DT (2017) Medicinal cannabis: history, pharmacology, and implications for the acute care setting. P&T. Pharmacy and Therapeutics 42: 180–188.

Convention on psychotropic substances (1971) Convention on psychotropic substances. United Nations, New York.

Darkovska-Serafimovska M, Serafimovska T, Arsova-Sarafinovska Z, Sasho Stefanoski S, Keskovski Z, Balkanov T (2018) Pharmacotherapeutic considerations for use of cannabinoids to relieve pain in patients with malignant diseases. Journal Pain Research 11: 837–842. https://doi.org/10.2147/JPR.S160556

de Fonseca FR, Del Arco I, Bermudez-Silva FJ, Bilbao A, Cippitelli A, Navarro M (2005) The endocannabinoid system: physiology and pharmacology. Alcohol and Alcoholism 40(1): 2–14. https://doi.org/10.1093/alcalc/agh110

Eskander JP, Spall J, Spall A, Shah RV, Kaye AD (2020) Cannabidiol (CBD) as a treatment of acute and chronic back pain: a case series and literature review. Journal Opioid Management 16(3): 215–218. https://doi.org/10.5055/jom.2020.0570

Felder CC, Glass M (1998) Cannabinoid receptors and their endogenous agonists: review. Annual Review of Pharmacology and Toxicology 38: 179–200. https://doi.org/10.1146/annurev.pharmtox.38.1.179

Fellermeier M, Eisenreich W, Bacher A, Zenk MH (2001) Biosynthesis of Cannabinoids, Incorporation experiments with 13C-labeled glucoses. European Journal of Biochemistry 268(6): 1596–1604. https://doi.org/10.1046/j.1432-1033.2001.02030.x

Fischer B, Single E, Room R, Poulin C, Sawka E, Thompson H, Topp J (1998) *Cannabis* use in Canada: policy options for control. Policy Options 34–38.

Frane N, Stapleton E, Iturriaga C, Ganz M, Rasquinha V, Duarte R (2022) Cannabidiol as a treatment for arthritis and joint pain: an exploratory cross-sectional study. Journal Cannabis Research 4(1): 1–47. https://doi.org/10.1186/s42238-022-00154-9

García-Gutiérrez MS, Navarrete F, Gasparyan A, Austrich-Olivares A, Sala F, Manzanares J (2020) Cannabidiol: A potential new alternative for the treatment of anxiety, depression, and psychotic disorders. Biomolecules 10(11): e1575. https://doi.org/10.3390/biom10111575

Gordon R (1987) An operational classification of disease prevention. In: Steinberg JA, Silverman MM (Eds) Preventing Mental Disorders. US Department of Health and Human Services, Rockville, 20–26.

Gorter R, Butorac M, Pulido-Cobian E, van der Sluis W (2005) Medical use of cannabis in the Netherlands. Neurology 64(5): 917–919. https://doi.org/10.1212/01.WNL.0000152845.09088.28

Grotenhermen F (2003) Pharmacokinetics and pharmacodynamics of Cannabinoids. Clinical Pharmacokinetic 42(4): 327–360. https://doi.org/10.2165/00003088-200342040-00003

Hall W, MacPhee D (2002) *Cannabis* and cancer. Addiction 97(3): 243–247. https://doi.org/10.1046/j.1360-0443.2002.00003.x

Hall W, Pacula R (2003) *Cannabis* as a legal substance. *Cannabis* use and dependence: public health and public policy (Chapter 18). Cambridge University Press, Cambridge, 298 pp. https://doi.org/10.1017/CBO9780511470219

Hall W, Solowij N (1998) Adverse effects of cannabis. Lancet 1352(9140): 1611–1616. https://doi.org/10.1016/S0140-6736(98)05021-1

Harder VS, Morral AR, Arkes J (2006) Marijuana use and depression among adults: Testing for causal association. Addiction 101(10): 1463–1472. https://doi.org/10.1111/j.1360-0443.2006.01545.x

Henquet C, Krabbendam L, Spauwen J, Kaplan C, Lieb R, Wittchen HU, van Os J (2005) Prospective cohort study of cannabis use, predisposition for psychosis, and psychotic symptoms in young people. British Medical Journal 330(7481): 1–11. https://doi.org/10.1136/bmj.38267.664086.63

Hermush V, Ore L, Stern N, Mizrahi N, Fried M, Krivoshey M, Staghon E, Lederman VE, Bar-Lev Schleider L (2022) Effects of rich Cannabidiol oil on behavioral disturbances in patients with dementia: a placebo controlled randomized clinical trial. Frontiers in Medicine 9: e951889. https://doi.org/10.3389/fmed.2022.951889

Holdcroft A, Maze M, Dore C, Tebbs S, Thompson S (2006) A multicenter dose-escalation study of the analgesic and adverse effects of an oral cannabis extract (Cannador) for postoperative pain management. Anesthesiology 104(5): 1040–1046. https://doi.org/10.1097/00000542-200605000-00021

Hussain T, Jeena G, Pitakbut T, Vasilev N, Kayser O (2021) *Cannabis sativa* research trends, challenges, and new-age perspectives. iScience 24(12): e03391. https://doi.org/10.1016/j.isci.2021.103391

Iffland K, Grotenhermen F (2020) An update on safety and side effects of Cannabidiol: a review of clinical data and relevant. Animal Studies Biomedical Research International 2020: e3902740. https://doi.org/10.1155/2020/3902740

Ilias Y, Rudaz S, Mathieu P, Christen P, Veuthey JL (2005) Extraction and analysis of different *Cannabis* samples by headspace solid-phase microextraction combined with gas chromatography mass spectrometr. Journal of Separation Science 28(17): 2293–2300. https://doi.org/10.1002/jssc.200500130

Iversen L (2003) *Cannabis* and the brain. Brain 126(6): 1252–1270. https://doi.org/10.1093/brain/awg143

Jadoon KA, Tan GD, O'Sullivan SE (2017) A single dose of Cannabidiol reduces blood pressure in healthy volunteers in a randomized crossover study. JCI Insight 2(12): e93760. https://doi.org/10.1172/jci.insight.93760

Junior NCF, dos Santos-Pereira M, Guimarães FS, Del Bel E (2020) Cannabidiol and cannabinoid compounds as potential strategies for treating

Parkinson's disease and l-DOPA-induced dyskinesia. Neurotoxicity Research 37(1): 12–29. https://doi.org/10.1007/s12640-019-00109-8

Kaul M, Zee PC, Sahni AS (2021) Effects of cannabinoids on sleep and their therapeutic potential for sleep disorders. Neurotherapeutics 18(1): 217–227. https://doi.org/10.1007/s13311-021-01013-w

Kilaru A, Chapman KD (2020) The endocannabinoid system. Essays Biochemistry 64(3): 485–499. https://doi.org/10.1042/EBC20190086

King L, Carpentier C, Griffiths P (2005) *Cannabis* potency in Europe. Addiction 100(7): 884–886. https://doi.org/10.1111/j.1360-0443.2005.001137.x

Kumar RN, Chambers WA, Pertwee RG (2001) Pharmacological actions and therapeutic uses of cannabis and cannabinoids. Anaesthesia 56(11): 1059–1068. https://doi.org/10.1111/j.1365-2044.2001.02269.x

McLaren J, Swift W, Dillon P, Allsop S (2008) *Cannabis* potency and contamination: a review of the literature. Addiction 103(7): 1100–1109. https://doi.org/10.1111/j.1360-0443.2008.02230.x

Mittleman MA, Lewis RA, MacLure M, Sherwood JB, Muller JE (2001) Triggering myocardial infarction by marijuana. Circulation 103(23): 2805–2809. https://doi.org/10.1161/01.CIR.103.23.2805

Moussouttas M (2004) *Cannabis* use and cerebrovascular disease. The Neurologist 10(1): 47–53. https://doi.org/10.1097/01.nrl.0000107493.19282.b0

Musty RE (2004) Natural cannabinoids: interactions and effects. In: Guy G, Whittle B, Robson P (Eds) The medicinal uses of *Cannabis* and Cannabinoids. London Pharmaceutical Press, London, 165–204.

Pertwee RG (1997) Pharmacology of Cannabinoid CB1 and CB2 receptors. Pharmacology and Therapeutics 2(74): 129–180. https://doi.org/10.1016/S0163-7258(97)82001-3

Pitts JE, O'Neil PJ, Leggo KP (1990) Variation in the THC content of illicitly imported cannabis products – 1984–1989. Journal of Pharmacy and Pharmacology 42(12): 817–820. https://doi.org/10.1111/j.2042-7158.1990.tb07032.x

Pope HG, Gruber AJ, Hudson JI, Cohane G, Huestis MA, Yurgelun-Todd D (2003) Early-onset cannabis use and cognitive deficits: what is the nature of the association? Drug and Alcohol Dependence 69(3): 303–310. https://doi.org/10.1016/S0376-8716(02)00334-4

Rogeberg O, Elvik R (2016) Response: *Cannabis* intoxication, recent use and road traffic crash risks. Addiction 111(8): 1495–1498. https://doi.org/10.1111/add.13443

Russo E (1998) *Cannabis* for migraine treatment: the once and future prescription? And historical and scientific review. Journal Pain 76(1–2): 3–8. https://doi.org/10.1016/S0304-3959(98)00033-5

Russo M, Calabrò RS, Naro A, Sessa E, Rifici C, D'Aleo G, Leo A, De Luca R, Quartarone A, Bramanti P (2015) Sativex in the management of multiple sclerosis-related spasticity: Role of the corticospinal modulation. Neural Plasticity: e656582. https://doi.org/10.1155/2015/656582

Rustichelli C, Ferioli V, Baraldi M, Zanoli P, Gamberini G (1998) Analysis of cannabinoids in fiber hemp plant varieties (*Cannabis sativa* L.) by high-performance liquid chromatography. Chromatographia 47(3/4): 215–222. https://doi.org/10.1007/BF02467674

Sawtelle L, Holle LM (2021) Use of cannabis and cannabinoids in patients with cancer. Annales Pharmacotherapy 55(7): 870–890. https://doi.org/10.1177/1060028020965224

Schilling JM, Hughes CG, Wallace MS, Sexton M, Backonja M, Moeller-Bertram T (2021) Cannabidiol as a rreatment for chronic pain: a survey of patients' perspectives and attitudes. Journal Pain Research 14: 1241–1250. https://doi.org/10.2147/JPR.S278718

Single convention on narcotic drugs (1961) Single convention on narcotic drugs. United Nations, New York.

Smith N (2005) High potency cannabis: the forgotten variable. Addiction 100(10): 1558–1560. https://doi.org/10.1111/j.1360-0443.2005.01295.x

Sirikantaramas S, Morimoto S, Shoyama Y, Ishikawa Y, Wada Y, Shoyama Y, Taura F (2004) The gene controlling marijuana psychoactivity: Molecular cloning and heterologous expression of Δ1- tetrahydrocannabinolic acid synthase from *Cannabis sativa* L. The Journal of Biological Chemistry 279(38): 39767–39774. https://doi.org/10.1074/jbc.M403693200

Suraev AS, Marshall NS, Vandrey R, McCartney D, Benson MJ, McGregor JS, Ronald R, Grunstein RR, Hoyos CM (2020) Cannabinoid therapies in the management of sleep disorders: a systematic review of preclinical and clinical studies Sleep Medicine Reviews 53: e101339. https://doi.org/10.1016/j.smrv.2020.101339

UNODC (2007) The emergence of „new cannabis" and the reassessment of health risks. Chapter 2.3 in World drugs report, 2006, United Nations Office on Drugs and Crime, Vienna.

U.S. Food and Drug Administration (1906) Statement from FDA Commissioner Scott Gottlieb, M.D., on signing of the Agriculture Improvement Act and the agency's regulation of products containing cannabis and cannabis-derived compounds. USA.

Überall MA (2020) A review of scientific evidence for THC:CBD oromucosal spray (Nabiximols) in the management of chronic pain. Journal Pain Research 13: 399–410. https://doi.org/10.2147/JPR.S240011

Villanueva V, Carreño-Martínez M, Gil Nagel-Rein A, López-González FJ (2021) New therapeutic approach in Dravet syndrome and Lennox-Gastaut syndrome with Cannabidiol. Review Neurology 72(S01): S1–S10. https://doi.org/10.33588/rn.72S01.2021017

Wodak A, Reinarman C, Cohen PDA, Drummond C (2002) For and against: cannabis control: costs outweigh the benefits. British Medical Journal 324(7329): 105–106. https://doi.org/10.1136/bmj.324.7329.105

Zajicek JP, Sanders HP, Wright DE, Vickery PJ, Ingram WM, Reilly SM, Nunn AJ, Teare LJ, Fox PJ, Thompson AJ (2006) Cannabinoids in multiple sclerosis (CAMS) study: Safety and efficacy data for 12 months follow up. Journal Neurology Neurosurgery Psychiatry 76(12): 1664–1669. https://doi.org/10.1136/jnnp.2005.070136

Zuardi A (2006) History of cannabis as a medicine: A review. Revista Brasileira de Psiquiatria 28(2): 153–157. https://doi.org/10.1590/S1516-44462006000200015