REVIEW

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Cannabidiol - therapeutic and legal aspects

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Cannabidiol (CBD) is an alkaloid present in *Cannabis sativa*, along with tetrahydrocannabinol (THC) and more than 100 other substances belonging to a group of compounds called cannabinoids. Whereas the legal status and medical use of Cannabis is a controversial issue in many countries, inconsistent legislation makes CBD status even more complicated. Some CBD products are legal in some countries, while banned in other countries, further compounding the confusion. In 2018, the Food and Drug Administration (FDA) approved the first CBD containing medical product, Epidiolex®, for the treatment of paediatric seizures. Currently, several clinical trials are in progress for the potential treatment of neurologic and behavioural disorders. CBD's current legal and regulatory status is a continuously evolving issue; the current review is presenting historical and present information regarding the use of CBD products worldwide.

1. Introduction

The Cannabis family comprises the *Cannabis sativa* and *Cannabis indica* species. *Cannabis* plant has been used for ages to produce hemp fibre (for clothing, rope and paper), seeds which can be used as animal feed and also as a medicinal plant. Cannabidiol (CBD) is one of the main alkaloids found in the composition of the *Cannabis* plants together with other 103 identified alkaloids (Lafaye et al. 2017).

The two major neuroactive components in *Cannabis* plants are: the main psychoactive alkaloid, tetrahydrocannabinol (THC) and the non-psychoactive alkaloid, CBD (Ibarra-Lecue et al. 2018). Taking into consideration the current legislation there are small differences regarding the amounts of THC admitted in the hemp preparations, ranging between 0.05 and 0.6%. As a result, if the plant contains THC it presents a high illicit use and interest, consequently, its cultivation is prohibited by national laws (Wilkinson et al. 2016). Among the *Cannabis* illicit preparations, we can mention the following: marijuana (a mixture of leaves, flowers, and seeds of the hemp plant), hashish (obtained from unfertilized buds) and also oils which can be prepared easily because the alkaloids are lipophilic (Chandra et al. 2019).

Currently, CBD is used as an active ingredient in the following preparations, Epidiolex® – oral solution (contains only CBD) and Sativex® – oromucosal spray (contains both CBD and THC) (Giacoppo et al. 2017, Rekand 2014, Bartner et al. 2018, Lucas et al. 2018).

The legal status of *Cannabis* alkaloids is different from one country to another, as there are countries in which the THC and CBD are classified in the same class of prohibited substances while in other countries CBD products are legal (Corroon and Kight 2018).

Taking into consideration that on the legal market via the internet or in different shops, CBD can be found in many pharmaceutical and cosmetical formulations we consider that a systematic review of CBD therapeutic use and legal status around the world can be an interesting topic for the professionals in the pharmaceutical field.

2. CBD chemical and pharmacological characterization

The chemical structures of CBD and THC are presented in Fig. 1. CBD has a molecular mass of 314.5 g/mol, the same as THC. Structurally the two alkaloids differ as CBD is a bicyclic compound while THC is tricyclic. CBD is a white crystalline powder with an

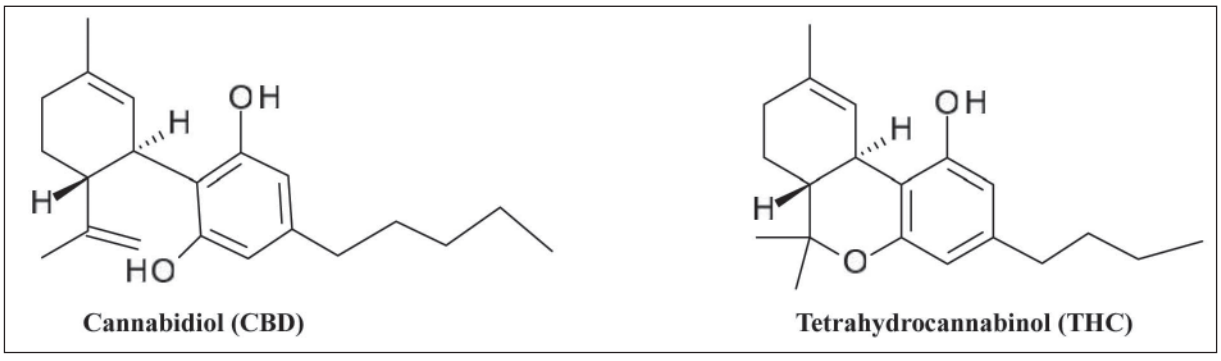

Fig. 1: Chemical structure of CBD and THC.

extremely low solubility in water of approximatively 1 mg/L being included in the second class using the Biopharmaceutical Classification System (BCS II), with low solubility and high permeability (https://www.drugbank.ca/drugs/DB09061).

There are several routes of administration for CBD, each with its advantages and disadvantages. After oral administration of CBD, the maximum concentration is reached after 3 hours, however, bioavailability is low; gastrointestinal absorption is also low and unpredictable because of its low water solubility. The low bioavailability after oral administration is linked also with its metabolization into the main metabolites 11-hydroxycannabidiol (11-OH-CBD) and 7-hydroxycannabidiol (7-OH-CBD) while the transformation of CBD into 1'-hydroxycannabidiol (1'-OH-CBD), 2-hydroxycannabidiol (2'-OH-CBD), 3'-hydroxycannabidiol (3'-OH-CBD), 4'-hydroxycannabidiol (4'-OH-CBD), 5'-hydroxycannabidiol (5'-OH-CBD), 6α-hydroxycannabidiol (6α-OH-CBD) and 6β-hydroxycannabidiol (6β-OH-CBD) ensues less often. By inhaling or by smoking higher concentrations are reached in comparison with oral administration. Due to the lipophilic character, it can be administered sublingually. Sublingual administration has a similar bioavailability to oral administration but presents less variability (Huestis 2007).

CBD is strongly distributed in highly vascularized organs such as the heart, lungs, and liver (Gaston et al. 2017; Dinis-Oliveira 2016). If it is administered for a longer period, there is a high risk of accumulation in the fatty tissue especially in obese patients (Hunt and Jones 1980). The distribution volume is over 30 L when CBD is administered intravenously while, when administered by inhalation, decreases to a maximum of 4 L (Lucas et al. 2018).

The isoenzymes responsible for the CBD metabolization are CYP2C19, CYP3A4, CYP1A1, CYP1A2, CYP2C9, CYP2D6 (Huestis 2007, Zendulka et al. 2016). A scheme of CBD metabolism is presented in Fig. 2.

Elimination of CBD occurs usually after 24-36 hours varying as a function of the administration route (Gamble et al. 2018; Consroe et al. 1991).

Many types of effects have been associated with CBD and they seem to be related to a complex pharmacodynamic mechanism. CBD does not activate the cannabinoid receptors (CB_1 and CB_2), acting more like an antagonist for the CB_2 receptor and antagonist modulator for CB_1. This may explain the lack of psychotropic effects. Depending on the concentration it can be an antagonist for the G protein-coupled receptor 55 (GPR_{55}). It also has an agonist effect on the following receptors: serotonin 1A receptor ($5\text{-}HT_{1A}$), adrenergic receptors (α_3, α_1) and, transient receptor potential ankyrin 1 ($TRPA_1$). At high concentrations, it can act as an agonist on peroxisome proliferator-activated receptor gamma (PPAR-γ) and on the vanilloid receptors: transient receptor potential cation channel subfamily V member 1 and member 2 ($TRPV_1$ and $TRPV_2$). Due to the polyphenolic structural characteristics, CBD can act as a strong antioxidant (Szaflarski and Bebin 2014; Tham et al. 2019; Smith and Zheng 2016).

CBD is one of the cannabinoids found in the *Cannabis* plant with a high pharmacologic and therapeutic potential (Zuardi et al. 1982). CBD has some obvious advantages in comparison with THC as it does not present addiction risks and tachyphylaxis. Recent studies on both substances showed that CBD has an anxiolytic effect while THC may induce anxiety (Niesink and van Laar 2013).

Another advantage of CBD is related to the absence of psychotic effects during administration. Some studies showed that CBD might be used for the patient suffering from schizophrenia while others pointed out the fact that THC might induce sleepiness (Nicholson et al. 2004; Mao et al. 2015).

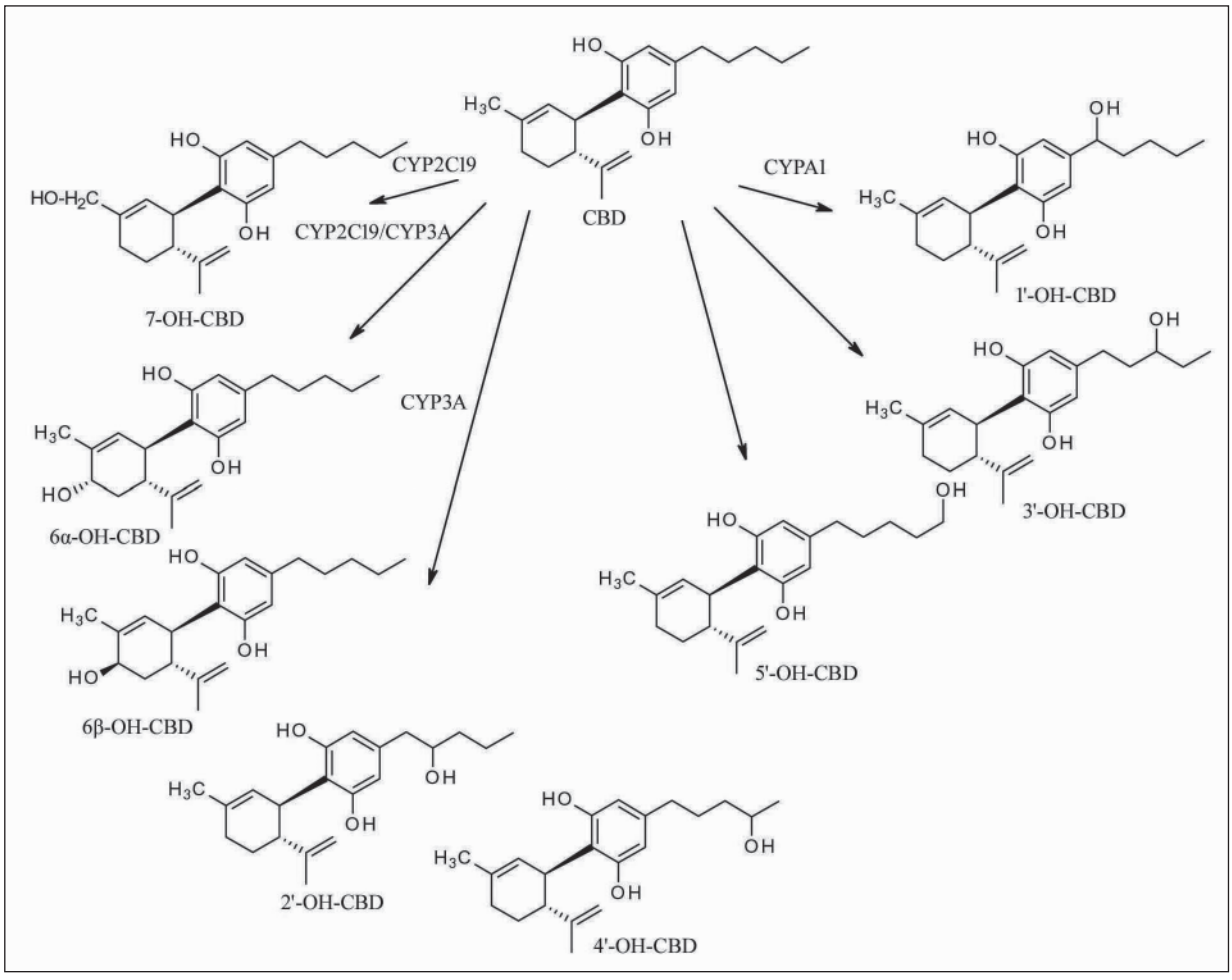

Fig. 2: CBD metabolic pathways.

3. CBD therapeutic use

CBD was administered in many studies to verify its potential effects in epilepsy treatment; the results showed that it was more effective on partial and generalized seizures than in seizures localized in the temporal lobe. Intraperitoneal administration of 100 mg/body weight (bw) of CBD decreased the probability of tonic-clonic seizures (Mao et al. 2015).

As in the other diseases, the way the seizures are induced is important. CBD has positive effects in the treatment of seizures induced by administrating pentylenetetrazol (PTZ), picrotoxin, or penicillin G while when pilocarpine was used to induce the seizures no effects were observed. The mortality rate decreased while administrating PTZ, picrotoxin and, penicillin G, while in the case of pilocarpine remained the same (Mao et al. 2015).

In a clinical trial including 15 patients (11 females) with temporal lobe epilepsy, patients received 300 mg CBD for 18 weeks; 4 patients did not present any seizures during the trials (Carlini and Cunha 1981).

In another study conducted on 34 patients, the effect of CBD in Dravet Syndrome was verified at concentrations of 5-10-20 mg/bw. During the 4-week treatment, it has been observed that less than 4 seizures occurred (Devinsky et al. 2018a). In another study, 120 patients were enrolled, among them, 58% were women aged between 2-18 years old. The patients received a CBD dose of 20 mg/bw orally for 14 weeks (Devinsky et al. 2018b). During both trials, it has been observed that the frequency of seizures decreased but the levels of liver aminotransferases increased which may conduct to hepatic pathologies (Devinsky et al. 2018a, b).

Epidiolex® is an oily solution where sesame oil and alcohol are used as solvents and it is utilized for the treatment of Lennox Gastaut and Dravet syndromes associated with seizures for patients older than 2 years. The dosage starts with 2.5 mg/bw twice daily and it can increase up to 20 mg/bw/day (Sekar and Pack 2019; Abu-Sawwa and Stehling 2020).

CBD products might be used off-label for the treatment of other medical conditions. Epidiolex® can be prescribed for epilepsy-related diseases but in the future other curative effects might be approved. At this point, if a physician is prescribing CBD-containing drugs off label might encounter several issues since insurance companies might not cover the costs of the drug. Possible off-label use of CBD includes also pain relief (Cohen and Sharfstein 2019). Various dietary supplements are sold on the market and many of them are containing CBD. The dietary supplements are used as adjuvants in the treatment of Parkinson disease, various types of epilepsy, or anxiety (Trudeau et al. 2019). Also, anti-aging effect has been related to CBD (Tura et al. 2019).

Table 1: Approved pharmaceutical products which contain only CBD

Name	Substances contained	Approval year	Website/Reference	Approved by
Epidiolex (Greenwich, United States of America (USA).	Contains 100 mg/ml CBD	June 2018	https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd https://www.ema.europa.eu/en	FDA and European Medicines Agency (EMA)

4. CBD potential pharmaceutical use

It has been proven that CBD can be used therapeutically to treat anxiety; high concentrations of 300-1500 mg/day of CBD have been well-tolerated without the occurrence of side effects. The receptor responsible for the antianxiety effect is 5 HT_1, CBD acting as an agonist on this receptor (Linge et al. 2016).

It can be observed that the results regarding CBD use in anxiety management are mixed; some of them showing the fact that CBD might reduce anxiety in higher doses while in others an anxiolytic effect was not noticed.

The results of the studies that linked to the possible use of CBD in Parkinson disease are also mixed. In a study, Parkinson disease was induced by the administration of 6-hydroxy-dopamine (6-OH-dopamine) to rats. After the administration of 3 mg/bw

Table 2: Studies of CBD potential anxiolytic effects

Study design and duration	CBD pharmaceutical formulation, control dose and route	Results	Reference
47 subjects (humans) with an anxiety disorder. Diagnosis established by clinical evaluation. Study duration: 3 months. Analysis of the results using the Hamilton Anxiety Rating Scale	Capsules Oral route 25 mg/day and 75 mg/day	The anxiety score decreases from 13 to less than 10 after 2 months and it remained under 10 after 3 months which indicates a mild severity.	Shannon et al. (2019)
24 subjects with Parkinson disease. Anxiety was induced by a Simulated Public Speaking Test (SPST). Study duration: the interval between the first and the second experiment was 15 days. Analysis of the results: The Unified Parkinson's Disease Rating Scale, Hoehn and Yahr Scale, Schwab and England Scale	Gelatine capsules Oral route 300 mg/day	CBD decreased the anxiety induced by the SPST	De Faria et al. (2020)
36 subjects (Male mice and C57/6J controls. Kept for 12h:12h light-dark schedule, food and water provided ad libitum). Mice received intraperitoneal injection 30 min before starting the behavioural testing.	Alcoholic solution (Tween 80, Absolute alcohol and NaCl 0.9% - 1:1:18) 5mg/bw 20 mg/bw CBD	5 mg/bw did not influence the anxiety effect while the higher concentration decreased the anxiety.	Zieba et al. (2019)
440 male and female mice C57BL/6J (B6). Kept on a 12:12 h reverse light cycle. The injections were made during the active dark phase.	Alcoholic solution (Tween 80, absolute alcohol and NaCl 0.9% - 1:1:18) 5 mg/bw 10 mg/bw 20 mg/bw	THC produces an anxiogenic effect while CBD does not present an anxiolytic effect.	Kasten et al. (2019)

CBD, it has been observed that the dopamine levels in the putamen have increased. CBD may be used in the early stages of Parkinson disease and its therapeutic effect may be linked to the antioxidant effect which is tissue specific. For example, when N18TG murine neuroblastoma cell was used, no effect occurred, while when mesencephalic murine was used the CBD had the antioxidant effect and the glutathione level increased, too (Lastres-Becker et al. 2005).

CBD has been used in clinical trials and the results showed significant reductions in the positive and negative effects while no effect was seen on the cognitive function (Zuardi et al. 2009).

Hyperactivity is one of the symptoms of schizophrenia, which can be induced in animals by using amphetamine or ketamine. Administration of doses between 50 and 60 mg/bw of CBD in animal experiments conducted to the normalization of the hyperlocomotion previously induced by using dopamine receptors agonists (Moreira and Guimaraes 2005; Long et al. 2010; Gururajan et al. 2011). Another symptom that may occur in patients with schizophrenia is the inability of processing/filtering unnecessary information. In animal studies, this effect is measured by using the pre-pulse inhibition (PPI) of the startle response. Studies showed that CBD attenuates the PPI induced by amphetamine administration in Swiss mice and Sprague-Dawley rats (Gururajan et al. 2012). Concentrations between 3 and 30 mg/bw showed to be less effective on the PPI while concentrations between 1 and 3 mg/bw normalized hyperlocomotion (Deiana et al. 2015).

In a case-control study, patients between 22 and 33 years old, received placebo from day 1 to day 5; 1280 mg of oral CBD from day 6 to day 35, placebo from day 36-40 and in the end olanzapine for 15 days; mixed results were obtained. In some cases, CBD showed improvement while in other cases no improvement was observed (Zuardi et al. 2006).

Table 3: Legal status of CBD, CBD oil and industrial hemp worldwide

Country	CBD	CBD oil	Hemp	Approved pharmaceutical product containing cannabinoids	Organisation /Legislative Instrument	Reference website
Australia	Legal[a]	Legal[a]	Legal	Sativex®	The Poisons Standard	https://www.legislation.gov.au/Details/F2020L00017
Austria	Legal[b]	Legal[c]	Legal[d]	Sativex® Dronabinol® Nabilone®	EMCDDA	http://www.emcdda.europa.eu/countries/drug-reports/2019/austria/drug-laws-and-drug-law-offences_en
Canada	Legal[a]	Legal[a]	Legal [a, d]	Sativex®	Controlled Drug and Substances Act	http://laws-lois.justice.gc.ca
Czech Republic	Legal[d]	Legal[d]	Legal[d]	Sativex®	EMCDDA Criminal Code of the Czech Republic	http://www.emcdda.europa.eu/countries/drug-reports/2019/czechia_en http://www.ejtn.eu/PageFiles/6533/Criminal%20Code%20of%20the%20Czech%20Republic.pdf
France	Legal[e]	Legal[e]	Legal	Sativex®	EMCDDA	http://www.emcdda.europa.eu/countries/drug-reports/2019/france_en
Germany	Legal[e]	Legal[e]	Legal[e]	Sativex® Dronabinol® Nabilone®	EMCDDA	http://www.emcdda.europa.eu/countries/drug-reports/2019/germany_en
Greece	Legal[e]	Legal[e]	Legal[e]	None approved yet	EMCDDA	http://www.emcdda.europa.eu/publications/topic-overviews/cannabis-policy/html_en
Hungary	Legal[e]	Legal[e]	Legal[e]	Marinol®	EMCDDA	http://www.emcdda.europa.eu/countries/drug-reports/2019/hungary_en
Italy	Legal[f]	Legal[f]	Legal[g]	Sativex®	EMCDDA	http://www.emcdda.europa.eu/countries/drug-reports/2019/italy_en
Romania	Legal	Legal	Legal	None approved yet	Law No. 339/2005.	https://cmvro.ro/files/download/legislatie/stupefiante-psihotrope/Legea_339_2005_stupefiante_psihotrope-consolidata.pdf
Russia	Illegal	Illegal	Legal	None approved yet	Government of the Russian Federation	https://www.wto.org/english/thewto_e/acc_e/rus_e/WTACCRUS48A5_LEG_56.pdf
Spain	Legal[e]	Legal[e]	Legal[e]	Sativex® Dronabinol® Nabilone® Epidiolex®	EMCDDA	http://www.emcdda.europa.eu/countries/drug-reports/2019/spain_en
The Netherlands	Legal[h]	Legal[h]	Legal[e]	Standardised medicinal *Cannabis* flower	EMCDDA	http://www.emcdda.europa.eu/countries/drug-reports/2019/netherlands_en
The United Kingdom	Legal[e]	Legal[e]	Legal[a]	Sativex®	EMCDDA	http://www.emcdda.europa.eu/system/files/publications/11355/united-kingdom-cdr-2019.pdf
United States of America	Illegal[i]	Illegal[i]	Legal[d]	Sativex® Dronabinol® Epidiolex®	FDA - Regulation of Cannabis and Cannabis-Derived Products.	https://www.fda.gov/news-events/public-health-focus/fda-regulation-cannabis-and-cannabis-derived-products-including-cannabidiol-cbd

a Legal as long as you have a government license b In Austria CBD is legal to be used in aromatherapy. It is forbidden to be used in food or cosmetics. c Only if it is prepared in a pharmacy as magistral preparations, otherwise in supplements it is strongly prohibited d Legal as long as THC concentration is below 0.3, in the Czech Republic this implies for technical hemp while medicinal hemp with higher THC values is legal with a medical prescription. e Legal as long as THC concentration is below 0.2%. f Legal as long as THC concentration is below 0.6%. Available with prescription. g Legal as long as THC is lower than 0.2%, also if it is higher but is not exceeding 0.6% it is not punishable by laws. h Legal as long as THC concentration is below 0.05%. i It is illegal under federal law

In a clinical study, 88 patients received 1000 mg of CBD daily and an antipsychotic for 6 weeks. The patients that received CBD beside the usual antipsychotic treatment showed no improvements in negative and cognitive symptoms of schizophrenia while an improvement in the positive symptoms was observed (McGuire et al. 2018).

Alzheimer disease can be induced in mice by using β-amyloid administered in the right dorsal hippocampus. Doses between 2.5 mg and 10 mg showed that CBD blocks the nitric oxide synthase with the result of decreased Reactive Oxygen and Nitrogen Species (ROS, RNS) levels and interleukin 1 β which is associated with the neurodegenerative process. In a study, when Alzheimer disease was induced using β-amyloid, CBD showed improved cognitive performance and lower levels of pro-inflammatory cytokines (TNF α and IL-6) (Martin-Moreno et al. 2011).

5. CBD legal status

As a result of their high popularity, many dietary supplements containing CBD were developed and marketed, starting from soft capsules containing both CBD and CBDA (cannabidiolic acid) continuing with hard capsules containing a lipophilic gel and ending with various oily solutions with different concentrations of CBD. It is expected that in future years, the CBD dietary supplements business will reach billions of euros worldwide. Dietary supplements are defined as nutritional products whose purpose is to fill a normal diet. They are concentrated sources of nutrients or other substances with physiological and nutritional effects marketed as capsules, tablets, pills, ampoules with liquid or powder. The nutrients are defined as vitamins and minerals. Because CBD is an active pharmaceutical ingredient and it cannot be included in the vitamin class nor it has any physiological effects, the use of CBD in dietary supplements is not legal in all countries. In the USA there are lots of supplements containing CBD which have been prohibited as a result of the lack or absence of the declared amount of CBD (Cogan 2019; Wheeler et al. 2020).

According to the Controlled Substance Act, CBD is listed in Schedule I of prohibited substances (together with both THC and marijuana) while the newly approved product Epidiolex® that contains CBD is listed in Schedule V. Schedule V includes pharmaceutical formulations with limited amounts of certain narcotics (Controlled Substances Act, 2018; Hudak and Stenglein 2017). The import, acquisition, distribution, and possession of THC and marijuana is prohibited by law. As a result of the Farm Bill Act, hemp has become legal with the following amendment, it cannot have a concentration of THC higher than 0.3% so that hemp would not exert psychotropic effects. Also, CBD can be extracted from the plant, but CBD limits are not provided (Hemp Farming Act 2018). Even though the hemp has become legal, FDA maintains the authority in verifying the products containing hemp or hemp-derived compounds. Considering that in the USA, many dietary supplements are sold which contain CBD, FDA stated that beside Epidiolex® there is no other pharmaceutical formulation accepted which contains only CBD and does not recommend the use of the supplements found on the market because CBD is a drug with restricted use and it cannot be found legally in dietary supplements. However, by accepting the Epidiolex® solution FDA recognizes the benefit and therapeutically effect of CBD (Controlled Substances Act 2018).

In Hungary, distribution and use of Cannabis are prohibited. The cultivation is permitted only on restricted areas and only seeds that are metallically sealed can be used. The testing of Cannabis plants and the experimental and scientific cultivation can be done with the approval of the National Institute of Pharmacy and Nutrition. Possession of quantities higher than 100 g of cannabis are illicit and can be punished with imprisonment (162/2003. (X. 16.) Government Decree, Hungary).

In Austria, the industrial hemp with concentrations below 0.3% after blossoming can be used for industrial and medicinal purposes. The recreational use of cannabis is not prohibited while buying and possession are considered illegal. CBD oil is considered licit and there are also a few formulations that are used such as Dronabinol which contains also 2.5 mg THC and Sativex which contains CBD (2.7 mg) and THC (2.5 mg) that can be used with prescription. The products derived from flowers and fruits are excluded by the narcotics law. Like in the USA, dietary supplements are prohibited (Pohl and Natterer 2019).

The information found on the European Monitoring Centre for Drugs and Drug Addiction (EMCDDA) showed that in the Czech Republic, hemp is not prohibited but there is a maximum amount of 0.3% of THC admitted by law enforcement for the production of fibres and seeds. Here also appear age restrictions, as only subjects over 18 years old can receive medical hemp. There is a maximum weight of *Cannabis* of 180 g/month admitted that a person can have but if a person is caught having over 10 g of cannabis or possessing medicinal hemp without a prescription (with the amount of THC larger than 0.3 %) there is a huge risk of imprisonment. The country from which the Czech Republic usually imports Cannabis is the Netherlands, however few other countries such as Canada are mentioned as countries from which the Czech Republic admits importing. Prescribing CBD and THC is very difficult due to bureaucracy so there are a few physicians that can prescribe the cannabinoids or the pharmaceutical formulations due to the restrictions regarding the diagnosis and medical specialization (Act No. 167/1998 Coll., Czech Republic; EMCDDA, 2019).

In Romania, THC and 5 other isomers can be found in Table I in the class of narcotics. This table realized in 2005 and updated in 2018 contains prohibited plants and substances without a therapeutic effect. CBD is not included. The cannabis plant, Cannabis resins, tinctures, extracts, and Dronabinol can be found in Table II which includes narcotic plants and substances which have an interest in medicine but are the subject of strict control. As a result of the high popularity, we can find a lot of dietary supplements with CBD but their concentration might be very low (Law No. 339/2005).

Currently, in Romania, no pharmaceutical formulation containing CBD has been approved by the National Drug Agency. Many products containing CBD refer to the fact that CBD is not found in the prohibited list, so it is considered that CBD is legal (https://www.anm.ro/nomenclator/medicamente).

Numerous supplements containing CBD are marketed worldwide and none of the producers has received any bans, excepts for the USA where the FDA does not recommend using CBD supplements due to the unknown concentration of CBD. Another fact that has to be taken into consideration is that the hemp seeds contain only traces of THC and CBD while the hemp plant contains on average less than 0.3% THC (depending on the country). The average concentration of CBD is between 12-18% (Cohen and Sharfstein 2019).

By evaluation of the studies in which both the THC and CBD levels were established, it has been observed that the concentration of THC in the resins increased in the United Kingdom, Italy, and France while in the Netherlands the concentration remained

Table 4: THC: CBD ratios in cannabis resins in different countries

Country	THC:CBD ratio/year			References
Netherlands	2.66 (2005)	6.5 (2009)	3.95 (2015)	Niesink et al. (2015)
United Kingdom	0.86 (2005)	1 (2009)	2.74 (2015)	Potter et al. (2008)
Italy	-	2.18 (2010)	3.66 (2013)	Zamengo et al. (2013, 2014)
France	2(2005)	2 (2009)	6 (2016)	Dujourdy and Besacier (2017)
Romania		4.1 (2011)		Trofin et al. (2012)

constant. We can also mention the fact that resins tend to have an increased concentration of THC while the CBD concentration is small or missing. We can conclude that the THC:CBD ratio is increased because the THC concentration in the resins has been increasing while the CBD concentration remains the same or decreased dramatically (Freeman et al. 2019; Potter et al. 2008; Dujourdy and Besacier 2017; Pijlman et al. 2005).

Another study which had as a central theme the quantification of CBD in the cannabis plant showed a descending slope of the CBD concentration, decreasing from 0.37 to 0.17%. The same situation emerged in the case of hashish samples. Also, the CBD concentrations in the hashish at the end of the study (2017) were higher than in the cannabis plant at the beginning of the study (2008). The only product in which the concentration of CBD increased was the hash oil where the concentration almost doubled from 0.2% in 2008 to 0.39 in 2017 (Chandra et al. 2019).

As can be seen in the Table in most of the countries the THC:CBD ratio is increasing. The only country where the ratio decreased is the Netherlands that can be explained as a result of strict regulations (even though using for recreational purposes is legal) since they rarely import cannabis from other countries and they have strict amounts of cannabis available for recreational use. In the United Kingdom, the ratio has tripled from 2005 up to 2015 the same as in France from 2009 until 2016, while in Italy in 3 years the ratio almost doubled. (Niesink et al. 2015, Potter et al. 2008, Zamengo et al. 2013, 2014, Dujourdy and Besacier 2017).

6. Conclusions

Because CBD has a complex mechanism of action there is a great potential of using it in the treatment of different medical conditions. The first and the only FDA-approved CBD preparation – Epidiolex® is used for the treatment of seizures associated with Dravet and Lennox-Gastaut Syndromes. The main problem in obtaining other pharmaceutical products is the high lipophilic profile and strict legislation. In many countries CBD is legal, but in others its regulatory status is not clear.

The organizations responsible for the presence and occurrence of new products containing CBD are having a strict position, most of them denying the therapeutic in the effect of dietary supplements because the CBD concentration is smaller than declared.

In some European countries the medicinal use of cannabis is legal so also the use of CBD products is legal, but legislation is also strict; consequently, availability of the drug being slowed by bureaucracy. However, cannabis legal status has changed recently in many countries.

The THC:CBD ratio is an important parameter; in many EU countries the THC level has increased while the CBD level decreased. The Netherlands is one of the few countries where the THC:CBD ratio decreased. The legal status of the CBD was presented in numerous countries. It has been shown that even if the countries from Europe are part of the European Union, the legislation regarding the THC maximum amount differs from country to country; each country has its strict legislation. In the future, many diseases could be included in the list of the illnesses treated with CBD.

Conflicts of interest: None declared.

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