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ORIGINAL ARTICLES AND REVIEWS

Pharmacology and legal status of cannabidiol

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Abstract
Cannabidiol (CBD) is the second most abundant cannabinoid present in *Cannabis sativa* L. It is not associated with psychotropic activity and is capable to mitigate the psychotomimetic effects produced by tetrahydrocannabinol (THC). The latest cannabis decriminalization policies and the high applicability in therapeutic and technologic-industrial fields, have determined an exponential marketing growth of foods, cosmetics and in particularly medicinal products containing CBD, which are easily available for consumers. Most importantly, on 2018 United States Food and Drug Administration approved CBD oral solution with the trade name of Epidiolex® for the treatment of two rare and severe forms of epilepsy, "Lennox-Gastaut syndrome" and "Dravet syndrome", in pediatric patients. The aim of this review was to focus on pharmacology and on legal status of CBD, to highlight the lack of harmonization of international regulatory laws over the marketing authorization of CBD-based products.

Key words
- cannabidiol (CBD)
- epilepsy
- law
- legal status
- policies

INTRODUCTION

Cannabidiol (CBD) or 2-[(6R)-6-Isopropenyl-3-methyl-2-cyclohexen-1-yl]-5-pentyl-1,3-benzene-diol [1] is one of the more 100 phytocannabinoids present in *Cannabis sativa* L. [2-4]. It is the second major pharmacologically active component of the plant and the most prevalent in the fibre-type hemp [4]. It was isolated for the first time in 1940, and its structure was described by Mechoulam *et al.* in 1963 [1, 5]. CBD is a meroterpenoid obtained from the alkylation of an alkyl resorcinol with a monoterpene unit [6]a lot of attention has been paid to the compounds present in medicinal Cannabis sativa L., such as Δ 9 -Tetrahydrocannabinol (Δ 9 -THC, it is substituted in position 1 by a methyl group, in position 3 by a 2,6-dihydroxy-4-pentylphenyl group, and in position 4 with a prop-1-en-2-yl group [2]. From the chemical structure of CBD *(Table 1)*, it is easy to recognize the presence of two hydroxyl groups and according to Borges *et al.* 2013, CBD has potential antioxidant activity because of the cation free radicals show several resonance structures in which the unpaired electrons are mainly distributed on the ether and alkyl groups, as well as on the benzene ring [2].

In this review, we described the pharmacology and legal status of CBD in different countries, drawing attention to the lack of harmonization of international regulatory laws over the marketing authorization of CBD-based foods, cosmetics and medicinals.

MATERIALS AND METHODS

A literature search was performed on multidisciplinary databases such as PubMed, Web of Science, international agencies or institutional websites including: World Health Organization, US Food and Drug Administration (FDA), US Drug Enforcement Administration (DEA), European Monitoring Centre for Drugs and Drug Addiction, European Medicines Agency, European Food Safety Authority (EFSA), Italian Medicines Agency, Italian Public Administration, National Academies of Sciences, Engineering, and Medicine to identify the most relevant literature (up to November 2019). The search terms used only or in combination were: cannabidiol, CBD, phytochemistry, pharmacology, pharmacokinetics, pharmacodynamics, medical use, adverse effects, reactions, toxicity, legal and regulatory. The main keywords cannabidiol and CBD were searched alone and in association to each of the others. Only scientific articles written in English were included, whereas for institutional websites both Italian and English sources were taken into consideration. All sources were screened independently by two of the authors to determine their relevance and appropriateness in the framework of the current report.

RESULTS AND DISCUSSION

The initial search produced about 2800 sources, but only 29 were included for the purposes of this review. The first aim of this manuscript was focused on: 1)

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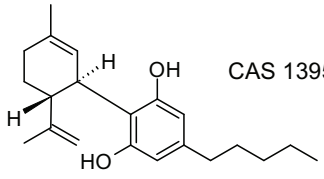
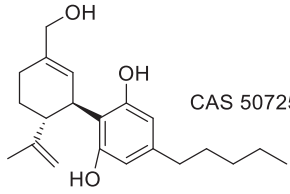
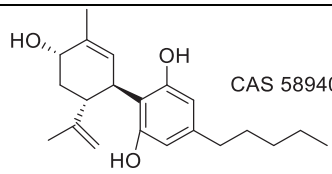
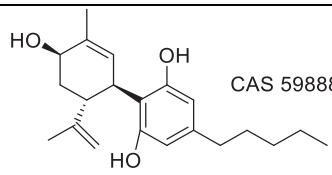
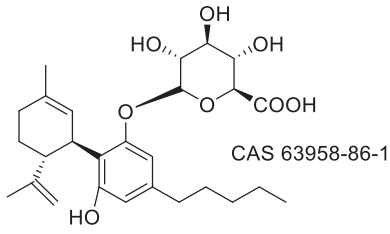
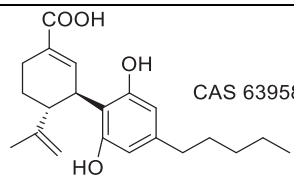
Table 1
Cannabidiol (CBD) and main metabolites in human

Structure	Molecular formula	Chemical names	
 CAS 13956-29-1	$C_{21}H_{30}O_2$	Cannabidiol	
Main metabolites in human			
Structure	**Molecular formula**	**Chemical names**	**CYP 450 isoform**
 CAS 50725-17-2	$C_{21}H_{30}O_3$	7-Hydroxy Cannabidiol	CYP2C19 CYP3A4
 CAS 58940-28-6	$C_{21}H_{30}O_3$	6a-Hydroxy-cannabidiol	CYP2C19 CYP3A4
 CAS 59888-03-8	$C_{21}H_{30}O_3$	6 β-Hydroxy-cannabidiol	CYP2C19 CYP3A4
 CAS 63958-86-1	$C_{27}H_{38}O_8$	Cannabidiol β-D-Glucuronide	UGT1A7, UGT1A9, UGT2B7
 CAS 63958-77-0	$C_{21}H_{28}O_4$	7-Nor-7-carboxycannabidiol	CYP2C19 CYP3A4

pharmacology and toxicology of CBD including pharmacokinetics, pharmacodynamics, adverse effects and interactions, while the second aim was to describe 2) the legal status of CBD and to provide an overview about American and European legislation, with a special focus on the Italian *scenario*.

Pharmacokinetics

Pharmacokinetics processes of CBD are dynamic and may change over time, depending on the route of administration and the frequency or magnitude of exposure [7]. CBD is highly lipophilic and for that reason can easily pass across biological barriers and it is rapidly

absorbed. Inhalatory and oral administrations are the most common routes for drug formulation containing CBD [7, 8]. Oral absorption seems to have more variability and less bioavailability compared to inhalatory one, probably due to an intensive first-pass metabolism [9]. Distribution of CBD is time dependent and begins upon absorption, into fatty tissues and highly perfused organs such as: brain, heart, lung, and liver, quickly decreasing its plasma concentrations [7, 9]. Plasma protein binding, primarily to lipoproteins, of CBD, is similar to the one of THC and is about 97%. For this reason, CBD intake can cause concentration increase of co-administered drugs, displacing them from protein linkage [10] and causing possible adverse effects. CBD is extensively metabolized in liver and in intestine by different isoforms of cytochrome P450 (CYP) such as: CYP2C19 and CYP3A4 [1, 10, 11] (all main metabolites are reported in *Table 1*), forming predominantly 7-hydroxy-cannabidiol (7-OH-CBD) and 7-carboxy-cannabidiol (7-COOHCBD), and 6-hydroxy-cannabidiol as minor metabolite [1, 8]. The metabolic pathway of CBD may involve other isoforms of CYP450 such as CYP1A2, -2B6, -2C8, -2C9, -2E1, -2J2, and -3A5/7 [1, 9]. The hydroxylation reactions occur furthermore at positions 1"-5" of the aliphatic pentyl- and position 10 on the propenyl- substituent [8, 11]. These metabolites may be further oxidized to form dihydroxylated metabolites and CBDoic acid derivatives [11]. At last UGT_{1A7}, UGT_{1A9}, and UGT_{2B7} isoforms [1] of 5'-diphosphoglucuronosyltransferase (UGT), which catalyze glucuronidation of xenobiotics, create more easily excreted products [12]. Metabolites are primarily excreted with feces and in a minor amount (16% *ca.*) [13] with urine, while a large proportion of CBD (33%) is excreted unchanged in feces [8]. The slow release, the redistribution phenomenon from deep lipid-storage compartments and the significant enterohepatic circulation contribute to a long terminal half-life elimination of CBD, with the average amount post inhalation of 31±4 hours and from 2 to 5 days after repeated daily administrations in chronic cannabis users [7, 9]. In a series of recent studies involving the smoking of "light cannabis" containing 0.16% THC and 5.8% CBD [14-16], the highest CBD concentrations in oral fluid (OF), serum and blood were observed on the samples collected 0.5 h after the start of smoking and the compound was measurable in those biological fluids up to 4 hours after administration [14]. Following smoking of four "light cannabis" cigarettes with a one h interval between each cigarette, CBD concentrations in blood serum and OF overlapped with those obtained after smoking a single cigarette, suggesting that CBD is poorly absorbed after repeated smoking and that this is not the preferential route to administer it. As a justification to this result, it has to be said that this is the first-time that a product containing negligible amounts of psychotropic THC and significant concentration of CBD (58 mg per cigarette) was smoked in a controlled clinical trial, and that participants were cigarette smokers with some "light cannabis" experience. In fact, given that CBD does not preferentially volatilize compared to THC, a trial on more experienced "light cannabis" smokers could confirm or deny that possibility. Indeed, CBD pharmaceutical preparation are based on tablets and oily drops [17].

Pharmacodynamics

To date CBD mechanisms of action are not fully elucidated. Thanks to its high lipophilicity CBD crosses the blood-brain barrier (BBB) [4] modulating central nervous system (CNS) [1]. Most central CBD effects are mediated by the activation of endocannabinoid system through the modulation of cannabinoids (CB_r) 1,2 receptors, which are $G_{i/o}$ protein-coupled receptors [11, 18] present at a high density in the frontal cortex, basal ganglia, hippocampus, and cerebellum, and at a minor density in the hypothalamus, nucleus accumbens, and amygdala [11, 19]. CB_{1r} are located predominantly at the presynaptic terminals of neurons while postsynaptic localization has rarely been observed [11]. Their activation inhibits the presynaptic release of many neurotransmitters such as: γ-aminobutyric acid (GABA), glutamate, acetylcholine, serotonin, and noradrenaline [18]. CB_{2r} are principally expressed in peripheral tissues [18] and are associated with cells governing immune function [19], although the receptorial density in brain is very low and predominantly located at mesolimbic DA (DopAminergic) system [18]. CBD possesses a very low affinity for the CB_1 and CB_2 receptors [3, 20, 21] acting as negative allosteric modulator of the CB_{1r} [22] or inverse agonist of CB_{2r} [23]. Moreover, it can increase concentrations of anandamide through the inhibition of fatty acid amide hydrolase (FAAH), its main degradative enzyme [4, 22], and the blockade of its reuptake, promoted by fatty acid-binding protein (FABP) [4, 18, 22]. For that reason CBD can modulate, through presynaptic CB_{1rs}, the release of certain neurotransmitters in particular key brain zones. The dampen of neuronal excitability through the reduction of glutamate release, indirectly protects against the development of cannabis use disorder (CUD) [22] and attenuates psychotomimetic and anxiogenic effects induced by high doses of THC in humans. These observations suggested that this cannabinoid could possess antipsychotic and anxiolytic properties [5, 18, 20, 22]. Experimentally, CBD was successfully used in humans for reducing psychotic symptoms of schizophrenia, thanks to its partial agonist activity on dopamine D2 receptors similarly to atypical antipsychotics [20]. It also reduces anxiety and stress symptoms [3, 20]. In this regard, the anxiolytic effect exerted by CBD has been mainly related to its agonist activity towards serotonin type 1A ($5HT_{1A}$) receptors [3]. Botanical preparation containing THC acid precursor (THCA-A) CBD acid precursor (CBDA) and cannabigerol acid (CBGA) were successfully used for the treatment of neurodegenerative diseases such as Huntington and possibly Alzheimer and Parkinson [3,20]. These evidences suggest that acute administration of CBD may reduce withdrawal symptoms of drugs dependence and may also contribute to improve cognitive performances [3]. CBD is a promising therapeutic agent approved for reducing seizures in many children with Dravet syndrome, a severe treatment-resistant form of childhood epilepsy [24]. Analgesic myorelaxant

and antiepileptic actions of CBD are achieved through the increasing of inhibitory tone in cortical and striatal membranes obtained from the inhibition of GABA reuptake and the positive allosteric modulation of $GABA_A$ receptor [25]. Thanks to its lack of psychoactivity, CBD is one of the most interesting compounds potentially useful in various models of pathologies such as inflammatory and autoimmune disorders like multiple sclerosis, arthritis, and cancer [6]a lot of attention has been paid to the compounds present in medicinal Cannabis sativa L., such as Δ 9 -Tetrahydrocannabinol (Δ 9 -THC. The agonist activity on peroxisome proliferator-activated receptor gamma (PPARγ) [26], the competitive inhibition of adenosine uptake [23], the antagonism over adenosine receptor A2A [27] and the activation of Transient Receptor Potential Subfamily V member 1 and 2 (TRPV1,2) [21, 28], mediated by CBD produce several changes. Namely, significant reduction in release of IL-2 (Interleukin), TNF-α (Tumor Necrosis Factor), IFN-c (Interferon), IL-6, IL-12, IL-17, eotaxin-1 (CCL11) and COX-2 (Cyclooxygenase), and iNOS (inducible Nitric Oxide Synthases) expression [27], decreasing the inflammatory event and exerting neuroprotective actions after hypoxic ischemic exposure [6] or decreasing the leukocyte infiltration in brain in some autoimmune diseases, like multiple sclerosis [27]. As regards cancer, CBD has exhibited antiproliferative and proapoptotic activities through the antagonism over G protein-coupled receptors (GPR) 55 [3], modulating the tumorigenesis in different types of cancer, including breast, lung, colon, brain, and others [6].

Adverse effects and interactions

CBD is by definition: the major nonpsychoactive phytocannabinoid derived from cannabis [5] and, thanks to its good safety profile and the lack of euphoric effects, is the most interesting cannabinoid [4]. However, CBD is not a biologically inert compound and its complex pharmacology offers tremendous therapeutic potential but, also, the potential for adverse effects and drug-drug interactions. Pharmacodynamics and pharmacokinetics interactions from cannabinoids may occur via simple competitive inhibition, noncompetitive (allosteric) inhibition, or at the level of gene expression of the cannabinoid receptors, biotransformation enzymes, and transport proteins [9]. The metabolic routes of cannabinoids primarily involve cytochrome P450 oxidases (CYP) enzymes which are implicated in the primary metabolism and biotransformation of the majority of therapeutic agents and xenobiotics [12]. It is easy to understand that these compounds are susceptible to, or complicit as, inhibitors or inducers of these enzymes. The decrease in the metabolic activity of individual CYPs can increase the plasma levels of their substrates, and symptoms of toxicity could appear. In the opposite direction, increased CYP activity will decrease the efficacy of its substrates, and can lead to the failure of a therapy [10]. The above reported studies on "light cannabis" smoking showed that after smoking up to 232 mg CBD in four hours time caused sleepiness. It has to be said that few data exist in the international literature concerning the side effects of CBD intake in healthy individuals. The most recent evidence on cannabinoids effectiveness on sleep refer to CBD therapeutic potential for the treatment of insomnia [29]. This capability is due to its anxiolytic, antipsychotic and neuroprotective properties, which prompted for its potential use in epilepsy, substance abuse and dependence, post-traumatic stress, depression, and finally sleep disorders [5]. However, this beneficial CBD feature should be considered when the substance is used by healthy individuals, where this anxiolytic and relaxing effects may be dangerous in normal daily activities such as driving or working.

Legal status in United States of America

As cannabis compound, CBD was reported in the schedule I of Controlled Substances Act (CSA) which prohibits "manufacture, distribution, or dispensation, as well as its possession with intent to manufacture, distribute, or dispense" of all those substances, that have a high potential for abuse or have no currently accepted medical use in treatment in the United States of America (US) [30]. On June 25th, 2018 FDA approved Epidiolex® (CBD) oral solution for the treatment of two rare and severe forms of epilepsy, Lennox-Gastaut syndrome and Dravet syndrome, in pediatric patients [31]. This is the first FDA-approved drug that contains a purified drug substance derived from marijuana, schedule I of CSA [32]. For that reason, FDA prepared and transmitted a report of CBD to justify the necessity of re-scheduling CBD, due to scientific evidences of its therapeutic benefits. On September 27th, 2018 the Department of Justice and DEA announced that Epidiolex®, was placed in schedule V, as a "drug with lower potential for abuse than Schedule IV containing limited quantities of certain narcotics", the least restrictive schedule of the CSA [33]. It is necessary to underline that CSA did not distinguish between CBD obtained from recreational, medical or industrial cannabis (hemp). On December 20th, 2018, with the Agriculture Improvement Act, hemp was definitely removed from schedule I and became legal, so any cannabinoid or derivatives, including CBD, obtained from hemp are legal, if and only if that hemp is produced under the federal law, while all other cannabinoids, produced in any other setting, remain illegal and scheduled in the first table of CSA [34], except for the limited circumstances e.g. a medically approved benefit. On June 16th 2019, the FDA released a document recognizing the significant public interest in cannabis-derived compounds, expressing, at the same time, concern for the exponential increase of illegal products that violate the Federal Food, Drug and Cosmetic Act (FD&C Act) [35]. From 2015 to 2019 FDA sent several warring letters to companies that commercialized products containing CBD because they were marketed as unapproved new drugs adding CBD to food [36]. It is essential to underline that aside Epidiolex ®, no other CBD drug products were FDA-approved and for that reason they cannot be distributed or sold in interstate commerce [35]. CBD products are excluded from the dietary supplement definition under section 201(ff) of the FD&C Act [35, 37]. Nonetheless, ingredients as hulled hemp seed, hemp seed proteins powder and hemp seed oil, that are

derived from parts of the cannabis plant that do not contain CBD, might be able to be marketed as dietary supplements or be added to food [35]. In the first case, this can happen only if dietary supplements comply requirements related to Current Good Manufacturing Practices and are correctly labeled to eliminate any possible risk of illness or injury [37]. In the second case, only after approval by FDA or if CBD addition to food is generally recognized as safe [35]. At last, cosmetics containing CBD are not restricted by any regulation. However, all ingredients must comply with all applicable requirements and cannot be used if they cause adulteration or misbranding of the product or could be injurious to users [37]. So it seems that the 2018 Farm Bill, the primary agricultural and food policy tool of the federal government explicitly preserved FDA's authority to regulate products other than medicines containing cannabis or cannabis-derived compounds (CBD in particular) under the FD&C Act. On the other hand, the Farm Bill has no effect on state-legal cannabis programs, in which cannabis and derived compounds (CBD in particular) were legalized for medical and recreational purposes, that are declaimed illegal under the federal law [38].

Legal status in European Union

In European Union (EU) there is no harmonized law on CBD use. Indeed, currently the criminal or administrative response towards CBD use is under the responsibility of each EU Member State. Actually, medicinal products containing CBD, such as: Sativex® and Epidiolex® (since September 19th, 2019), are authorized in many EU countries, and, in some of them, under certain conditions, are reimbursed by the national health insurance system [40]. Any medicinal product containing CBD placed for sale or distribution on the market in a Member State must require a Community marketing authorization, released by the European Agency for the Evaluation of EMA, in accordance with the Title I article 3 of Regulation (EEC) N. 2309/93 [41]. The marketing authorization shall be valid throughout the Community. On the contrary, the rejection of a Community marketing authorization shall constitute a prohibition on the placing on the market of the medicinal product throughout the Community in compliance with the Title II article 12 of Regulation (EEC) N. 2309/93 [41]. In the past few years there has been an increase in the availability of cannabis based products (herb, hemp, oils) that contain CBD, referred as "light cannabis" [17]. All extracts of Cannabis sativa L. and any product to which CBD, synthetically obtained or not, is added as ingredient, have to be considered as novel foods and strictly controlled under the novel food Regulation ((EU) 2015/2283) [42]. As in case of medicinal products, novel foods require a community authorization for the suppling in EU Member States market which is released by the EFSA [42,43]. Others Cannabis based products containing CBD may be used in cosmetics placed on the EU market if they are "safe for human health when used under normal or reasonably foreseeable conditions of use" in accordance with articles 3 and 4 of the Chapter II of the Cosmetic Regulation (Regulation (EU) No 1223/2009) [44], as to say: if they not contain any substances listed in the Annex II and are "obtained from cannabis, cannabis resin, cannabis extracts and cannabis tinctures originating from the seeds and leaves that are not accompanied by the fruiting tops of the cannabis plant" [43]. Therefore, whereas US legal status of CBD is currently well defined throughout Federal States, EU one is not homogeneous at moment, nor extensively regulated, with some countries, such as Italy, with no legal measures at all.

Legal status in Italy

Currently, in Italy, there are no laws that ban CBD and at moment CBD is not yet registered as a medicinal. Due to this law vacancy, some hemp shops freely offer CBD products (oil, crystals, etc).

CONCLUSIONS

Thanks to its safe therapeutic profile and its lack of psychoactivity, CBD is one of the most interesting compounds, with a lot of reported pharmacological effects in different models of pathologies, from inflammatory and neurodegenerative diseases, to epilepsy, autoimmune disorders like multiple sclerosis, arthritis, schizophrenia, cancer and many others. Even if pharmaceutical and therapeutic profile of CBD is deeply notorious, its legal status, in different countries around the world, isn't clear and harmonized. The widespread growth of markets selling products containing CBD (medicinal products, foods and cosmetics) is not only an "American" reality, but also involves many Europeans Countries, and according to recent market research studies it will continue growing exponentially over the next few years. Actual legislative acts of different governments to control drugs, foods and cosmetics containing CBD, which are easily available for consumers, are nowadays inappropriate to support the international and intranational market without a systematic revision and could cause an important public health threat.

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Conflict of interest statement

None of the authors have any conflict of interest.

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